








ORIGINAL RESEARCH

Trajectories of Left Ventricular Ejection Fraction After Acute Decompensation for Systolic Heart Failure: Concomitant Echocardiographic and Systemic Changes, Predictors, and Impact on Clinical Outcomes

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BACKGROUND: Prospective longitudinal follow-up of left ventricular ejection fraction (LVEF) trajectories after acute cardiac decompensation of heart failure is lacking. We investigated changes in LVEF and covariates at 6-months' follow-up in patients with a predischARGE LVEF $\leq 40\%$, and determined predictors and prognostic implications of LVEF changes through 18-months' follow-up.

METHODS AND RESULTS: Interdisciplinary Network Heart Failure program participants ($n=633$) were categorized into subgroups based on LVEF at 6-months' follow-up: normalized LVEF ($>50\%$; heart failure with normalized ejection fraction, $n=147$); mid-range LVEF ($41\%–50\%$; heart failure with midrange ejection fraction, $n=195$), or persistently reduced LVEF ($\leq 40\%$; heart failure with persistently reduced LVEF, $n=291$). All received guideline-directed medical therapies. At 6-months' follow-up, compared with patients with heart failure with persistently reduced LVEF, heart failure with normalized LVEF or heart failure with midrange LVEF subgroups showed greater reductions in LV end-diastolic/end-systolic diameters (both $P<0.001$), and left atrial systolic diameter ($P=0.002$), more increased septal/posterior end-diastolic wall-thickness (both $P<0.001$), and significantly greater improvement in diastolic function, biomarkers, symptoms, and health status. Heart failure duration <1 year, female sex, higher predischARGE blood pressure, and baseline LVEF were independent predictors of LVEF improvement. Mortality and event-free survival rates were lower in patients with heart failure with normalized LVEF ($P=0.002$). Overall, LVEF increased further at 18-months' follow-up ($P<0.001$), while LV end-diastolic diameter decreased ($P=0.048$). However, LVEF worsened ($P=0.002$) and LV end-diastolic diameter increased ($P=0.047$) in patients with heart failure with normalized LVEF hospitalized between 6-months' follow-up and 18-months' follow-up.

CONCLUSIONS: Six-month survivors of acute cardiac decompensation for systolic heart failure showed variable LVEF trajectories, with $>50\%$ showing improvements by ≥ 1 LVEF category. LVEF changes correlated with various parameters, suggesting multilevel reverse remodeling, were predictable from several baseline characteristics, and were associated with clinical outcomes at 18-months' follow-up. Repeat hospitalizations were associated with attenuation of reverse remodeling.

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Key Words: acute heart failure ■ left ventricular ejection fraction ■ morbidity ■ mortality ■ natriuretic peptide ■ recovery

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CLINICAL PERSPECTIVE

What Is New?

- A relevant proportion of patients diagnosed with heart failure with reduced ejection fraction after an episode of acute cardiac decompensation, including 41% of those with severely depressed ejection fraction (left ventricular ejection fraction [LVEF] <30%), experienced significant improvements in LVEF within the following 6 months.
- The majority of patients showed variable LVEF trajectories after acute cardiac decompensation and transitioned between currently defined LVEF-based heart failure categories; serial long-term LVEF assessment showed an association between disease progression (based on rehospitalization) and worsening LVEF as a surrogate of reversal/attenuation of reverse remodeling.

What Are the Clinical Implications?

- Because of its association with other remodeling parameters, LVEF (and especially LVEF trajectory) is a useful surrogate marker for risk stratification and outcome prediction following discharge from the hospital after acute cardiac decompensation.
- Normalization of LVEF may not indicate true disease recovery, highlighting the need for ongoing heart failure therapy.
- Given the changes in LVEF over time, making therapeutic decisions based on a single LVEF measurement after acute cardiac decompensation seems inappropriate; individual LVEF trajectories during disease progression need to be considered in heart failure phenotyping to facilitate personalized care approaches.

Nonstandard Abbreviations and Acronyms

A	late atrial filling velocity
ACD	acute cardiac decompensation
E	left ventricular early diastolic filling velocity
e'	peak early annular velocity
FUP18	18-month follow-up
FUP6	6-month follow-up
GDMT	guideline-directed medical therapies
HF_nEF	heart failure with normalized ejection fraction
INH	Interdisciplinary Network Heart Failure
MR-proANP	midregional pro-atrial natriuretic peptide
sTVG	peak systolic tricuspid valve gradient

Repeat episodes of acute cardiac decompensation (ACD) occur throughout the heart failure (HF) trajectory. ACD is associated with injury and dysfunction of the heart and other organ systems, and patients with ACD frequently require hospitalization.¹ Clinical and functional recovery after ACD is often incomplete; abnormal loading conditions and augmented wall stress may induce adverse changes at the cellular and anatomic level, enhance disease progression, and increase the risk for adverse clinical outcomes. Although originally described after experimental myocardial infarction,² left ventricular (LV) remodeling involving alterations in cardiac architecture and systolic and diastolic myocardial dysfunction may also develop in response to other types of myocardial injury.³

Knowledge that activation of the renin–angiotensin–aldosterone axis and the adrenergic nervous system is implicated in this process drove clinical trials investigating the effects of neurohormonal inhibition on mechanisms of ventricular remodeling and patient outcomes. Early studies including patients with HF with reduced left ventricular ejection fraction (HF_rEF) showed, for example, that the angiotensin-converting enzyme inhibitor enalapril prevented progressive left ventricular (LV) dilatation and systolic dysfunction.⁴ Subsequent evidence demonstrated that other medications used as part of guideline-directed medical therapies (GDMT, eg, β -blockers or mineralocorticoid receptor antagonists) are also capable of attenuating or reversing remodeling and improve LV ejection fraction (LVEF), and that there are positive correlations between the effects of an intervention on LV volumes and function and its effect on mortality.^{5–8}

Improved LVEF is, in principle, considered a poor surrogate of contractility because of its dependence on LV volumes and loading conditions.⁹ However, evidence from observational studies suggests that patients with improvement or even normalization of previously impaired LVEF represent a different clinical entity from those with persistently reduced or preserved LVEF.^{8,10,11} Prospective longitudinal studies on the course of LVEF and other cardiac function and morphology parameters from a clearly defined time point during the HF trajectory are currently lacking, and there is no information on predictors of these changes, associated biomarker trends, and prognostic implications in the setting of ACD.

This prospective study investigated patients hospitalized for ACD with a predischarge LVEF of $\leq 40\%$, who received GDMT as tolerated throughout follow-up. Aims of the study were (1) to examine the spectrum of changes in LVEF and other parameters of cardiac function and morphology between baseline assessment before hospital discharge and at 6-month follow-up (FUP6) using quantitative echocardiography; (2) to evaluate associated changes in

patient characteristics, including symptoms, health status, and biomarkers of myocyte stress and injury, and inflammation; (3) to identify baseline parameters that predict changes in LVEF at FUP6 and assess their impact on the risk of mortality and rehospitalization between FUP6 and 18-months' follow-up (FUP18); and (4) to describe longer-term LVEF trajectories in FUP18 survivors.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patient Sample

The investigator-initiated Interdisciplinary Network Heart Failure (INH) program (ISRCTN 23325295) studies the effects of nurse-coordinated disease management (HeartNetCare-HF) compared with usual care on all-cause mortality and morbidity after hospitalization for ACD. Study design and primary results in the first 715 participants were reported previously.¹² In brief, patients were eligible if aged ≥ 18 years and hospitalized for ACD (dyspnea at rest plus at least 1 of the following: raised jugular venous pressure, peripheral edema, or pulmonary congestion [clinical or chest radiography]). Patients from 9 sites in lower Franconia or Baden-Wuerttemberg, Germany, with a LVEF $\leq 40\%$ measured before discharge were randomly assigned 1:1 to either HeartNetCare-HF or usual care. The only exclusion criteria were new-onset structural heart disease (eg, type 1 myocardial infarction), lack of written informed consent, or logistic or health reasons precluding participation in a telephone-based intervention. The trial was conducted according to Good Clinical Practice guidelines and Declaration of Helsinki 2002 principles, and was approved by all responsible ethics committees.

This substudy included all INH participants who attended the FUP6 visit in person and had 2-dimensional echocardiograms whose quality allowed for unambiguous determination of LVEF at baseline and FUP6. Patients were divided in subgroups based on their LVEF at FUP6: those with LVEF $>50\%$ were categorized as having normalized LVEF (HF_nEF); those with LVEF between 41% and 50% as having HF with mid-range LVEF (HF_{mr}EF); and those with LVEF $\leq 40\%$ as having HF_rEF. Uptitration of GDMT to target doses was part of the INH study protocol.¹²

Baseline Examination and Follow-Up

Patients underwent physical examination, laboratory assessment, ECG, echocardiography, and

psychometric evaluation using the Kansas City Cardiomyopathy Questionnaire¹³ at baseline and follow-up visits that took place every 6 months. Follow-up was centralized and occurred either at the INH outpatient clinic or by structured telephone-based interview.

Information on vital status and hospital admissions was obtained from patients, hospital discharge letters, and medical files, and adjudicated by INH team members blinded to study intervention according to prespecified criteria. For deceased patients, date and cause of death were ascertained using death certificates. "Hospitalization" was defined as unplanned hospital admission with at least 1 overnight stay.

Echocardiography

Echocardiography was performed as part of routine care using a prespecified protocol based on American Society of Echocardiography recommendations.¹⁴ Two-dimensional parasternal long- and short-axis views and apical views were recorded. LVEF was determined using Simpson's biplane or monoplane method, and LV end-diastolic dimensions (LVEDD) and LV end-systolic dimensions, wall thickness, and left atrial end-systolic diameter measured from left parasternal M-mode echocardiograms. LV diastolic function was examined where feasible. LV early diastolic filling velocity (E), late atrial filling velocity (A), E-wave deceleration time, and the E/A ratio were determined by pulsed-wave Doppler using the apical 4-chamber view. Peak early diastolic annular velocity (e') was derived from the pulsed-wave tissue-Doppler signal at the lateral mitral annulus. Systolic pulmonary artery pressure was estimated from the peak systolic tricuspid valve gradient (sTVG) using continuous-wave Doppler.

Biomarkers

Biosamples were collected at all visits (baseline, FUP6, FUP12, and FUP18), stored immediately at -80°C and analyzed after completion of FUP18. At baseline and FUP6, NT-proBNP (amino-terminal pro-brain natriuretic peptide), hs-CRP (high-sensitivity C-reactive protein), and interleukin-6 levels were measured with the IMMULITE 2000 system; cardiac troponin I concentrations were determined with the ADVIA Centaur TnIUltra system (both Siemens Healthineers, Erlangen, Germany). Midregional pro-atrial natriuretic peptide (MR-proANP), which was measured using a commercial fluoro-immunoassay (BRAHMS MR-proANP KRYPTOR; BRAHMS GmbH, Hennigsdorf, Germany), was determined at baseline, FUP6, and FUP18. See Data S1 for details.

Data Analysis and Statistical Analysis

Continuous variables are reported as mean±SD or median (quartiles), as applicable, and categorical variables as counts and percentages. Baseline characteristics were compared between subgroups using the χ^2 test or ANOVA as appropriate. Within subgroups, changes were assessed with a paired *t* test, and differences between subgroups using ANCOVA adjusted for age, sex, and the baseline value of each variable. Binary logistic regression models were used to evaluate the impact of MR-proANP levels on the risk of incident hospitalization and investigate univariable and multivariable associations of potential baseline predictors with LVEF improvement at FUP6. A stepwise backward variable selection was used to determine which baseline parameters were independent predictors of LVEF improvement at FUP6, starting from the full model including the study intervention and all baseline variables showing significant differences between subgroups and having <10% missing values (Table S1). Variables retaining prognostic significance ($P<0.05$) in the multivariable model were thus identified as independent predictors. Associations between HF category defined at FUP6 and event-free survival between FUP6 and FUP18 were analyzed using Cox proportional hazard regression analysis. Age, sex, baseline LVEF, and New York Heart Association class I/II versus III/IV were entered in multivariable Cox models, and hazard ratio and 95% CI values were determined. Sensitivity analyses were performed, which included additional adjustments. Clinical covariates were selected based on a priori knowledge of predictors of clinical outcomes, such as renal dysfunction and NT-proBNP level, and also the presence of hypertension or diabetes mellitus, use of β -blocker therapy, duration of HF, and ischemic cause of HF. Kaplan–Meier curves were constructed for visualization. The impact of ≥ 1 rehospitalization on LVEF changes and associated changes in LVEDD and MR-proANP levels between FUP6 and FUP18 was assessed using an ANCOVA model with the interaction term of hospitalization and subgroup and adjustment for the FUP6 value of each variable. In case of lack of significance between subgroups, a pooled overall effect was calculated. Estimated effects with corresponding 95% CIs and *P* values are given. All biomarker levels were log-transformed for calculation.

All tests are 2-sided. $P<0.05$ were considered statistically significant. Statistical analyses were performed using SPSS 25 (IBM, Munich, Germany) and Stata16 (StataCorp, College Station, TX).

RESULTS

Baseline Patient Characteristics

Of 1022 potential participants, 633 were included (Table 1); of 389 ineligible patients (38.1%), 104

(10.2%) died within 6 months of discharge, and 285 (27.9%) did not have adequate echocardiograms available at baseline and FUP6. Compared with eligible patients, ineligible patients were older (71 ± 12 versus 65.8 ± 12.4 years, $P<0.001$), more often female (33.2% versus 25.8%, $P=0.013$), and in New York Heart Association functional class III-IV (53.2% versus 37.8%, $P<0.001$), had a longer HF duration (HF known for >1 year in 72.0% versus 58.5%, $P<0.001$), and a higher comorbidity burden (renal dysfunction 53.1% versus 37.6%, $P<0.001$; anemia 42.7% versus 27.2%, $P<0.001$; diabetes mellitus 42.4% versus 31.3%, $P=0.001$). Echocardiographic parameters were comparable to those of eligible patients.

Participants with improved LVEF at FUP6 were younger, more often female, had a shorter HF duration, higher blood pressure and heart rate, and lower natriuretic peptide levels at baseline. They were also less likely to have an ischemic HF cause or a left bundle branch block. Other biomarkers, comorbidity profile, clinical signs of congestion, health status, and GDMT did not differ between subgroups. Overall, mean LVEF was $30\pm 8\%$. Between-group differences in baseline LVEF were statistically significant, but numerically small. In the subgroup of patients with adequate measurements, those with improved LVEF at FUP6 had lower LVEDD and LVESD, higher end-diastolic wall thickness, and lower cardiac filling pressures as estimated from peak sTVG (Table 1).

Changes at FUP6

The proportions of patients with LVEF <30% or 30% to 40% decreased substantially between baseline and FUP6 (Figure 1A). Of those with a baseline LVEF of 30% to 40%, 61.2% had either normalized LVEF or showed midrange impairment at FUP6 compared with 41.6% of patients with LVEF <30% (Figure 1B). Overall, mean LVEF increased to $41.4\pm 11.6\%$ at FUP6 ($+11.4\pm 11.8\%$ versus baseline, $P<0.001$).

Patient characteristics at FUP6 and the magnitude of changes between baseline and FUP6 across subgroups are given in Table S2 and in Table 2, respectively. Patients with HF_{NEF} or HF_{mrEF} also showed significantly greater reductions in LVEDD, LVESD, and left atrium, a more pronounced increase in LV end-diastolic wall thickness, better normalization of diastolic relaxation and filling parameters, and a greater reduction in peak sTVG. In addition, New York Heart Association class and health status improved more in the HF_{NEF} and HF_{mrEF} subgroups, while changes in hemoglobin, leukocytes, and renal and hepatic function did not differ between subgroups. Compared with baseline, all biomarker levels declined markedly at FUP6. While NT-proBNP, MR-proANP, and cardiac troponin I levels were significantly lower in patients with improved LVEF versus patients with persistent HF_{rEF}, hs-CRP, and

Table 1. Baseline Patient Demographic and Clinical Characteristics in the Overall Study Population and in Patient Subgroups Based on LVEF Fraction at 6-Month Follow-Up

	All Patients (n=633)	HFrEF (n=291)	HFmrEF (n=195)	HFNrEF (n=147)	P Value	n
Demographics						
Age, y	65.8±12.4	67.1±12.0	65.4±11.3	63.7±14.1	0.023	633
Male sex, n (%)	470 (74.2)	232 (79.7)	142 (72.8)	96 (65.3)	0.004	633
Heart failure characteristics						
Ischemic etiology, n (%)	296 (46.8)	154 (52.9)	87 (44.6)	55 (37.4)	0.007	633
Duration of HF <1 y, n (%)	263 (41.5)	89 (30.6)	90 (46.1)	84 (57.1)	<0.001	575
NYHA functional class	2.37±0.57	2.38±0.58	2.33±0.54	2.41±0.58	0.459	633
NYHA class I, n (%)	16 (2.5)	7 (2.4)	6 (3.1)	3 (2.0)		
NYHA class II, n (%)	378 (59.7)	174 (59.8)	119 (61.0)	85 (57.8)		
NYHA class III, n (%)	226 (35.7)	102 (35.1)	69 (35.4)	55 (37.4)		
NYHA class IV, n (%)	13 (2.0)	8 (2.7)	1 (0.5)	4 (2.7)		
Comorbidities/risk factors, n (%)						
Hypertension	477 (75.4)	211 (72.5)	157 (80.5)	109 (74.1)	0.124	633
Renal dysfunction*	238 (37.6)	123 (42.3)	68 (34.9)	47 (32.0)	0.07	633
Left bundle branch block	198 (31.5)	116 (40.1)	52 (26.8)	30 (20.5)	<0.001	629
Diabetes mellitus†	198 (31.3)	92 (31.6)	58 (29.7)	48 (32.7)	0.836	633
Anemia‡	172 (27.2)	78 (26.8)	51 (26.2)	43 (29.3)	0.801	633
Atrial fibrillation§	166 (26.2)	72 (24.7)	51 (26.2)	43 (29.3)	0.598	632
Clinical examination						
Mean arterial pressure, mm Hg	88.6±12.3	86.4±11.3	90.1±12.5	90.9±13.3	<0.001	633
Heart rate, beats/min	78.7±18.3	76.9±18.5	81.1±18.7	78.9±17.0	0.043	633
BMI, kg/m ²	27.1±4.6	26.7±4.2	27.5±4.8	27.5±4.9	0.116	632
Any sign of congestion , n (%)	269 (47.2)	125 (47.7)	77 (44.0)	67 (50.4)	0.526	633
Laboratory parameters						
eGFR, mL/min per 1.73 m ²	68.9±25.5	66.4±24.7	70.1±27.4	72.1±24.2	0.062	633
Hemoglobin, g/dL	13.7±1.9	13.7±1.9	13.8±1.9	13.4±2.1	0.155	633
Leukocytes, 1000/μL	8.1±3.0	8.1±3.0	8.4±3.3	7.9±2.4	0.253	633
GPT, U/L	28.0 [18.3, 46.1]	27.5 [19.0, 45.5]	26.6 [18.9, 46.3]	31.2 [17.9, 48]	0.869	623
GGT, U/L	52.2 [31.2, 104.1]	52.9 [31.4, 112.5]	48.4 [29.4, 105.0]	57.0 [33.1, 97.0]	0.603	616
NT-proBNP, pg/mL	2508.5 [925.5, 5637.5]	3308.0 [1059.0, 7043.0]	2121.5 [947.0, 4909.5]	2042.5 [666.5, 4384.5]	0.001	584
MR-proANP, pmol/L	290.6 [180.6, 426.4]	321.7 [216.7, 480.6]	296.4 [167.3, 407.5]	239.2 [152.1, 355.0]	<0.001	583
cTnI, ng/mL	0.039 [0.020, 0.074]	0.042 [0.023, 0.081]	0.035 [0.017, 0.079]	0.038 [0.019, 0.060]	0.092	568
hs-CRP, mg/L	8.0 [2.9, 20.3]	7.5 [2.6, 19.3]	7.9 [2.9, 19.8]	8.9 [3.8, 24.1]	0.397	599
IL-6, pg/mL	4.0 [2.0, 9.3]	3.9 [2.0, 9.5]	3.9 [2.0, 9.3]	4.2 [2.0, 9.0]	0.891	598
Echocardiography						
LVEF, %	30.0±7.5	28.0±7.5	31.0±7.0	32.1±7.0	<0.001	633
LVEDD, mm	61.7±8.8	64.2±9.2	60.5±8.0	58.5±7.5	<0.001	606
LVESD, mm	51.3±10.1	54.1±10.2	49.5±9.7	48.2±8.7	<0.001	529
LAESD, mm	46.1±7.5	46.7±7.6	45.9±7.3	45.1±7.4	0.099	590
IVSd, mm	11.2±2.5	11.0±2.4	11.1±2.3	11.9±3.0	0.001	591
LVPWd, mm	10.9±2.3	10.6±2.3	10.9±2.1	11.3±2.5	0.016	590
E-wave, cm/s	79.4±29.2	78.3±28.2	81.1±31.4	79.0±27.8	0.733	358
A-wave, cm/s	64.8±28.4	64.5±29.9	65.1±27.5	65.2±26.4	0.982	328
Deceleration time, ms	199.6±98.0	191.3±96.0	199.8±92.2	218.7±109.5	0.147	342
IVRT, ms	109.9±44.9	110.7±43.9	113.9±50.2	101.7±38.8	0.502	153
e', cm/s	8.4±5.8	8.7±4.7	8.2±7.5	7.8±5.2	0.712	205
sTVG, mm Hg	37.1±14.2	39.5±15.4	35.2±12.0	35.0±13.6	0.009	398

(Continued)

Table 1. Continued

	All Patients (n=633)	HFrEF (n=291)	HFmrEF (n=195)	HFnEF (n=147)	P Value	n
E/A	1.5±1.1	1.5±1.5	1.2±0.8	1.2±0.7	0.428	157
E/e'	14.3±11.6	13.1±10.9	15.1±13.0	15.7±10.8	0.405	200
HF therapy [¶] , n (%)						
ACEi/ARB	579 (91.5)	259 (89.0)	183 (93.8)	137 (93.2)	0.12	633
β-Blocker	545 (86.1)	248 (85.2)	176 (90.3)	121 (82.3)	0.092	633
MRA	285 (45.0)	143 (49.1)	84 (43.1)	58 (39.5)	0.127	633
Diuretics	547 (86.4)	257 (88.3)	167 (85.6)	123 (83.7)	0.38	633
Biventricular pacemaker/ICD	60 (9.5)	43 (14.8)	11 (5.6)	6 (4.1)	<0.001	632
Psychometry						
KCCQ Clinical Summary Score	63.0±23.6	61.7±23.7	64.6±24.1	63.4±22.9	0.430	566
KCCQ Overall Summary Score	57.8±22.8	56.3±22.8	60.8±23.1	56.7±22.2	0.127	528
Type of HF care, n (%)						
Usual care	309 (48.8)	149 (51.2)	98 (50.3)	62 (42.2)	0.181	633
HeartNetCare-HF	324 (51.2)	142 (48.8)	97 (49.7)	85 (57.8)		

Values are given as n (%), mean±SD, or median [quartiles]. P values refer to χ^2 test or ANOVA (on log scale for biomarkers), as appropriate. A-Wave indicates peak late diastolic mitral flow velocity; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; BMI, body mass index; cTnI, cardiac troponin I; e', peak early diastolic velocity by pulsed wave tissue Doppler imaging at the lateral mitral annulus; eGFR, glomerular filtration rate (Modification of Diet in Renal Disease formula); E-Wave, peak early diastolic mitral flow velocity; GGT, gamma-glutamyltransferase; GPT, glutamate-pyruvate transaminase; HF, heart failure; HFmrEF, heart failure with mid-range left ventricular ejection fraction (LVEF 41–50%); HFnEF, heart failure with normalized left ventricular ejection fraction (LVEF >50%); HFrEF, heart failure with reduced left ventricular ejection fraction (LVEF ≤40%); hs-CRP, high sensitive C-reactive protein; ICD, Implantable cardioverter-defibrillator; IL-6, interleukin 6; IVRT, isovolumic relaxation time; IVSd, end-diastolic interventricular septal thickness; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAESD, left atrial end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVPWd, left ventricular end-diastolic posterior wall thickness; MRA, mineralocorticoid receptor antagonist; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, amino-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; and sTVG, systolic tricuspid valve gradient (estimated from peak tricuspid valve regurgitant flow velocity).

*eGFR <60 mL/min per 1.73 m².

†History of diabetes mellitus.

‡Hemoglobin <12 g/dL in women and <13 g/dL in men.

§From 12-lead ECG.

||At least 1 of the following: peripheral edema, elevated jugular venous pressure, or pulmonary rales.

¶At discharge.

interleukin-6 levels did not differ between subgroups at FUP6 (Table S2). With the exception of hs-CRP, average changes were significantly greater in patients with improved LVEF (Table 2), but with substantial variability (Figure 2). Heart rate at FUP6 was lower in all subgroups (Table S2), but decreased significantly more in patients with improved LVEF (Table 2 and Figure S1, left). Concomitantly, mean blood pressure increased slightly, but significantly, but the magnitude of change did not differ between subgroups (Table 2 and Figure S1, right). The proportions of patients taking each substance class within GDMT was high at baseline but increased even further at FUP6 (Table 2).

Clinical Outcomes and Correlates of LVEF Changes

At FUP18, 51 patients (8.1%) had died (32 HFrEF, 15 HFmrEF, 4 HFnEF). Mortality risk decreased when LVEF at FUP6 was better, but only patients with HFnEF had a significantly reduced risk of all-cause death compared with patients with HFrEF and HFmrEF on Cox regression analysis ($P=0.012$

and $P=0.05$, respectively, Figure 3A). The composite death or hospitalization end point occurred in 259 patients (40.9%) and those in the HFnEF group had significantly fewer events versus those in the HFrEF group ($P=0.002$), but not the HFmrEF group (Figure 3B). There were 92 events (14.5%) of the composite death and hospitalization for HF end point; again, the event rate was lower in the HFnEF group compared with the HFrEF ($P<0.001$), but not the HFmrEF, group (Figure 3C). Results were similar in all sensitivity analyses (Table S3).

Female sex and various clinical, echocardiographic, and laboratory parameters were either positively or negatively associated with LVEF improvements at FUP6 on univariable analysis (Table S1). In the multivariable model, shorter HF duration was the strongest independent predictor of LVEF improvement, followed by female sex, and higher baseline blood pressure and LVEF. Ischemic HF cause, left bundle branch block, higher LVEDD, and NT-proBNP were independent predictors of a reduced likelihood of LVEF improvement (Figure 4). All variables remained independent predictors when study intervention was included in the model.

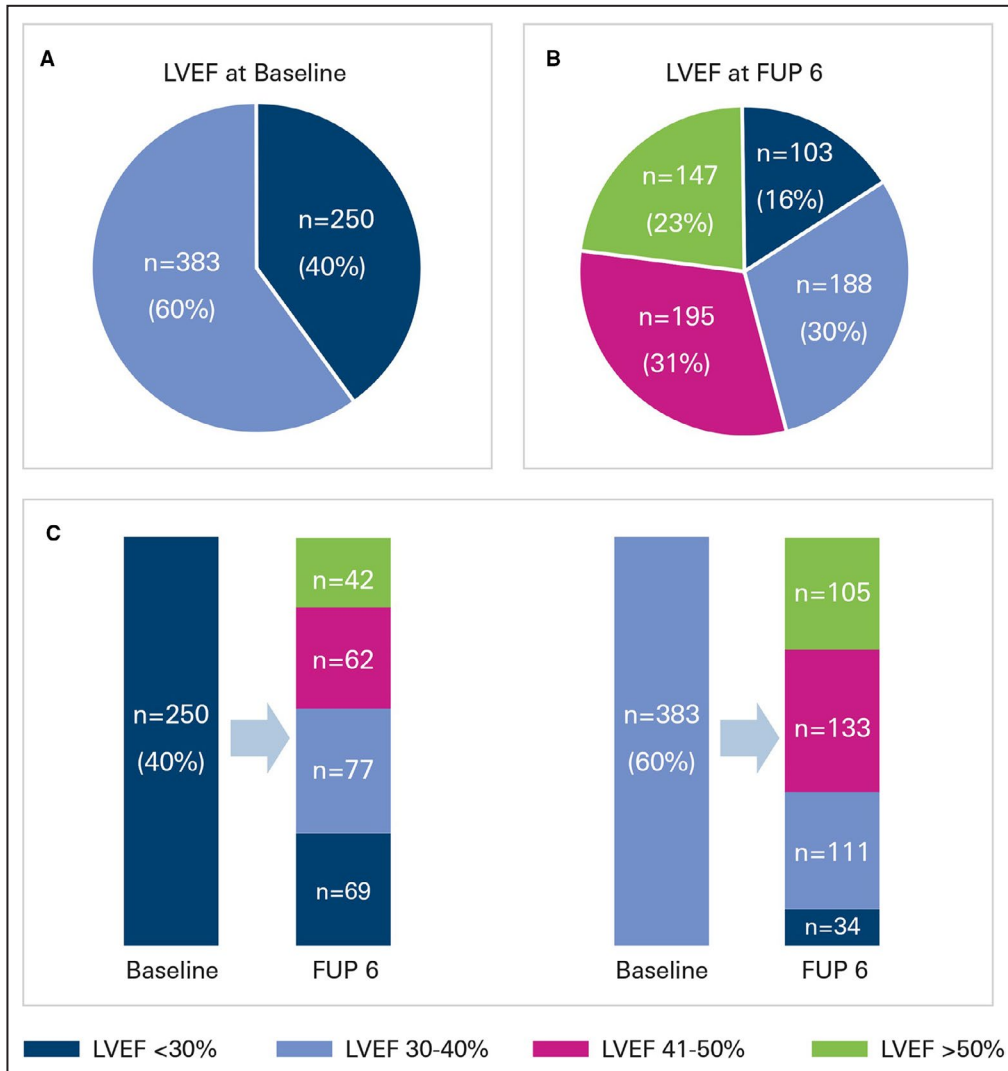


Figure 1. Distribution of left ventricular ejection fraction (LVEF) at baseline (A) and at 6-month follow-up (FUP 6) (B) in 633 study participants with LVEF \leq 40% at enrollment, and the distribution of LVEF at FUP6 depending on whether LVEF at baseline was $<$ 30% (left) or 30% to 40% (right) (C).

Changes Between FUP6 and FUP18

Table S4 displays longitudinal changes in LVEF, LVEDD, and MR-proANP up to FUP18. Overall, mean LVEF continued to improve in FUP18 survivors ($P<0.001$). Average LVEF did not change between FUP6 and FUP18 in patients with HF_nEF, but improved in those with HF_mrEF or HF_rEF ($P=0.002$ and $P<0.001$, respectively). LVEF trajectories varied considerably in individual patients. Figure 5 shows numbers of patients transitioning between LVEF categories between FUP6, FUP12, and FUP18 (numbers in brackets denote subsets of patients hospitalized in the preceding 6 months). Columns depict the proportion of patients currently in each LVEF category for each time point and those deceased between follow-ups. Transitions between the subgroups

defined at FUP6 resulted in broad overlap at FUP12 and FUP18 (Figure S2). LVEDD decreased slightly in all FUP18 survivors ($P=0.048$), but changes within subgroups were not significant. Overall, MR-proANP did not change at FUP18; levels decreased significantly between FUP6 and FUP18 only in patients with HF_rEF ($P=0.006$). Irrespective of subgroup, FUP6 MR-proANP levels were associated with readmissions between FUP6 and FUP18 (odds ratio per 2-fold change, 2.6 [1.9–3.4]; $P<0.001$).

Hospital admissions between FUP6 and FUP18 were associated with alterations in the trajectories of LVEF, LVEDD, and MR-proANP (Figure 6). The effect was greatest in the HF_nEF subgroup, where LVEF decreased at FUP18 if patients experienced ≥ 1 intercurrent hospital admission, while increasing in those

Table 2. Changes From Baseline to 6-Month Follow-Up in the Overall Study Population and in Patient Subgroups Based on LVEF at 6 Months

	n	Change From Baseline to 6-mo Follow-Up				P Value
		All Patients (n=633)	HFrEF (n=291)	HFmrEF (n=195)	HFNEF (n=147)	
Clinical examination						
NYHA functional class	633	-0.33±0.78	-0.21±0.77	-0.33±0.71	-0.59±0.83	<0.001
NYHA class I, n (%)		+121 (19.1)	+43 (14.8)	+36 (18.5)	+42 (28.6)	
NYHA class II, n (%)		-37 (5.8)	-27 (9.3)	-8 (4.1)	-2 (1.4)	
NYHA class III, n (%)		-79 (12.5)	-15 (5.2)	-28 (14.4)	-36 (24.5)	
NYHA class IV, n (%)		-5 (0.8)	-1 (0.3)	0	-4 (2.7)	
Mean arterial pressure, mm Hg	632	1.6±15.7	1.9±14.3	2.0±15.3	0.6±18.7	0.148
Heart rate, beats/min	632	-10.7±19.6	-7.4±18.9	-13.8±20.3	-12.9±19.0	0.004
BMI, kg/m ²	625	0.50±2.36	0.43±1.92	0.66±2.92	0.44±2.32	0.406
Any sign of congestion*, n (%)	624	-115 (18.2)	-49 (16.8)	-34 (17.4)	-32 (21.8)	
Laboratory parameters						
eGFR, mL/min per 1.73m ²	632	-1.19±19.35	-0.81±18.13	-0.69±19.08	-2.60±21.95	0.611
Hemoglobin, g/dL	630	-0.01±1.59	0.1±1.56	-0.17±1.63	0.01±1.57	0.074
Leukocytes, 1000/μL	630	-0.4±2.8	-0.4±3.0	-0.4±2.6	-0.3±2.4	0.588
GPT, U/L	621	-3.8 [-19.9, 4.3]	-3.3 [-18.7, 4.2]	-3.8 [-19.3, 3.6]	-5.8 [-21.0, 4.9]	0.678
GGT, U/L	614	-7.0 [-29.9, 6.7]	-6.1 [-25.5, 7.0]	-6.0 [-31.2, 6.1]	-9.8 [-39.0, 6.9]	0.062
NT-proBNP, pg/mL	507	-689.0 [-2498.0, 80.0]	-501.5 [-2462.0, 393.0]	-718.0 [-2788.5, 12.5]	-959.0 [-2380.0, -192.2]	<0.001
MR-proANP, pmol/L	561	-20.4 [-117.6, 44.4]	1.9 [-93.6, 73.6]	-38.6 [-168.8, 34.0]	-50.0 [-127.7, 8.7]	<0.001
cTnl, ng/mL	429	-0.011 [-0.040, 0.002]	-0.008 [-0.042, 0.004]	-0.041 [-0.013, 0.003]	-0.016 [-0.035, -0.002]	0.019
hs-CRP, mg/L	472	-3.1 [-14.7, -0.2]	-3.0 [-13.6, -0.1]	-2.7 [-13.9, 0.5]	-4.4 [-17.8, -0.7]	0.725
IL-6, pg/mL	560	-0.2 [-3.5, 0.3]	0.0 [-3.2, 1.0]	-0.3 [-4.2, 0.2]	-0.3 [-4.0, 0.1]	0.045
Echocardiography						
LVEF, %	633	+11.4±11.8	+3.2±8.9	+14.2±7.7	+23.9±8.0	<0.001
LVEDD, mm	591	-1.4±8.6	+0.5±8.2	-2.5±8.7	-3.7±8.6	<0.001
LVESD, mm	499	-5.1±10.5	-2.1±9.7	-6.1±11.0	-9.5±9.7	<0.001
LAESD, mm	578	-2.0±7.6	-1.0±7.5	-2.7±8.0	-3.0±7.0	0.002
IVSd, mm	577	+0.7±2.6	+0.5±2.6	+1.1±2.5	+0.4±2.7	<0.001
LVPWd, mm	577	+0.5±2.6	+0.4±2.5	+0.8±2.5	+0.4±2.8	<0.001
E-wave, cm/s	310	-9.7±30.5	-7.3±32.2	-14.1±31.2	-7.6±24.3	0.186
A-wave, cm/s	296	+11.5±31.2	+7.1±33.9	+11.8±28.8	+20.7±27.3	0.002
Deceleration time, ms	279	+53.0±125.9	+50.1±127.5	+58.3±132.1	+50.7±113.9	0.249
IVRT, ms	112	+11.8±56.1	+18.4±60.0	-5.9±52.3	+19.8±47.6	0.104
e', cm/s	168	-1.0±9.5	-2.1±5.1	-0.7±7.7	+0.9±3.6	0.069
sTVG, mm Hg	328	-6.1±14.9	-5.4±16.0	-7.6±14.6	-5.7±13.0	0.011
E/A	141	-0.3±1.4	-0.2±1.8	-0.2±0.8	-0.4±0.6	0.184
E/e'	161	-2.5±12.3	+0.1±12.7	-5.0±12.7	-4.3±9.9	0.036
Heart failure therapy, n (%)						
ACEi/ARB	633	+8 (1.3)	+6 (2.1)	+1 (0.5)	+1 (0.7)	
β-Blocker	632	+30 (4.7)	+11 (3.8)	+5 (2.6)	+14 (9.5)	
MRA	633	+61 (9.6)	+19 (6.5)	+27 (13.8)	+15 (10.2)	
Diuretics	633	+13 (2.1)	+6 (2.1)	+7 (3.6)	0	
New biventricular pacemaker/ICD	572 [†]	47 (8.2)	29 (11.7)	15 (8.2)	3 (2.1)	<0.001

(Continued)

Table 2. Continued

	n	Change From Baseline to 6-mo Follow-Up				P Value
		All Patients (n=633)	HFrEF (n=291)	HFmrEF (n=195)	HFpEF (n=147)	
Psychometry						
KCCQ Clinical Summary Score	536	+10.7±22.3	+9.5±23.3	+11.0±20.6	+12.5±22.6	0.090
KCCQ Overall Summary Score	484	+12.2±22.0	+10.6±23.4	+10.6±19.9	+17.6±21.1	0.005

Values are mean±SD or median [quartiles]. *P* values refer to ANCOVA *t* test for differences in change from baseline to 6-month follow-up between subgroups, adjusted for age, sex, and respective baseline variables. A-Wave indicates peak late diastolic mitral flow velocity; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; BMI, body mass index; cTnI, cardiac troponin I; e', peak early diastolic velocity by pulsed wave tissue Doppler imaging at the lateral mitral annulus; eGFR, glomerular filtration rate (Modification of Diet in Renal Disease formula); E-Wave, peak early diastolic mitral flow velocity; GGT, γ -glutamyltransferase; GPT, glutamate-pyruvate transaminase; HFmrEF, heart failure with midrange left ventricular ejection fraction (LVEF 41%–50%); HFpEF, heart failure with normalized left ventricular ejection fraction (LVEF >50%); HFrEF, heart failure with reduced left ventricular ejection fraction (LVEF ≤40%); hs-CRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillator; IL-6, interleukin 6; IVRT, isovolumic relaxation time; IVSd, end-diastolic interventricular septal thickness; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAESD, left atrial end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVPWd, left ventricular end-diastolic posterior wall thickness; MRA, mineralocorticoid receptor antagonist; MR-proANP, midregional pro-atrial natriuretic peptide; NT-proBNP, amino-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; and sTVG, peak systolic tricuspid valve gradient (estimated from peak tricuspid valve regurgitant flow velocity).

*At least 1 of the following: peripheral edema, elevated jugular venous pressure, or pulmonary rales.

[†]Defined only for patients who did not have such a device at baseline.

without (adjusted mean difference -5.8% [95% CI -9.4 , -2.1] with versus without hospitalization; $P=0.002$, Table S4). In the HFmrEF and HFrEF subgroups, concordant but smaller changes occurred, but these were not statistically significant. Similarly, LVEDD increased in patients with HFpEF experiencing readmission but decreased if they did not (adjusted mean difference 3.3 [0.6–6.1] mm; $P=0.017$), and MR-proANP levels at FUP18 were higher in patients with HFpEF with versus without readmission (mean adjusted ratio 1.20 [1.00–1.43]; $P=0.047$). Again, concordant nonsignificant changes occurred in the HFmrEF and HFrEF subgroups (Table S4).

DISCUSSION

Multiple cardiac and extracardiac triggers may cause ACD that, irrespective of cause, implicates volume overload and augmented LV wall stress. In the current study, participants might have experienced adverse remodeling secondary to the acute hemodynamic derangement during the event. Animal data support this concept, showing that even in the absence of ischemia, short elevations of end-diastolic LV pressure cause cardiac troponin release, apoptosis, and reversible myocardial stunning,¹⁵ and that exposure to such pathological stress may induce remodeling even if transient.¹⁶ In this context, the term “remodeling” refers to “plasticity” of the heart (ie, the ability to adapt its size, shape, and function to prevailing conditions in relatively short periods of time, driven by molecular, cellular and interstitial alterations, which may be reversible upon removal or attenuation of causative factors).^{17–19} The majority of our patients, who survived 6 months following ACD, showed reverse remodeling

within this period while receiving GDMT, and this was associated with favorable clinical outcomes.

LVEF is the most commonly applied measure of cardiac performance, and is used for functional and structural HF phenotyping.²⁰ However, its value as a measure of myocardial contractility and suitability for HF phenotyping has also been questioned.^{9,21} Current European Society of Cardiology guidelines categorize patients with HF into 3 phenotypes based on LVEF: HFrEF, HFmrEF, or heart failure with preserved ejection fraction (HFpEF).²² In routine clinical care, therapeutic decisions are often informed by predischARGE echocardiographic assessment of LVEF. The current findings highlight important limitations of the practice to categorize patients as having HFrEF, HFmrEF, or HFpEF at this point because of the marked variability of subsequent LVEF trajectories. They also emphasize that a single LVEF measurement should, in principle, not be used to guide treatment after ACD, particularly when LVEF improves on GDMT. This supports current US and European guideline recommendations, which state that repeat LVEF assessment must be performed after a minimum of 3 to 6 months of GDMT before consideration of implantable cardioverter-defibrillator implantation.^{22,23}

In our study, comprehensive longitudinal patient characterization identified remodeling and its reversal as a multifactorial and complex systemic process inadequately reflected by LVEF and volume estimates alone. Nevertheless, the data revealed close associations between LVEF changes and changes in systemic remodeling parameters. This demonstrates the practical usefulness of this surrogate marker for risk stratification and outcome prediction despite its limitations.

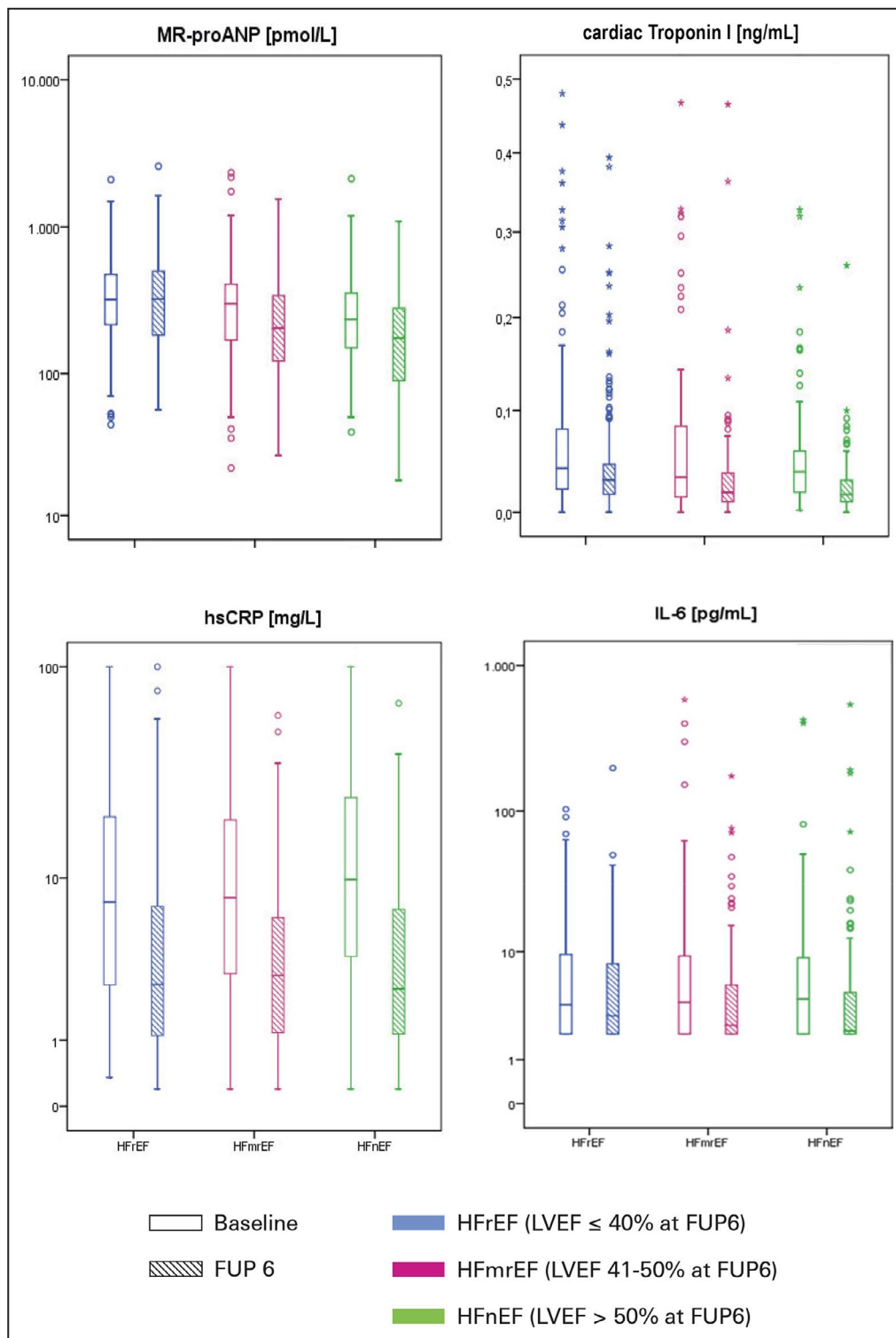


Figure 2. Biomarker levels at baseline (empty bars) and at 6-month follow-up (FUP6, hatched bars).

Shown are box plots in subgroups according to left ventricular ejection fraction (LVEF) at FUP6. HFmrEF, heart failure with midrange LVEF (41–50%); HFneEF, heart failure with normalized LVEF (>50%); HFReEF, heart failure with reduced LVEF (≤40%). **A**, MR-proANP, midregional atrial natriuretic peptide; **(B)** cardiac troponin I; **(C)** hsCRP, high-sensitivity C-reactive protein; and **(D)** IL-6, interleukin 6.

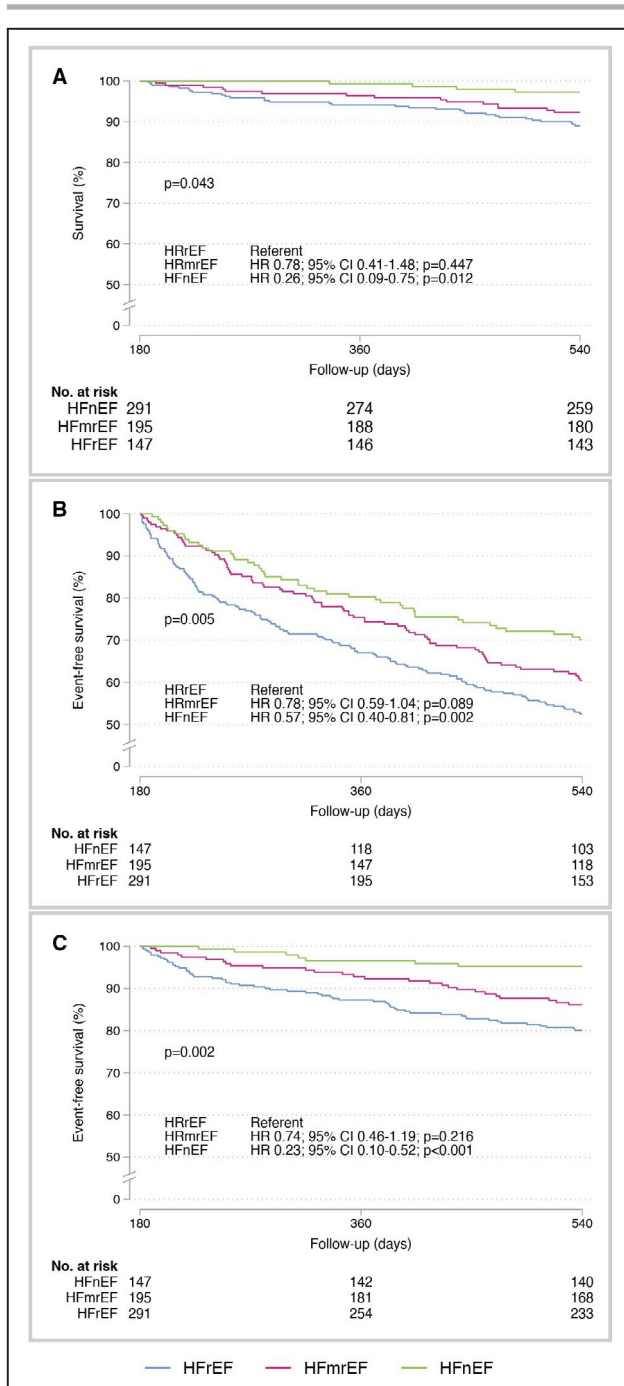


Figure 3. Kaplan-Meier curves showing survival from all-cause death (A), the composite of all-cause death and all-cause hospitalization (B), and the composite of all-cause death and hospitalization for heart failure (C) in subgroups according to left ventricular ejection fraction (LVEF) at 6-month follow-up. HFmrEF indicates heart failure with midrange LVEF (41%–50%); HFnEF, heart failure with normalized LVEF (>50%); HFrEF, heart failure with reduced LVEF (\leq 40%); and HR, hazard ratio. HR values are adjusted for age, sex, baseline LVEF, and New York Heart Association class.

In this large cohort of patients discharged after ACD with LVEF \leq 40%, the majority improved either to the HFmrEF category or normalized their LVEF while undergoing GDMT. Of note, 41% of patients with severely

depressed LVEF at baseline ($<$ 30%) had either normalized or midrange recovered LVEF at 6 months after an ACD event. To our knowledge, no previous study has prospectively evaluated the course of LVEF from this clearly defined time point of the HF trajectory (ie, the day of discharge from the hospital after ACD). Our results demonstrate that in this setting LVEF improvements were more frequent and pronounced than previously observed in chronic or mixed chronic and acute HFrEF populations. Our findings complement and expand community-based cohort studies^{8,10,11,24–31} and secondary analyses of treatment trials,^{4–7,32–36} which consistently reported that patients with HFrEF may experience improvement of previously reduced LVEF over time.

In our study, LVEF improvement was associated with significantly reduced LVEDD and LVESD (as surrogates for the reversal of abnormal chamber size), thus enabling better efficiency of myocardial contraction. At FUP6, patients with HFrEF had a higher sTVG (as a surrogate of pulmonary congestion) and had NT-proBNP levels that were twice as high as those in the HFmrEF and HFnEF subgroups (although a substantial proportion of patients with HFnEF had abnormal, albeit lower, NT-proBNP levels at FUP6 despite apparent normalization of LV systolic function). Taken together, our observations demonstrate that reverse remodeling after ACD represents a multilevel (cardiac and systemic) reversal toward a more normal clinical phenotype, and that this occurs in patients with a normalization of LVEF after ACD (HFnEF) and, to a lesser extent, in those with partial recovery of LVEF (HFmrEF).

The main independent baseline predictors of HFrEF persistence were a \geq 1-year history of HF and ischemic HF cause. Thus, both duration and nature of the underlying disease proved relevant in our study. HF duration is a plausible surrogate for the time of exposure to prolonged/repeat hemodynamic derangements leading to a gradual decline of the potential for repair, irrespective of HF cause.³⁷ In accordance, Solomon et al reported that the number of previous HF hospitalizations was a strong predictor of adverse clinical outcomes in patients with chronic HF.³⁸ Similarly, 2 other studies with prospective assessment of LVEF trajectories in HFrEF cohorts revealed that shorter HF duration was associated with better LVEF improvement, particularly in patients with nonischemic HF.^{8,28} Less LVEF improvement in patients with ischemic HF has also been reported in many previous studies in populations with HFrEF.^{**} Similar to other observations,^{29,34} we also identified worse baseline LVEF, larger LV cavity size, and left bundle branch block (along with low blood pressure) as additional independent predictors of lack of LVEF improvement at FUP6. Also consistent

**References 11,24,25,27,31,33,34,36.

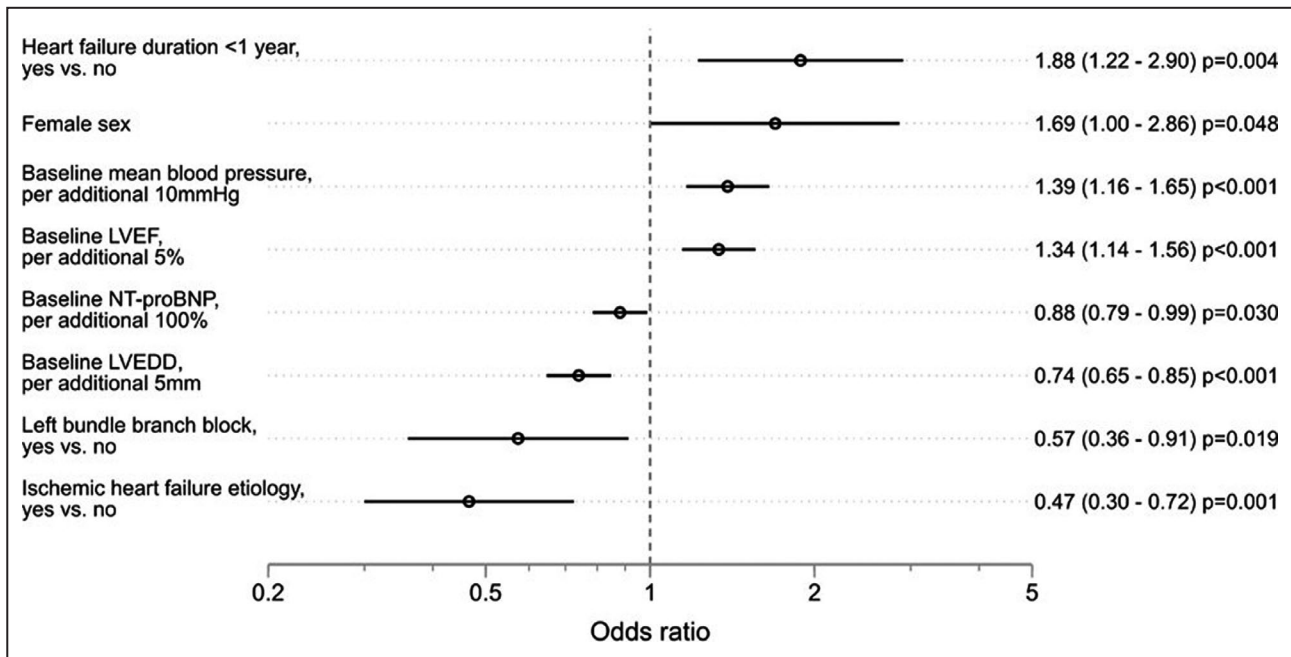


Figure 4. Baseline variables independently associated with improvement in left ventricular ejection fraction (LVEF) at 6-month follow-up, shown as odds ratio values (95% CIs) with corresponding *P* values (derived using a stepwise backward selection process; *P*<0.05; n=467).

LVEDD indicates left ventricular end-diastolic diameter; and NT-proBNP, N-terminal pro-brain natriuretic peptide.

with existing data,^{11,27} female sex was independently associated with LVEF normalization. Reasons are unclear, but may include diverse factors such as sex-related differences in the time course and pathophysiology of cardiovascular disease,³⁹ consecutive distinct pathophysiological alterations (predisposing men to HFrEF and myocardial infarction, and women to hypertensive heart disease and HFpEF) and a differential cardiac response to stimuli such as pressure overload.⁴⁰

Baseline NT-proBNP was significantly correlated with LVEF changes at FUP6 in univariable and multivariable analyses. Despite a more pronounced decrease of NT-proBNP and cardiac troponin I in patients with improved LVEF, a sizeable proportion had abnormal levels at FUP6, suggesting more and ongoing myocardial stress and injury. Of note, a substantial proportion of patients with HFpEF had abnormal cardiac troponin I levels (albeit comparatively lower) at FUP6, despite apparent normalization of LV systolic function. Patients with HFrEF had significantly higher average cardiac troponin I both at baseline and FUP6, suggesting more and ongoing myocardial injury.⁴¹ Conversely, and consistent with literature,^{10,34} baseline hsCRP levels were similarly elevated in all subgroups, and declined comparably at FUP6. An early inflammatory response to tissue injury has been recognized as critical for tissue healing to begin,⁴² but processes that augment the intensity and/or duration of inflammation have been related to adverse

LV remodeling in preclinical studies.⁴³ Interestingly, and compatible with this concept, interleukin-6 levels declined significantly more in patients who showed improved LVEF.

Taken together, these findings reemphasize the need to distinguish between “myocardial remission,” which is associated with clinical stabilization and reversal of many aspects of the HF phenotype but not necessarily with freedom from recurrent worsening HF events, and true “myocardial recovery.”³⁷ They provide a valid rationale for continuation of GDMT in such populations to prevent relapses, as recently observed in the TRED-HF (Withdrawal of Pharmacological Treatment for Heart Failure in Patients with Recovered Dilated Cardiomyopathy) trial.⁴⁴ This is consistent with recent *Journal of the American College of Cardiology (JACC)* Scientific Expert Panel recommendations for the management of patients with HF with recovered LVEF, which propose that GDMT be continued indefinitely until the complex pathobiology of remodeling and its reversal is better understood.⁴⁵

This first prospective study of LVEF trajectories in patients with HF enrolled at the time of hospital discharge after ACD with an LVEF ≤40% also showed close correlations between the degree of LVEF improvement at FUP6 and the occurrence of adverse clinical outcome events at FUP18. Greater LV improvements were associated with lower mortality risk and fewer all-cause or HF-related hospitalizations. Overall,

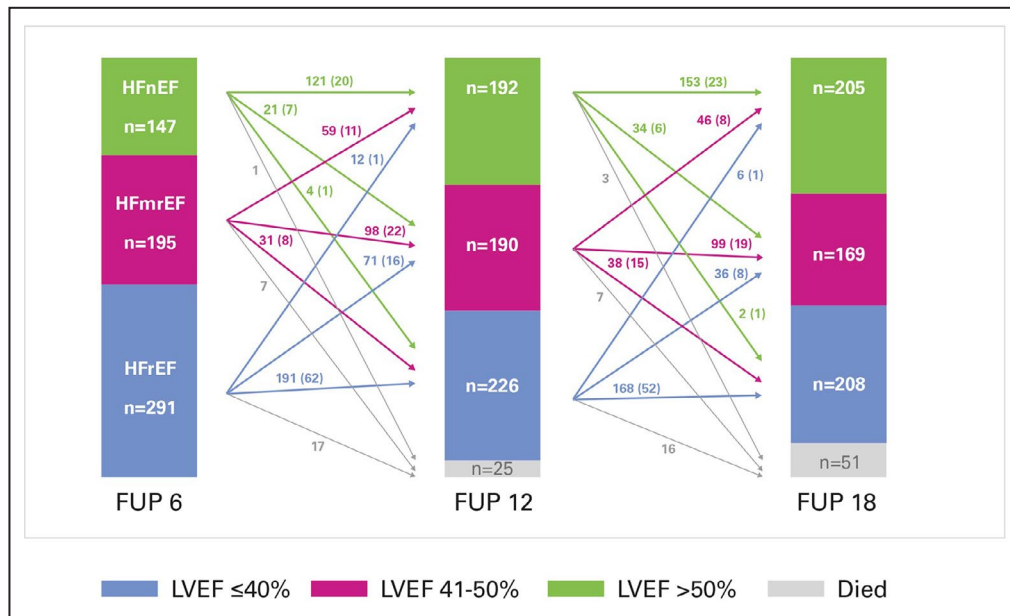


Figure 5. Changes in left ventricular ejection fraction (LVEF) between assessment at 6-month follow-up (FUP 6) and follow-up assessments at 12 and 18 months (FUP 12, FUP 18), and proportion of patients in each LVEF category at each time point.

HFmrEF indicates heart failure with midrange LVEF; HFNfEF, heart failure with normalized LVEF; and HFrfEF, heart failure with reduced LVEF. Numbers besides arrows indicate the number of patients transitioning between subgroups (or dying), while the number in brackets gives the portion of patients with hospitalization in the preceding 6 months. Patients deceased between FUP6, FUP12, and FUP18 are indicated in gray. Patients with missing LVEF values at FUP12 or FUP18 (n=55, n=67) remained in their previous LVEF category.

these observations are consistent with those of Ghimire et al, who found that patients with an initial LVEF $\leq 40\%$ who had a $\geq 10\%$ improvement after 17 months went on to be at significantly lower risk for all-cause death, hospitalization, emergency room visits, assist device placement, or cardiac transplant over the next 2.7 years.²⁷ Kalogeropoulos et al and de Groote et al also reported lower adverse clinical outcome rates in patients with improved LVEF versus HFrfEF over 3 to 4.4 years' follow-up.^{11,33} This suggests that HFmrEF or HFNfEF represent distinct clinical entities that need to be considered separately from HFpEF (for example, in clinical trials).

The current investigation, which focused on LVEF trajectories over 12 months, demonstrated additional increases in average LVEF in both the HFmrEF and HFrfEF groups. This might be not only because of further optimization of GDMT, which was pursued throughout the study, but also because of death of the sickest patients. However, serial prospective LVEF assessments every 6 months provided a unique opportunity to relate individual LVEF changes to clinical outcome events, revealing an association between clinical worsening (as tracked by rehospitalization) and worsening LVEF as a surrogate for attenuation/reversal of reverse remodeling.

Concordant trends in other remodeling parameters support this hypothesis. Pathophysiologically, this might be caused by reduced hemodynamic reserve because of persistent hemodynamic congestion; residual HF signs and symptoms in patients from all HF categories at FUP6 and elevated levels of cardiac troponin I and MR-proADM levels (the latter predicting the risk of rehospitalization across all subgroups) support this possible relationship. Under these circumstances, even modest incremental rises in filling pressures might have triggered the return of clinical congestion.⁴⁶ Precipitating factors may have included worsening of the cardiac substrate (for example, ongoing myocardial damage), but also non-compliance with GDMT or noncardiac factors such as worsening renal function.⁴⁷ Notably, in our study, all-cause deaths and both composite end points occurred less frequently in the HFNfEF subgroup, which also had the lowest sTVG at FUP6. Consistent with previous observations, where $\approx 50\%$ of deaths and rehospitalizations following ACD were secondary to conditions other than worsening HF,⁴⁸ Kaplan–Meier plots indicated that the majority of outcome events in our study occurred after other triggering events, but nevertheless appeared to contribute to HF disease progression.

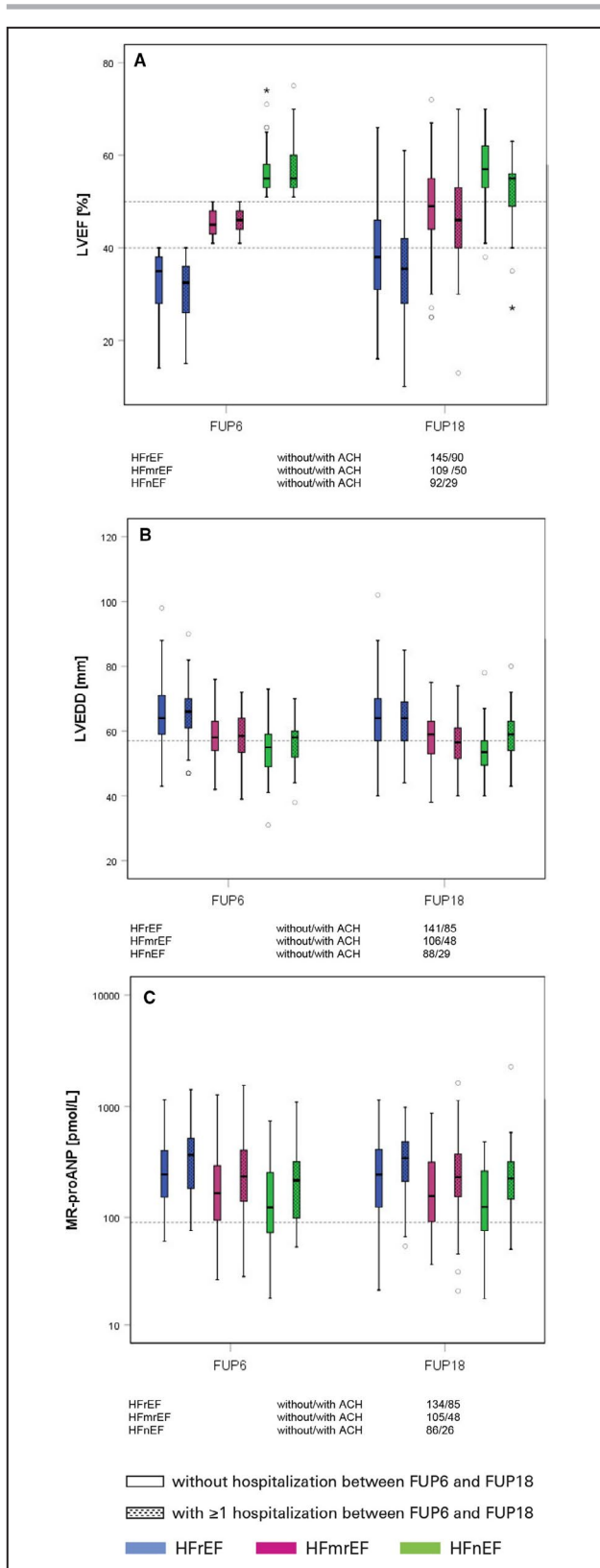


Figure 6. Trajectories of left ventricular ejection fraction (LVEF, A), left ventricular end-diastolic diameter (LVEDD, B), and midregional pro-atrial natriuretic peptide (MR-proANP, C) in patients alive at 18 months.

Shown are box plots for LVEF subgroups created at 6-month follow-up (FUP6) and subdivided according to hospitalization status between FUP6 and 18-month follow-up (FUP18). ACH indicates all-cause hospitalization; HFmrEF, heart failure with midrange LVEF (41%–50%); HFpEF, heart failure with normalized LVEF (>50%); and HFrEF, heart failure with reduced LVEF (≤40%). Figures depict only patients with values available from both FUP6 and FUP18.

echocardiography using a prespecified protocol, and the clearly defined time point of study entry after an episode of ACD.¹² However, an important limitation is the lack of generalizability. All study centers were from 1 country (Germany), and race was predominantly White. Moreover, although the INH Study had few exclusion criteria, participants had to have a LVEF ≤40% at hospital discharge after ACD.¹² Therefore, patient selection meant that there was no serial assessment of LVEF and other concurrent changes in patients with HFmrEF or HFpEF at baseline. Finally, the study population only included 6-month survivors after ACD who had 2 consecutive echocardiograms available for LVEF assessment at baseline and FUP6, and were then followed up every 6 months. This introduces several possibilities of significant selection bias. Nonparticipants had more severe HF, with more symptoms and comorbidities, and a longer HF history. Thus, the proportion of patients with potential for reverse remodeling was probably overestimated. Our analysis controlled for the inevitable regression toward the mean effect by using an ANCOVA that corrects for the baseline variables, which helps to avoid biased analyses and increase the precision of estimates, thus improving the power of the analysis.

Although the use of device therapies and mineralocorticoid receptor antagonists was low (reflecting the era during which INH participants were recruited), most patients received angiotensin-converting enzyme inhibitor/ARB and β-blockers at baseline. Prescription rates, especially of mineralocorticoid receptor antagonists, had increased between the predischarge assessment and FUP6; uptitration of GDMT was recommended in both INH study arms¹² and pursued successfully throughout the 18-month follow-up.⁴⁹ Since all patients were well treated, outcome differences in subgroups were probably not because of differences in the quality of GDMT, including improvements in congestion during treatment with diuretics. However, specific changes in medication status are beyond the scope of the current analysis, and the study design does not allow determination of what proportion of improvements seen might reflect a response to optimized GDMT versus to what

Strengths and Limitations

Strengths of this study include the relatively large sample size with prospective longitudinal follow-up including planned 6-monthly serial quantitative

extent improvements were because of spontaneous resolution of myocardial injury caused by the ACD event. It is likely that a combination of both factors contributed.

To increase data reliability, only patients with echocardiograms allowing for unambiguous determination of LVEF were eligible; nevertheless, quantitative ultrasound assessments are inevitably subject to some variability.⁵⁰ Presuming that this variability is independent of the HF subgroups defined in our study, LVEF misclassification would likely bias concurrent changes of other factors toward the null, resulting in an under- rather than overestimation of the strength of their association with LVEF. Some echocardiographic variables were not collected in all patients, especially Doppler estimates of LV diastolic function and sTVG. We believe that available numbers were sufficient to demonstrate improvements in LV filling characteristics and concurrent decreases in LV filling pressure in patients with improved LVEF, but given the volume of missing data for some variables, these should be interpreted with caution. Finally, 6-monthly examinations may not have fully captured the dynamics of LVEF changes as a surrogate of remodeling and its reversal during the vulnerable phase early after ACD,⁴⁷ which would have required repeat examinations at shorter time intervals.

CONCLUSIONS

During prospective follow-up, significant LVEF improvement occurred within 6 months in the majority of patients diagnosed with HFrEF at the time of discharge after ACD. Many patients transitioned between LVEF categories as proposed by current European Society of Cardiology guidelines,²² and nearly one quarter experienced normalization of LVEF. Close associations between changes in LVEF and those in other metrics of cardiac and systemic reverse remodeling reveal that LVEF is a useful surrogate marker of remodeling and its reversal, with improvements predicting better longer-term clinical outcomes. Conversely, the longer-term LVEF trajectory showed that clinical worsening, as tracked by rehospitalization requirement, may reverse/attenuate previous reverse remodeling. Close associations between improvements in LVEF and both HF duration and cause of ischemia identify these variables as major predictors of the myocardial capacity for repair. Lastly, it is important to appreciate that patients with HFrEF who experience normalization of their LVEF to >50% are pathophysiologically and clinically distinct from those who primarily had HFpEF and also have an LVEF >50% after recovery from ACD.^{10,45} The HF trajectory after ACD seems a

suitable model for further prospective research to better understand remodeling and its reversal at a mechanistic and molecular level. Our findings call for consideration of individual LVEF trajectories in HF phenotyping and highlight the need for improved, personalized patient risk stratification and tailored care approaches.

ARTICLE INFORMATION

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Supplementary Material

Data S1

Tables S1–S4

Figures S1–S2

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Supplemental Material

Data S1.

SUPPLEMENTAL METHODS

Amino-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hsCRP), and interleukin-6 (IL-6) were measured with the IMMULITE 2000 system (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany); the inter-assay coefficient of variation for NT-proBNP was 6.4% at a concentration of 35.6 pg/mL and 4.0% at a concentration of 1,430 pg/mL. The assay measuring range was 21.3 to 32,855 pg/mL. For hsCRP the inter-assay coefficient of variation was approximately 3% at the recommended upper limit of normal (3 mg/L); the measuring range for the assay was 0.2-100 mg/L. For IL-6 the analytical sensitivity was 2 pg/mL with a measuring range from 2.0 pg/mL to 1000.0 pg/mL.

Mid-regional pro-atrial natriuretic peptide (MR-proANP) was determined using a commercial fluoroimmunoassay (BRAHMS MR-proANP KRYPTOR; BRAHMS GmbH, Hennigsdorf, Germany; lower detection limit 6.0 pmol/L). The intra-assay coefficient of variation was 10% and 20% for samples containing MR-proANP 23–3,000 pmol/L and 18–22.8 pmol/L, respectively. At 65 and 18 pmol/L MR-proANP, the interassay coefficients of variation were 10% and 20%, respectively.

Cardiac troponin I (cTnI) concentrations were determined with an ADVIA Centaur TnIUltra™ (Siemens Healthcare, Eschborn, Germany), with a minimum detection concentration of 0.006 ng/mL, and a potential range of results for the 99th percentile of 0.02–0.06 ng/mL, irrespective of sex.

Table S1. Baseline parameters predictive of improvement in left ventricular ejection fraction on univariable analysis.

Predictor	Odds ratio	95% CI	p-value
Duration of HF <1 year	2.40	1.71–3.37	<0.001
Female sex	1.72	1.19–2.48	0.004
LVEF, per 5% increase	1.39	1.25–1.56	<0.001
LV wall thickness, per 5 mm increase	1.34	1.10–1.63	0.004
MAP, per 5 mmHg increase	1.15	1.07–1.23	<0.001
Heart rate, per 10 beats/min increase	1.10	1.01–1.21	0.026
NT-proBNP, per two-fold increase	0.86	0.79–0.94	0.001
Age, per decade increase	0.85	0.75–0.97	0.015
LVEDD, per 5 mm increase	0.72	0.65–0.80	<0.001
MR-proANP, per two-fold increase	0.70	0.59–0.83	<0.001
Ischemic HF etiology, yes vs. no	0.63	0.46–0.87	0.004
Left bundle branch block, yes vs. no	0.47	0.34–0.67	<0.001

CI, confidence interval; HF, heart failure; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; Left ventricular (LV) wall thickness was calculated as (end-diastolic interventricular septal + posterior wall thickness)/2; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro brain natriuretic peptide.

Table S2. Patient demographic and clinical characteristics at 6-month follow-up in the overall study population and in patient subgroups based on left ventricular ejection fraction at 6 months.

	All patients (n=633)	HFrEF (n=291)	HFmrEF (n=195)	HFnEF (n=147)	<i>p-value</i>	n
Clinical examination						
NYHA functional class	2.04±0.71	2.18±0.73	2.01±0.67	1.82±0.64	<0.001	633
NYHA class I, n (%)	137 (21.6)	50 (17.2)	42 (21.5)	45 (30.6)		
NYHA class II, n (%)	341 (53.9)	147 (50.5)	111 (56.9)	83 (56.4)		
NYHA class III, n (%)	147 (23.2)	87 (29.9)	41 (21.0)	19 (12.9)		
NYHA class IV, n (%)	8 (1.2)	7 (2.4)	1 (0.5)	0		
Mean arterial pressure, mmHg	90.2±14.0	88.3±13.4	92.0±14.5	91.5±14.2	0.007	632
Heart rate, beats/minute	68.0±14.6	69.5±14.5	67.2±14.8	66.0±14.2	0.042	632
BMI, kg/m ²	27.7±4.8	27.2±4.3	28.1±5.3	27.9±4.9	0.067	626
Any sign of congestion, n (%)	154 (24.7)	76 (26.4)	43 (22.6)	35 (24.0)	0.631	624
Laboratory parameters						
eGFR, mL/min/1.73m ²	67.6±26.5	65.6±25.4	69.3±28.4	69.5±25.8	0.197	632
Haemoglobin, g/dL	13.7±1.6	13.7±1.6	13.7±1.6	13.4±1.7	0.095	633
Leukocytes, 1000/μL	7.8±2.6	7.7±2.3	8.0±3.3	7.6±2.2	0.250	630
GPT, U/L	22.5 [16.3, 31.2]	23.0 [16.3, 31.4]	22.3 [16.0, 31.6]	21.9 [16.5, 31.0]	0.914	631
GGT, U/L	39.0 [25.0, 75.0]	45.8 [28.7, 87.3]	34.4 [23.3, 67.5]	34.4 [23.0, 62.0]	0.025	631
NT-proBNP, pg/mL	1212.0 [363.0, 3087.0]	2161.5 [667.0, 5188.5]	808.0 [247.0, 2335.0]	554.0 [165.0, 1437.0]	<0.001	549
MR-proANP, pmol/L	245.2 [130.4, 408.4]	325.3 [187.3, 512.3]	201.9 [122.3, 340.7]	176.1 [90.3, 279.3]	<0.001	609
cTnI, ng/mL	0.023 [0.012, 0.041]	0.030 [0.016, 0.047]	0.020 [0.010, 0.037]	0.017 [0.009, 0.030]	<0.001	483
hsCRP, mg/L	2.6 [1.1, 6.7]	2.6 [1.1, 7.2]	3.0 [1.2, 6.3]	2.4 [1.1, 7.0]	0.984	504
Il-6, pg/mL	2.6 [2.0, 5.9]	3.0 [2.0, 7.9]	2.5 [2.0, 5.4]	2.2 [2.0, 4.7]	0.100	595

Echocardiography

LVEF, %	41.4±11.6	31.3±7.2	45.5±2.9	56.1±4.5	<0.001	633
LVEDD, mm	60.5±9.2	64.8±9.1	58.4±7.2	55.1±7.8	<0.001	613
LVEDS, mm	46.4±12.4	52.0±10.0	43.8±7.7	39.0±7.7	<0.001	581
LAESD, mm	44.2±7.9	45.8±7.8	43.3±7.8	42.1±7.6	<0.001	618
IVSd, mm	11.4±2.2	11.4±2.2	12.1±2.0	12.3±2.2	<0.001	615
LVPWd, mm	11.4±1.9	11.0±1.9	11.6±1.7	11.7±2.2	<0.001	589
E-Wave, cm/s	70.0±25.1	73.3±26.0	66.8±25.5	69.5±22.3	0.055	451
A-Wave, cm/s	77.0±27.2	72.4±30.1	78.8±24.7	83.1±23.4	0.003	444
Deceleration time, ms	252.2±97.1	241.6±100.8	263.3±97.4	258.2±88.2	0.111	424
IVRT, ms	121.1±41.8	122.2±47.3	121.7±39.2	118.2±34.2	0.713	431
e', cm/s	7.2±3.3	6.7±3.2	7.1±3.3	8.1±3.5	0.002	439
sTVG, mmHg	30.7±12.8	33.0±14.0	27.6±10.1	29.9±112.4	<0.001	497
E/A	1.1±0.8	1.3±1.0	1.0±0.7	0.9±0.5	<0.001	444
E/e'	11.7±7.4	12.8±7.4	11.4±8.4	10.2±5.6	0.010	429

Heart failure therapy, n (%)

ACEI/ARB	586 (92.7)	265 (91.1)	184 (94.4)	137 (93.8)	0.329	632
Beta-blocker	575 (91.0)	259 (89.3)	181 (92.8)	135 (91.8)	0.383	632
MRA	346 (54.7)	162 (55.7)	111 (56.9)	73 (49.7)	0.367	633
Diuretics	560 (88.5)	263 (90.4)	174 (89.2)	123 (83.7)	0.107	633
Biventricular pacemaker/ICD	107 (16.9)	72 (24.7)	26 (13.3)	9 (6.1)	<0.001	633

Psychometry

KCCQ Clinical Summary Score	73.4±22.1	70.9±21.5	74.5±21.5	76.9±19.9	0.024	591
KCCQ Total Symptom Score	77.0±22.7	74.7±24.0	77.2±22.8	81.0±19.6	0.027	602
KCCQ Overall Summary Score	70.2±22.1	67.6±22.8	70.9±21.7	74.3±20.5	0.017	565

Values are given as n (%), mean \pm standard deviation or median [quartiles].

P-values refer to chi-square test or ANOVA (if necessary on log data), as appropriate.

A-Wave, peak late diastolic mitral flow velocity; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; BMI, body mass index; cTnI, cardiac troponin I; e', peak early diastolic velocity by pulsed wave tissue Doppler imaging at the lateral mitral annulus; E-Wave, peak early diastolic mitral flow velocity; eGFR, glomerular filtration rate (Modification of Diet in Renal Disease formula); GGT, gamma-glutamyltransferase; GPT, glutamate-pyruvate transaminase; HFmrEF, heart failure with mid-range reduced left ventricular ejection fraction (LVEF 41-50%); HFnEF, heart failure with normalized left ventricular ejection fraction (LVEF >50%); HFrEF, heart failure with reduced left ventricular ejection fraction (LVEF \leq 40%); hsCRP, high sensitive C-reactive protein; ICD, Implantable cardioverter-defibrillator; IL-6, interleukin 6; IVRT, isovolumic relaxation time; IVSd, end-diastolic interventricular septal thickness; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAESD, left atrial end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVPWd, left ventricular end-diastolic posterior wall thickness; MRA, mineralocorticoid receptor blocker; MR-proANP, midregional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; sTVG, systolic tricuspid valve gradient (estimated from peak tricuspid valve regurgitant flow velocity).

Table S3. Sensitivity analyses.

	p-value and HR (95% CI)		
	Model 1	Model 2	Model 3
All-cause death			
p-value	0.43	0.026	0.053
HFmrEF vs HFrEF	0.78 (0.41–1.48)	0.65 (0.33–1.27)	0.75 (0.36–1.54)
HFnEF vs HFrEF	0.26 (0.09–0.75)	0.20 (0.06–0.67)	0.16 (0.04–0.72)
All-cause death and all-cause hospitalization			
p-value	0.005	0.007	0.006
HFmrEF vs HFrEF	0.78 (0.59–1.04)	(0.77 (0.57–0.81)	0.75 (0.55–1.02)
HFnEF vs HFrEF	0.57 (0.40–0.81)	0.57 (0.39–0.81)	0.54 (0.36–0.80)
All-cause death and hospitalization for HF			
p-value	0.002	0.001	0.002
HFmrEF vs HFrEF	0.74 (0.46–1.19)	0.66 (0.40–1.09)	0.68 (0.40–1.09)
HFnEF vs HFrEF	0.23 (0.10–0.52)	0.21 (0.09–0.49)	0.18 (0.07–0.47)

CI, confidence interval; HFmrEF, heart failure with mid-range ejection fraction; HFnEF, heart failure with normalized ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association.

Model 1: adjusted for age, sex, baseline LVEF, and NYHA class

Model 2: adjusted for age, sex, baseline LVEF, NYHA class, renal dysfunction, and NT-proBNP

Model 3: adjusted for age, sex, baseline LVEF, NYHA class, renal dysfunction, NT-proBNP, hypertension, diabetes, duration of heart failure, and ischemic cause of heart failure.

Table S4. Longitudinal changes in left ventricular ejection fraction, left ventricular end-diastolic diameter and mid-regional pro-atrial natriuretic peptide in the total cohort and according to subgroups based on left ventricular ejection fraction at 6 months.

	FUP6	FUP18	p-value
LVEF, %			
Total cohort (n=633, 515)	41.4±11.6	44.8±12.1	<0.001
HF _n EF (n= 147, 121)	56.1±4.5	55.4±7.4	0.159
HF _n EF with ACH (n=29)	56.8±5.8	51.3±7.6	
HF _n EF without ACH (n=92)	56.3±4.4	56.7±6.9	
Mean difference (with/without ACH) (95% CI)*		-5.8 (-9.4, -2.1)	0.002§
HF _n EF with HFH (n=1)	57.0	50.0	
HF _n EF without HFH (n=120)	56.4±4.7	55.4±7.4	
Mean difference (with/without HFH) (95% CI) [°]		Not done	
HF _{mr} EF (n=195, 159)	45.5±2.9	47.9±9.7	0.002
HF _{mr} EF with ACH (n=50)	45.9±2.7	46.3±10.8	
HF _{mr} EF without ACH (n=109)	45.5±2.9	48.6±9.1	
Mean difference (with/without ACH) (95% CI)*		-2.6 (-5.5, 0.3)	0.078§
HF _{mr} EF with HFH (n=9)	44.8±2.7	43.9±17.7	
HF _{mr} EF without HFH (n=150)	45.7±2.9	48.2±9.1	
Mean difference (with/without HFH) (95% CI) [°]		-3.6 (-9.5, 2.3)	0.230§
HFrEF (n=291, 235)	31.3±7.3	37.3±10.5	<0.001
HFrEF with ACH (n=90)	31.2±6.8	35.7±10.4	
HFrEF without ACH (n=145)	32.5±6.9	38.4±10.4	
Mean difference (with/without ACH) (95% CI)*		-1.7 (-4.0, 0.6)	0.136§
HFrEF with HFH (n=26)	29.1±7.6	33.7±11.2	
HFrEF without HFH (n=209)	32.4±6.7	37.8±10.3	
Mean difference (with/without HFH) (95% CI) [°]		-1.8 (-5.4, 1.9)	0.339§

*There is no significantly different effect of ≥ 1 ACH between the subgroups ($p=0.183$), therefore the overall effect of an ACH can be given as $-2.8 (-4.4, -1.2)$ $p=0.001$

[°]There is no significantly different effect of ≥ 1 HFH between the subgroups ($p=0.801$), therefore the overall effect of an HFH can be given as $-2.4 (-5.4, 0.7)$ $p=0.125$

§ p-values not adjusted for multiplicity

LVEDD, mm			
Total cohort (n=613, 511)	60.5±9.2	60.1±9.6	0.048
HF _n EF (n=143, 120)	55.1±7.8	54.6±7.4	0.903
HF _n EF with ACH (n=29)	56.2±7.4	58.3±8.5	
HF _n EF without ACH (n=88)	54.2±7.2	53.6±6.6	
Mean difference (with/without ACH) (95% CI)**		3.3 (0.6, 6.1)	0.017§
HF _n EF with HFH (n=1)	52.0	55.0	

HF _n EF without HFH (n=116)	54.7±7.3	54.8±7.4	
Mean difference (with/without HFH) (95% CI) ^{°°}		Not done	
HF _{mr} EF (n=189, 157)	58.4±7.2	57.7±7.6	0.096
HF _{mr} EF with ACH (n=48)	58.3±7.1	56.8±7.7	
HF _{mr} EF without ACH (n=106)	58.7±6.7	58.2±7.5	
Mean difference (with/without ACH) (95% CI) ^{**}		-1.1 (-3.3, 1.1)	0.326§
HF _{mr} EF with HFH (n=9)	59.7±8.4	60.2±9.4	
HF _{mr} EF without HFH (n=145)	58.5±6.8	57.6±7.5	
Mean difference (with/without HFH) (95% CI) ^{°°}		1.8 (-2.6, 6.2)	0.429§
HF _r EF (n=281,234)	64.8±9.1	64.4±9.8	0.076
HF _r EF with ACH (n=85)	65.4±8.4	64.1±9.0	
HF _r EF without ACH (n= 141)	65.2±9.4	64.6±10.2	
Mean difference (with/without ACH) (95% CI) ^{**}		-0.6 (-2.4, 1.1)	0.499§
HF _r EF with HFH (n= 24)	67.2±8.5	65.2±9.8	
HF _r EF without HFH (n= 202)	65.1±9.1	64.3±9.7	
Mean difference (with/without HFH) (95% CI) ^{°°}		-0.6 (-3.4, 2.2)	0.661§

^{**}There is are significantly different effects of ≥ 1 ACH between the subgroups (p=0.028), therefore an overall effect of an ACH cannot be given

^{°°}There is no significantly different effect of ≥ 1 HFH between the subgroups (p=0.634), therefore the overall effect of ≥ 1 HFH can be given as 0.1 (-2.2, 2.4) p=0.915

§ p-values are not adjusted for multiplicity

MR-proANP, pmol/L

Total cohort (n= 609, 502)	245.2 [130.4–408.4]	216.6 [114.7–362.3]	0.061
HF _n EF (n=141, 117)	176.1 [90.3–279.3]	150.5 [88.6–282.2]	0.468
HF _n EF with ACH (n=26)	217.4 [97.9–322.5]	226.3 [137.5–320.1]	
HF _n EF without ACH (n=86)	123.7 [72.5–255.6]	124.9 [76.2–264.6]	
Mean ratio (with vs. without ACH) (95% CI) ^{***}		1.20 (1.00, 1.43)	0.047§
HF _n EF with HFH (n=1)	374.9	351.2	
HF _n EF without HFH (n=111)	133.2 [75.0–260.1]	146.9 [80.7–282.2]	
Mean ratio (with vs. without HFH) (95% CI) ^{°°°}		Not done	
HF _{mr} EF (n=189, 157)	201.9 [122.3–340.7]	188.7 [109.0–327.2]	0.792
HF _{mr} EF with ACH (n=48)	235.6 [140.5–406.3]	231.8 [153.8–387.9]	
HF _{mr} EF without ACH (n=105)	166.1 [94.0–295.5]	156.9 [92.1; 321.8]	
Mean ratio (with vs. without ACH) (95% CI) ^{***}		1.02 (0.89, 1.17)	0.771§
HF _{mr} EF with HFH (n=9)	233.7 [185.9–408.6]	285.0 [203.3–449.5]	
HF _{mr} EF without HFH (n=144)	184.1 [102.4–309.2]	178.5 [103.1–324.5]	
Mean ratio (with vs. without HFH) (95% CI) ^{°°°}		1.26 (0.96, 1.66)	0.094§
HF _r EF (n=279, 228)	325.3 [187.3–512.3]	272.4 [154.7–443.1]	0.006
HF _r EF with ACH (n=85)	378.4 [182.5–529.7]	327.0 [206.0–483.1]	
HF _r EF without ACH (n=134)	245.0 [152.5–404.2]	244.1 [124.3–411.0]	
Mean ratio (with vs. without ACH) (95% CI) ^{***}		1.02 (0.91, 1.14)	0.765§

HFrEF with HFH (n=25)	463.4 [339.5–564.9]	391.1 [249.0–516.8]	
HFrEF without HFH (n=195)	259.3 [161.7–439.3]	261.0 [144.4–430.4]	
Mean ratio (with vs. without HFH) (95% CI) ^{°°°}		0.89 (0.75, 1.06)	0.198§

***There is no significantly different effect of ≥ 1 ACH between the subgroups ($p=0.269$), therefore the overall effect of ≥ 1 ACH can be given as increase by the factor 1.05% (0.97, 1.14) $p=0.223$

°°°There is no significantly different effect of HFH between the subgroups ($p=0.108$), therefore the overall effect of ≥ 1 HFH can be given as decrease by the factor 0.99 (0.85, 1.14) $p=0.845$

§ p-values are not adjusted for multiplicity

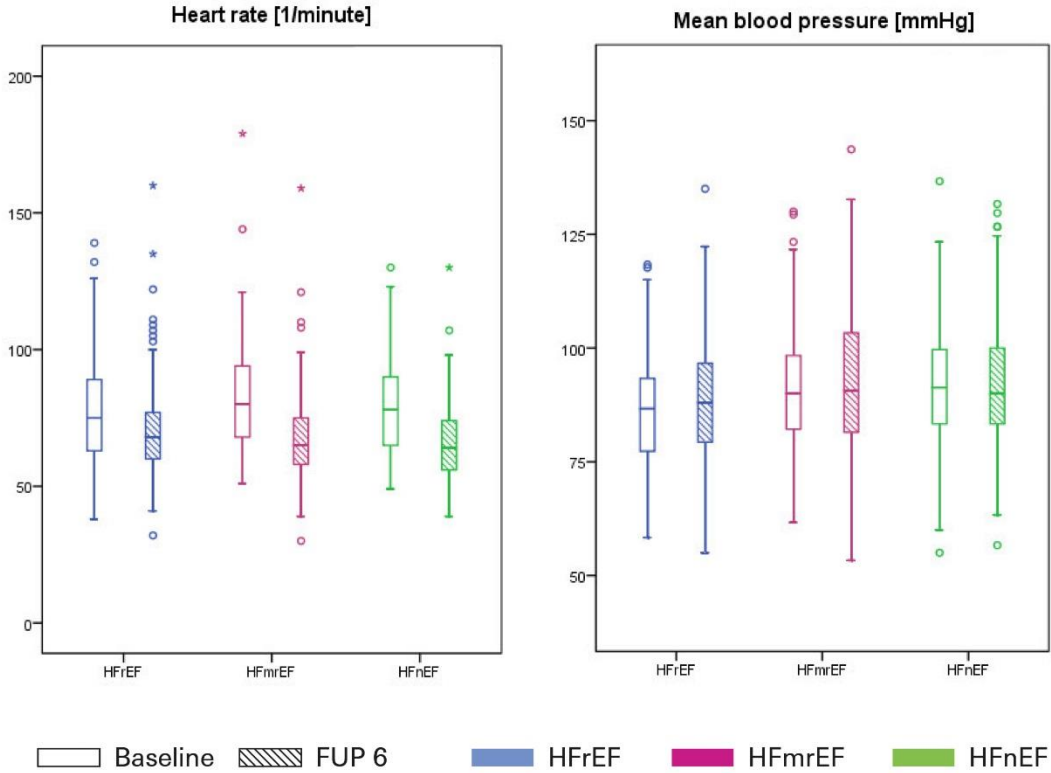
Information on changes in subsets with/without hospitalization between 6- and 18-month follow-up refers only to patients with measurements of the respective parameter available at both time points.

Values are mean \pm standard deviation, median [quartiles], mean difference (95% confidence interval) or mean ratio (95% confidence interval).

P-values refer to paired t-test for the total cohort and LVEF subgroups (HF_nEF, HF_{mr}EF and HF_rEF) and to main effects or pairwise comparisons from interaction effects from the differences to FUP6 ANCOVA models with hospitalization, subgroup (and their interaction) and respective FUP6 value.

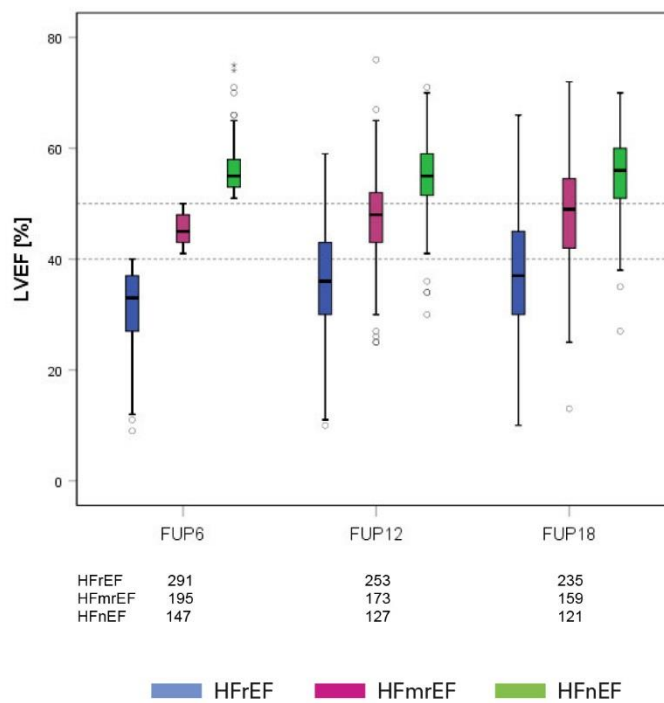
ACH, all-cause hospitalization; CI, confidence interval; FUP6, follow-up at six months; FUP18, follow-up at 18 months; HFH, heart failure-related hospitalization; HF_{mr}EF, heart failure with mid-range recovered left ventricular ejection fraction (LVEF 41-50%); HF_nEF, heart failure with normalized left ventricular ejection fraction (LVEF >50%); HF_rEF, heart failure with reduced left ventricular ejection fraction (LVEF \leq 40%); LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR-proANP, mid-regional pro-atrial natriuretic peptide.

Figure S1. Mean arterial blood pressure and heart rate at baseline (BL, empty bars) and at 6-month follow-up (FUP6, hatched bars).



Shown are box plots in subgroups according to left ventricular ejection fraction (LVEF) at FUP6. HFmrEF, heart failure with mid-range LVEF (41-50%); HFnEF, heart failure with normalized LVEF (>50%); HFrEF, heart failure with reduced LVEF ($\leq 40\%$).

Figure S2. Left ventricular ejection fraction (LVEF) at 6-month follow-up (FUP6), 12-month follow-up (FUP12) and 18-month follow-up (FUP18).



Shown are box plots in subgroups according to LVEF at FUP6. HFmrEF, heart failure with mid-range LVEF (41-50%); HFnEF, heart failure with normalized LVEF (>50%); HFrEF, heart failure with reduced LVEF ($\leq 40\%$).