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ORIGINAL - DEVICES

Heart failure with recovered ejection fraction (HFrecEF): A new entity with improved cardiac outcome

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Abstract

Background: Aim of the study was a better characterization of heart failure (HF) with recovered ejection fraction (HFrecEF) and undulating EF (HFuEF) with regard to re-hospitalization due to congestive HF (CHF), adequate electric therapies (AETs) and mortality compared to HF with reduced EF (HFrEF), mid-range EF (HFmrEF) and preserved EF (pEF).

Methods: Retrospective study of 342 participants with an implantable cardioverter defibrillator (ICD) for primary or secondary prevention. Type of HF was classified according to left ventricular EF with 4.7 ± 3.1 investigations for each patient.

Results: Re-hospitalization due to CHF was similar in HFrecEF (7 (9.5%)), HFmrEF (2(9.0%)) and pEF (8(12.9%); p = n.s.) and significantly higher in HFrEF (62(38.0%)) and HFuEF (6(28.6%); $p < .001$ compared to HFrecEF and HFrEF). AETs were significantly lower in HFrecEF (13(17.6%)) compared to HFrEF (57(35.0%)), HFmrEF (7(31.8%)), pEF (18(29.0%)) and HFuEF (6(28.6%); each $p < .01$ compared to HFrecEF). Mortality was similar in HFrecEF (6(8.1%)) compared to HFuEF (0(0%)), pEF (4(6.5%)) and HFmrEF (2(9.0%), p = n.s.) and significantly lower compared to HFrEF (52(31.9%), $p < .001$). HFrEF was the strongest predictor for mortality besides age and chronic renal insufficiency according to Cox Regression (each $p < .05$) opposite to arterial hypertension, diabetes, type of cardiomyopathy and secondary prevention ICD indication (each p = n.s.).

Conclusions: HFrecEF indicates as a new entity of HF with similar prognosis as pEF and HFmrEF with regard to re-hospitalization due to CHF and mortality and even better prognosis with regard to AETs. HFuEF showed similar rates of re-hospitalization due to CHF and AETs compared to HFrEF, but lower rates of mortality.

KEYWORDS
Congestive heart failure, recovered ejection fraction, undulating ejection fraction

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1 | INTRODUCTION

In the current guidelines of the European society of cardiology (ESC), heart failure (HF) is classified in HF with reduced ejection fraction (HFrEF), HF with mid-range EF (HFmrEF) and HF with preserved ejection fraction (HFpEF); the last two with additional elevated natriuretic peptides and structural heart disease or diastolic dysfunction.[1] The American Heart Association (AHA) guidelines further distinguish a group with improved EF, which previously had HFrEF and recovered to HFpEF which is supposed to distinct from those with persistently preserved or reduced EF.[2] HFrEF and HFpEF are well characterized but data on patients with recovery of left ventricular EF (LV-EF) are scarce. In clinical settings a recovery of LV-EF through different therapeutic strategies such as optimization of medical treatment, coronary revascularization, device therapy or natural course can often be observed, but long-term prognosis of these patients still is not clear. Beside the question of continuation of HF medication, the frequency of rhythm events after improvement of LV function and further need of ICD therapy is not investigated so far. Also, an additional group of HF patients exists with undulating EF which is not mentioned in the current guidelines and is investigated even less. Therefore, the aim of our study was a better characterization of patients with recovery of LV-EF and undulating EF and a comparison to subjects with preserved and reduced EF, particularly with regard to reduction of re-hospitalizations due to congestive heart failure and rhythm events as well as all-cause mortality in a collective of ICD patients.

2 | METHODS

2.1 | Study population

All patients who received an ICD for primary or secondary prevention at the University Hospital of Regensburg, Germany since February 2010 were included in the current analysis. Patients were eligible for enrolment if they were above 18 years old, had history of ICD-implantation at University Hospital of Regensburg, and if they gave written informed consent to participate in the study. Data for the present investigation were initially assessed retrospectively until the date of May 2018 and were afterwards assessed prospectively. The mean follow-up was 3.8 ± 2.4 years with repeated clinical evaluation, echocardiography investigations and ICD queries, usual with an interval of 3–6 months. Patients receiving cardiac resynchronization therapy (CRT) as well as patients with channelopathy or idiopathic ventricular tachycardia as indication for ICD-implantation were excluded from the present analysis. The study was approved by the local Ethics Committee. The investigation confirms with the principles outlined in the Declaration of Helsinki.[3]

2.2 | Classification of heart failure

Type of HF was classified according to the degree and development of LV-EF measured based on the modified biplane Simpson's method with 2D-echocardiography with a mean of 4.7 ± 3.1 investigations for each patient. Echocardiography was performed using a standard ultrasound system (Philips iE33 Philips Medical Systems, Hamburg, Germany). HFrEF was defined as continuous LV-EF < 40% since ICD implantation, confirmed in each echocardiographic investigation; pEF was defined as permanent LV-EF ≥ 50% since ICD-implantation, HFmrEF as permanent LV-EF between 40% and 49%. HF with recovered EF (HFrecEF) was defined as initial LV-EF < 40% at time of ICD-implantation and improvement to continuous LV-EF ≥ 40% which was confirmed in each echocardiography after improvement of LV function. If one following LV-EF was below 40% once again, HF was classified as HF with undulating EF (HFuEF) which was defined as alternating LV-EF below and above 40%.

2.3 | Endpoints

The endpoints of the study were re-hospitalization due to congestive heart failure, adequate electrical ICD therapies including electrical storm, ventricular fibrillation and ventricular tachycardia, inadequate electrical ICD therapies as well as all-cause-mortality.

2.4 | Statistical analysis

Descriptive statistics are presented as number and percentages for categorical data and as mean ± standard deviation for continuous data or median and IQR for non-normally distributed data. Student's *t*-test and ANOVA were used for comparison of normal distributed and independent data. Skewed data were evaluated by the non-parametric Mann-Whitney-*U* test. For a follow-up analysis, we constructed Kaplan Meier survival curves reflecting the relationship between the probability of reaching the endpoint death and time of follow-up. Multivariate cox proportional hazard analysis was performed as stepwise regressions with backward elimination to evaluate prognostic value of each marker. Hereby we analyzed HFrecEF and HFrEF in cox regression model with clinically relevant covariates for the endpoint mortality (age, hypertension, diabetes mellitus, chronic renal insufficiency, dilatative cardiomyopathy and secondary prevention ICD indication) as well as the different HF entities. Any p-value < .05 was considered to be statistically significant. Statistical analyzes were performed with SPSS version 25.0 software (SPSS Inc., Chicago, IL, USA).

3 | RESULTS

3.1 | Baseline characteristics

Baseline characteristics are displayed in Table 1. Of the 342 total study participants, patients suffered predominantly from HFrEF (163 (47.7%)), followed by HFrecEF (74 (21.6%)) and pEF (62 (18.1%)); patients with HFuEF (21 (6.1%)) and HFmrEF (22 (6.4%)) were the minority. Age was similar between the five groups (66.4 ± 14.7,

TABLE 1 Baseline characteristics in comparison of the different HF classes

	HFrEF	HFrecEF	HFuEF	HFmrEF	pEF	*p*-value
n (%)	163 (47.7)	74 (21.6)	21 (6.1)	22 (6.4)	62 (18.1)	
Age (years)	67.8 ± 14.0	66.4 ± 14.3	60.0 ± 16.0	68.4 ± 16.1	64.4 ± 15.6	.135
Male (*n* (%))	132 (81.0)	57 (77.0)	16 (76.2)	20 (90.9)	50 (80.6)	.511
EF initial (%)	30 ± 9	31 ± 9	35 ± 13	44 ± 5	58 ± 7	<.001
Type of prevention						
Primary (*n* (%))	115 (70.6)	50 (67.6)	14 (66.7)	1 (4.5)	14 (22.6)	<.001
Secondary (*n* (%))	48 (29.4)	24 (32.4)	7 (33.3)	21 (95.5)	48 (77.4)	<.001
Type of cardiomyopathy						
DCM (*n* (%))	64 (39.3)	31 (41.9)	5 (23.8)	3 (13.6)	0 (0.0)	<.001
CHD (*n* (%))	93 (57.1)	29 (39.2)	9 (42.9)	15 (68.2)	35 (56.5)	.041
Acute MI < 40 d (*n* (%))	7 (4.3)	1 (1.4)	1 (4.8)	2 (9.1)	7 (11.3)	.143
Acute MI > 40 d (*n* (%))	62 (38.0)	12 (16.2)	6 (28.6)	8 (36.4)	16 (25.8)	.009
HCM (*n* (%))	0 (0.0)	1 (1.4)	0 (0.0)	2 (9.1)	12 (19.4)	<.001
ARVD (*n* (%))	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.8)	.008
Takotsubo CMP (*n* (%))	1 (0.6)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	.852
Myocarditis (*n* (%))	4 (2.5)	2 (2.7)	3 (14.3)	2 (9.1)	1 (1.6)	.471
Secondary CMP (*n* (%))	5 (3.1)	8 (10.8)	3 (14.3)	1 (4.5)	1 (1.6)	.136
Muscular dystrophy (*n* (%))	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	.342
Comorbidities						
Arterial hypertension (*n* (%))	106 (65.0)	47 (63.5)	11 (52.4)	15 (68.2)	38 (61.3)	.824
Hyperlipidemia (*n* (%))	104 (63.8)	33 (44.6)	11 (52.4)	11 (50.0)	39 (62.9)	.050
Diabetes mellitus (*n* (%))	52 (31.9)	24 (32.4)	7 (33.3)	4 (18.2)	10 (16.1)	.074
Carotis stenosis (*n* (%))	13 (8.0)	2 (2.7)	0 (0.0)	1 (4.5)	3 (4.8)	.372
TIA/stroke (*n* (%))	23 (14.1)	9 (12.2)	3 (14.3)	2 (9.1)	7 (11.3)	.955
PAOD (*n* (%))	21 (12.9)	6 (8.1)	2 (9.5)	4 (18.2)	5 (8.1)	.631
COPD (*n* (%))	20 (12.3)	1 (1.4)	1 (4.8)	2 (9.1)	2 (3.2)	.009
CKD (*n* (%))	58 (35.6)	16 (21.6)	3 (14.3)	3 (13.6)	13 (21.0)	.018
Medication						
Beta blockers (*n* (%))	152 (93.3)	64 (86.5)	16 (76.2)	20 (90.9)	44 (71.0)	.008
ACE inhibitors/AT1 inhibitors/neprilysin inhibitors (*n* (%))	139 (85.3)	67 (90.5)	18 (85.7)	22 (100)	37 (59.7)	<.001
Spironolactone (*n* (%))	117 (71.8)	54 (73.0)	15 (71.4)	6 (27.3)	14 (22.6)	<.001
Diuretics (*n* (%))	143 (87.7)	60 (81.1)	15 (71.4)	14 (63.6)	33 (53.2)	<.001
Digitalis glycosides (*n* (%))	28 (17.2)	9 (12.2)	3 (14.3)	0 (0.0)	2 (3.2)	.021
Amiodarone/sotalol (*n* (%))	10 (6.1)	2 (2.7)	0 (0.0)	0 (0.0)	1 (1.6)	.276
Calcium channel blockers (*n* (%))	5 (3.1)	7 (9.5)	1 (4.8)	2 (9.1)	11 (17.7)	.039
Ivabradin (*n* (%))	9 (5.5)	5 (6.8)	2 (9.5)	0 (0.0)	1 (1.6)	.400
Statins (*n* (%))	100 (61.3)	31 (41.9)	9 (42.9)	15 (68.2)	41 (66.1)	.010

Values represent the mean ± standard deviation or numbers (percentages).

Abbreviations: ACE, angiotensin converting enzyme; ARVD, arrhythmogenic right ventricular dysplasia; AT1, angiotensin 1; CHD, coronary heart disease; CKD, chronic kidney disease; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disorder; DCM, dilatative cardiomyopathy; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; HF, heart failure; MI, myocardial infarction; PAOD, peripheral arterial occlusive disease; TIA, transient ischemic attack.

TABLE 2 Endpoints for the total study population in comparison of the different HF classes

	HFrEF	HFrecEF	HFuEF	HFmrEF	pEF	*p*-value
n (%)	163 (47.7)	74 (21.6)	21 (6.1)	22 (6.4)	62 (18.1)	
Re-hospitalization due to CHF (*n* (%))	62 (38.0)	7 (9.5)	6 (28.6)	2 (9.1)	8 (12.9)	<.001
AETs (*n* (%))	57 (35.0)	13 (17.6)	6 (28.6)	7 (31.8)	18 (29.0)	.076
Electric storm (*n* (%))	17 (10.4)	3 (4.1)	1 (4.8)	2 (9.1)	4 (6.5)	.423
VF (*n* (%))	19 (11.7)	3 (4.1)	2 (9.5)	2 (9.1)	5 (8.1)	.306
VT (*n* (%))	54 (33.1)	11 (14.9)	6 (28.6)	7 (31.8)	16 (25.8)	.036
IETs (*n* (%))	17 (10.4)	10 (13.5)	3 (14.3)	1 (4.5)	6 (9.7)	.767
Death (*n* (%))	52 (31.9)	6 (8.1)	0 (0.0)	2 (9.1)	4 (6.5)	<.001

Values represent numbers (percentages).
Abbreviations: AETs, adequate electric therapies; CHF, congestive heart failure; HF, heart failure; IETs, inadequate electric therapies; VF, ventricular fibrillation; VT, ventricular tachycardia.

p = n.s.). Patients were predominantly male (275 (80.4%)) with no sex differences between all groups (p = n.s.). In patients with HFrecEF (50 (67.6%)), HFrEF (115 (70.6%)) and HFuEF (14 (66.7%)) ICD was implanted predominantly for primary prevention opposite to subjects with pEF (14 (22.6%)) and HFmrEF (1 (4.5%)). DCM was the main cause for ICD implantation in patients with HFrecEF (31 (41.9%)) in contrast to ICM in the other groups. No cases of DCM were detected in pEF. No subjects with CRT were part of our study due to our exclusion criteria.

Chronic obstructive pulmonary disease (20 (12.3%)) and chronic renal insufficiency (58 (35.6%)) were significantly more frequent in HFrEF in contrast to other cardiovascular comorbidities like hypertension, hyperlipidemia, diabetes mellitus, carotis stenosis, transitory ischemic attack, apoplex and peripheral artery disease (p = n.s. between the groups).

Drug prescription concerning the renin-angiotensin-aldosterone axis, neprilysin inhibitors, betablockers and diuretics did not significantly differ between HFrecEF and HFrEF (p = n.s., Table 1).

3.2 | Follow up analysis

Mean observation period was 3.8 (IQR 1.9; 5.5) years. The endpoints re-hospitalization due to congestive heart failure (85 (24.9%)), adequate (101 (29.5%) and inadequate ICD therapies (37 (10.8%)) as well as mortality (64 (18.7%)) are displayed in Table 2. In subjects with HFrecEF, mean duration to recovering was 19.2 ± 22.8 months after ICD implantation.

Patients with HFrecEF had significant lower rates of re-hospitalization due to congestive heart failure (7 (9.5%)) compared to HFrEF (62 (38.0%)) and HFuEF (6 (28.6%), each p < .001) and similar rates compared to HFmrEF (2 (9.0%)) and pEF (8 (12.9%); each p = n.s.).

Adequate ICD therapies were also significantly lower in HFrecEF (13 (17.6%) compared to HFrEF (57 (35.0%)), HFmrEF (7 (31.8%)), pEF (18 (29.0%)) and HFuEF (6 (28.6%); each p < .01 compared to HFrecEF).

Inadequate electrical therapies including inadequate shocks showed no significant differences between the groups (p = n.s.).

TABLE 3 Multivariate Cox regression model in comparison of different risk factors

	HR (95 % CI)	*p*-value
HFrEF	7.84 (3.21–19.18)	<.001
Age	1.03 (1.01–1.05)	.018
CKD	0.56 (0.32–0.97)	.039
Secondary prevention ICD indication	1.54 (0.85–2.78)	.152
Diabetes mellitus	0.81 (0.47–1.40)	.457
Arterial hypertension	1.21 (0.72–2.06)	.471
DCM	1.22 (0.68–2.16)	.505
HFrecEF	1.15 (0.32–4.19)	.831

Abbreviations: CKD, chronic kidney disease; DCM, dilatative cardiomyopathy; HF, hazard ratio; ICD, implantable cardioverter defibrillator.

All-cause-mortality was similar in HFrecEF (6 (8.1%)) compared to HFuEF (0 (0%)), pEF (4 (6.5%)) and HFmrEF (2 (9.0%), each p = n.s.) and significantly lower in comparison to HFrEF (52 (31.9%), p < .001 compared to each other group, Table 2, Figure 1). Regarding head-to-head analysis of the different HF entities, only HFrEF was associated with increased mortality compared to all other groups with Cox Regression analysis (p < .001, Table S1). HFrEF was a strong predictor for mortality besides age and chronic renal insufficiency according to Cox Regression analysis (each p < .05, Table 3) opposite to arterial hypertension, diabetes mellitus, type of cardiomyopathy and secondary prevention ICD indication (each p = n.s., Table 3). In contrast, HFrecEF was not associated with increased mortality risk (p = n.s., Tables 3 and S1).

3.3 | Primary prevention

In primary prevention ICD indication, patients with HFrecEF had significant lower rates of re-hospitalization due to congestive heart failure (3 (6.0%)) in comparison to HFrEF (43 (37.4%), p < .001) and HFuEF (6 (42.9%), p < .05). No events could be observed in patients with pEF und HFmrEF (p < .05 in comparison to HFrecEF, Table 4). Average time to

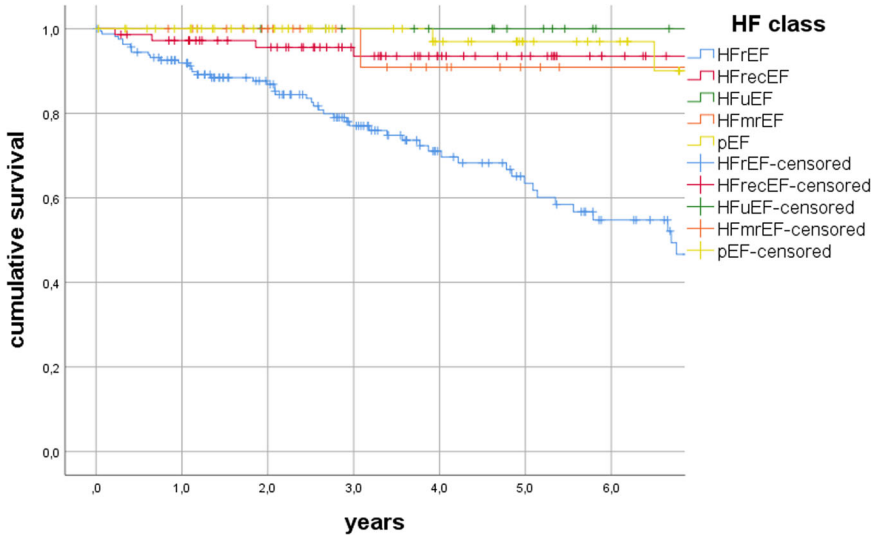

FIGURE 1 Kaplan-Meier curves for survival in the total study population [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Endpoints after ICD-implantation due to primary and secondary prevention ICD indication, in DCM and ICM

	HFrEF	HFrecEF	HFuEF	HFmrEF	pEF	*p*-value
Primary prevention (*n* (%))	**115 (59.3)**	**50 (25.8)**	**14 (7.2)**	**1 (0.5)**	**14 (7.2)**	
Re-hospitalization due to CHF (*n* (%))	43 (37.4)	3 (6.0)	6 (42.9)	0 (0.0)	0 (0.0)	<.001
AETs (*n* (%))	35 (30.4)	7 (14.0)	3 (21.4)	0 (0.0)	2 (14.3)	.183
Death (*n* (%))	35 (30.4)	5 (10.0)	0 (0.0)	0 (0.0)	1 (7.1)	.004
Secondary prevention (*n* (%))	**48 (32.4)**	**24 (16.2)**	**7 (4.7)**	**21 (14.2)**	**48 (32.4)**	
Re-hospitalization due to CHF (*n* (%))	19 (39.6)	4 (16.7)	0 (0.0)	2 (9.5)	8 (16.7)	.006
AETs (*n* (%))	22 (45.8)	6 (25.0)	3 (42.9)	7 (33.3)	16 (33.3)	.429
Death (*n* (%))	17 (35.4)	1 (4.2)	0 (0.0)	2 (9.5)	3 (6.3)	<.001
DCM (*n* (%))	**64 (62.1)**	**31 (30.1)**	**5 (4.9)**	**3 (2.9)**	**0 (0.0)**	
Re-hospitalization due to CHF (*n* (%))	20 (31.3)	2 (6.5)	3 (60.0)	0 (0.0)	0 (0.0)	.008
AETs (*n* (%))	25 (39.1)	5 (16.1)	1 (20.0)	3 (100.0)	0 (0.0)	.011
Death (*n* (%))	19 (29.7)	3 (9.7)	0 (0.0)	0 (0.0)	0 (0.0)	.062
ICM (*n* (%))	**93 (51.4)**	**29 (16.0)**	**9 (5.0)**	**15 (8.3)**	**35(19.3)**	
Re-hospitalization due to CHF (*n* (%))	38 (40.9)	2 (6.9)	3 (33.3)	1 (6.7)	5 (14.3)	<.001
AETs (*n* (%))	30 (32.3)	4 (13.8)	3 (33.3)	4 (26.7)	11 (31.4)	.237
Death (*n* (%))	30 (32.3)	3 (10.3)	0 (0.0)	1 (6.7)	3 (8.6)	.002

Values represent numbers (percentages).
Abbreviations: AETs, adequate electric therapies; CHF, congestive heart failure; DCM, dilatative cardiomyopathy, ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy.

re-hospitalization due to congestive heart failure in subjects with HFrecEF was 9.6 ± 4.8 months after ICD implantation for primary prevention and 8.4 ± 20.4 months before improvement of EF.

Adequate ICD therapies were similar in HFrecEF and pEF (p = n.s.) and most frequently in HFrEF (35 (30.4%), $p < .05$ compared to HFrecEF), followed by HFuEF (3 (21.4%), p = n.s. compared to HFrEF). No events were detected in HFmrEF (p = n.s. compared to HFrecEF, Table 4). Average time to occurrence of adequate electrical therapies was 9.6 ± 9.6 months after ICD implantation for primary prevention in patients with HFrecEF and 7.2 ± 20.4 months before recovering, however three patients had adequate electrical therapies after recovering.

Mortality was significantly lower in HFrecEF (5 (10.0%)) compared to HFrEF (35 (30.4%), $p = .001$, Figure 2 A), followed by pEF (1 (7.1%), p = n.s. in comparison of HFrecEF and pEF). No events could be observed in HFmrEF (p = n.s. compared to HFrecEF) and HFuEF ($p < .05$ compared to HFrecEF, Table 4).

3.4 | Secondary prevention

In secondary prevention ICD indication, subjects with HFrecEF had significant lower rates of re-hospitalization due to congestive heart failure

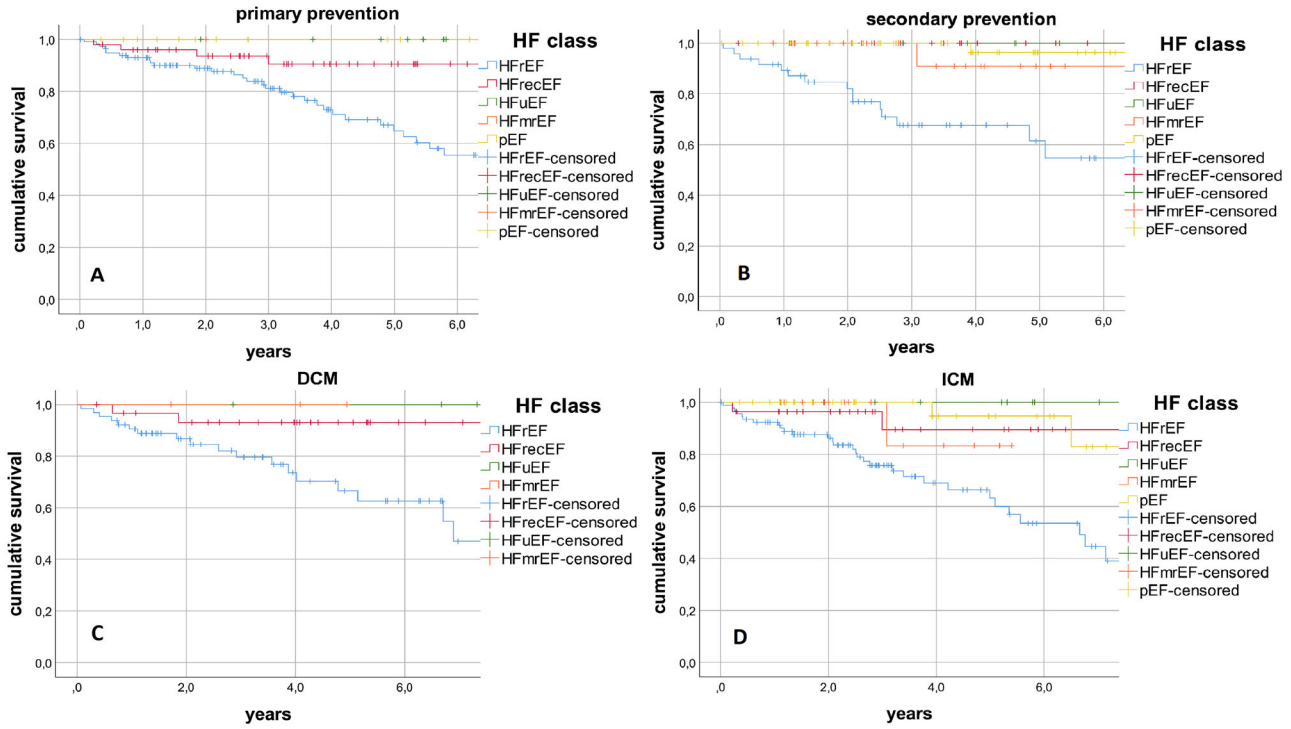

FIGURE 2 Kaplan-Meier curves for survival after (A) ICD-implantation due to primary prevention ICD indication, (B) after ICD-implantation due to secondary prevention ICD indication, (C) in patients with DCM (D) in patients with ICM [Color figure can be viewed at wileyonlinelibrary.com]

(4 (16.7%) compared to HFrEF (19 (39.6%); $p < .05$, Table 4) and similar rates compared to pEF (8 (16.7%)) and HFmrEF (2 (9.5%), each p = n.s.). No events were detected in HFuEF ($p < 0.05$ compared to HFrecEF, Table 4). Average time to re-hospitalization due to congestive heart failure was 8.4 ± 7.2 months in subjects with HFrecEF after ICD implantation for secondary prevention and 7.2 ± 8.4 months before improvement of EF.

Rates of adequate electrical therapies were similar between the five groups with a non-significant trend to lower event rates in HFrecEF (6 (25.0%) compared to HFrEF (22 (45.8%), $p = .056$, Table 4). Adequate electrical therapies in patients with HFrecEF occurred 7.2 ± 10.8 months after ICD implantation for secondary prevention and 3.6 ± 19.2 months before recovering with 44% of patients acquiring adequate electric therapy after recovering.

Mortality was significantly less frequent in HFrecEF (1 (4.2%)) compared to HFrEF (17 (35.4%); $p < .001$) and with similar rates in HFmrEF (2 (9.5%)), pEF (3 (6.3%)), and HFuEF (0 (0.0%), each p = n.s. compared to HFrecEF, Table 4, Figure 2 B).

3.5 | Dilatative cardiomyopathy

Re-hospitalization due to congestive heart failure was similar in HFrecEF (2 (6.5%) compared to HFmrEF (no events) and HFuEF (3 (60.0%), each p = n.s.) and significantly lower compared to HFrEF (20 (31.3%), $p = .001$).

Adequate electrical therapies were similar in HFrecEF (5 (16.1%) compared to HFuEF (1 (20%), p = n.s.) and significantly lower compared to HFrEF (25 (39.1%)) and HFmrEF (3 (100%), each $p < .05$).

Mortality was significantly less frequent in HFrecEF (3 (9.7%)) compared to HFrEF (19 (29.7%), $p < .05$) with no events in HFmrEF and HFuEF (each p = n.s. compared to HFrecEF, Table 4, Figure 2C).

3.6 | Ischemic cardiomyopathy

Rates of re-hospitalization due to congestive heart failure were similar in HFrecEF (2 (6.9%)) compared to HFmrEF (1 (6.7%)), pEF (5 (14.3%)) and HFuEF (3 (33.3%), p = n.s.) and significantly lower compared to HFrEF (38 (40.9%), $p < 0.001$, Table 4).

Adequate electrical therapies occurred significantly less often in HFrecEF (4 (13.8%), each $p < .05$, Table 4) compared to HFrEF (30 (32.3%)), pEF (11 (31.4%), HFmrEF (4 (26.7%)) and HFuEF (3 (33.3%), p = n.s. between the different groups).

Mortality was significantly higher in HFrEF (30 (32.3%)) compared to all other groups ($p < .05$, Table 4, Figure 2D).

4 | DISCUSSION

The aim of the current study was to evaluate the prognosis of patients with recovery of LV-EF in comparison to patients with HFrEF and pEF

to define a new subgroup of HF with possible modified therapeutic strategies.

In our study cohort we defined five groups of patients distinguishing between LV-EF at baseline and development over a period of at mean 3.8 years and a maximum of 9.2 years. Besides the common definition of HFrEF, HFmrEF and patients with preserved EF (pEF), we specified two further groups of patients: subjects with recovering to a stable LV-EF above 40% (HFrecEF) as well as patients with undulating EF below and above 40% (HFuEF).

In the current study, patients with HFrecEF had significantly lower rates of re-hospitalization due to congestive heart failure, adequate electrical therapies and mortality compared to subjects with HFrEF in the total study population and in the subgroups besides the group of secondary prevention ICD indication with non-significant lower rates of adequate electrical therapies in HFrecEF.

In comparison to pEF and HFmrEF, HFrecEF showed similar rates of re-hospitalization due to congestive heart failure and mortality, but significantly lower rates of adequate electrical therapies in the total study population. Only in primary prevention ICD indication, re-hospitalization due to congestive heart failure was higher in HFrecEF compared to pEF and HFmrEF, however number of cases were small in these groups. In conclusion, prognosis of HFrecEF was similar to pEF and HFmrEF in our collective and even better with regard to rhythm events, which is probably caused by higher rates of secondary prevention ICD indication in pEF and HFmrEF compared to HFrecEF.

In literature, results concerning the outcome after recovering of LV-EF differ due to varying study designs with different EF limits in the definition of HFrecEF, further partially HFmrEF was not included in earlier studies, and our collective of pEF did not have diastolic dysfunction, instead had normal LV-function with need of ICD therapy due to rhythm events.

Due to this varying study designs a wide recovery range of 10%—70%[4-9] has been described, in our collective 29% of patients with initial reduced LV-EF recovered to stable EF above 40%. Less frequent hospitalization rates[5,7,10] as well as lower mortality rates[5,10] in HFrecEF have been described in other, partly larger collectives (1057 subjects with a mean follow-up of 5.6 years in the collective of Lupon et al.[5] and 2166 participants with a follow-up of 3 years in the retrospective study of Kalogeropoulos et al.[10] with a mortality rate of 16.3% in HFrEF, 12.3% in HFpEF and 4.8% in HFrecEF[10]) which is congruent to the comparison of HFrecEF and HFrEF in our collective.

Mortality and hospitalization rates in HFpEF were larger in these above mentioned studies[5,7,10] compared to our collective but only few subjects had an ICD or CRT-D (3.4%,[5] 7.7%[10]) whereas all our pEF patients had an ICD and no diastolic dysfunction which may explain our lower mortality rates. HFpEF in literature is defined as normal LV-function ≥50% with evidence of cardiac dysfunction with cardiac symptoms due to abnormal LV filling and elevated LV filling pressures.[1,2] This feature is mainly associated to LV hypertrophy, enlargement of the left atrium and/or atrial fibrillation. Opposite to this definition of HFpEF our group of patients with pEF was different. pEF was defined as permanent LV-EF ≥ 50% since ICD-implantation and ICD was implanted due to other causes than HF such as idiopathic ventricular fibrillation, only few patients of pEF met criteria of HFpEF. Therefore, comparison of patients with HFpEF in the other mentioned collectives to our group of pEF is limited.

Mortality rate in HFrecEF was lower in the mentioned collectives[5,7,10] compared to our group, but in these collectives, patients with HFrecEF (in comparison to HFpEF) partly were younger (63.2 vs. 69.5 years), had shorter duration of HF (3 vs. 10 months and lower NYHA functional class (18.5% vs. 37.6% NYHA class III/IV),[5] had fewer comorbidities[7] or had more ICDs and CRTs (9.9% in HFrecEF vs. 3.4% in HFpEF[5] and 28.3% in HFrecEF vs. 7.7% in HFpEF[10]). In our analysis, patients with CRT were excluded as a potential option of improvement of LV function to get better comparability, so the described differences may be causal for different mortality rates. Further, these mentioned collectives did not consider rhythm events and ICD therapies contrary to our study, which expand our results.

Mortality rates in HFrEF were higher in our collective, which might be caused by exclusion of patients with CRT, further our patients with HFrEF were a little bit older (67.8 vs. 63[10] and 65.9 years[5]).

A further prospective study with 1821 patients with a median follow-up of 3.6 years described a better biomarker profile including BNP, uric acid, st2, sFlt-1 and TnI and a longer event-free survival in participants with recovering of EF above 50% compared to subjects with permanent reduced EF below 50% and to participants with preserved EF above 50%.[6]

In all mentioned studies, rhythm events were not collected in contrast to our cohort. Corresponding to the better outcome of HFrecEF compared to HFpEF in the studies mentioned above, we observed fewer rhythmical events in HFrecEF compared to pEF. This may be explained by a higher rate of secondary prevention ICD indication in pEF compared to HFrecEF.

Although recovery of LV-EF in HF has been described with improved outcome,[5-10] this entity has not been included in the current ESC HF guidelines so far,[1] but should be considered regarding our study results and the other mentioned publications.

In our collective, DCM was the main cause for ICD implantation in patients with HFrecEF in contrast to ICM in the other groups. Patients with DCM might recover to a higher percentage compared to subjects with ICM and have consequently a better prognosis. According to our results, a lower prevalence of coronary artery disease in patients with HFrecEF was also described in the collective of Kalogeropoulos et al.[10] (55.7% in HFrecEF vs. 65.4% in HFrEF and 62.2% in HFpEF), Lupon et al.[5] (35.2% in HFrecEF vs. 64.1% in HFrEF), Punnoose et al.,[7] Agra Bermejo et al.[8] and Basuray et al.[6] (16% in HFrecEF vs. 36% in HFrEF).

In contrast to our collective, CRT was not excluded in the other mentioned studies,[5,10] strength of our study in this context is the demonstration of a pure ICD collective with exclusion of potential confounders.

Medication intake concerning the renin-angiotensin-aldosterone axis, neprilysin inhibitors, betablockers and diuretics did not significantly differ between HFrecEF and HFrEF in our study population, so optimal medication treatment was not the underlying cause in varying outcome. Further, chronic alcohol consumption did not differ between HFrecEF and HFrEF, so recovery was probably not caused by removing

the underlying trigger in this case. Nevertheless, comorbidities such as chronic obstructive pulmonary disease and chronic renal insufficiency were more frequent in HFrEF compared to HFrecEF, which may contribute to a worse disease progression.

As a further explanation besides better medical treatment, device therapy or removal of underlying triggers such as toxins or tachycardia[11] for recovery of LV function a partial reserve remodeling has been discussed.[6] Despite better prognosis, only a minority of patients with HFrecEF recovered completely with normal echocardiography and normal neurohormonal profile in this investigation, so persistence of cardiomyopathy was assumed with the need of continuation of medical treatment.[6] This is confirmed by the finding of persisting global longitudinal strain abnormalities in HFrecEF[12-14] with a worse prognosis regarding hospitalization and death compared to complete recovery.[12]

In general, HF patients with an early recovery of LV-function do regularly not need an ICD for primary prevention corresponding to the current HF guidelines.[1,2] In contrast our patients of HFrecEF fulfilled all criteria for ICD-indication in primary prevention which means stable EF $\leq$ 35% for at least three months despite optimal medical treatment. In conclusion, all patients in our study collective with HFrecEF and primary prevention ICD-indication had a recovery of LV-function after at least three months corresponding to a late recovery which explains the need of an ICD contrary to an early recovery of LV-function with no necessity of an ICD. In literature there exists no differentiation of early and late recovery of LV-function. Further studies are required to discriminate these two features of early and late recovery, especially in the context of potential different outcomes.

In this context, the further need of ICD therapy after improvement of LV-EF remains unclear. Fewer rhythm events may justify no longer need of ICD therapy in primary prevention ICD indication but there were still three patients in our analysis with adequate electrical therapies after improvement of LV-EF above 40% with one patient suffering from electrical storm. The need of further prospective investigations exists to determine these few patients with persisting high arrhythmogenic potential. We propose an individual therapeutic approach in these subjects; prognosis concerning rhythm events improves, but is still elevated compared to the general population with rates of sudden cardiac death of 50–100/100,000 persons,[15] nevertheless, not only rhythm events are registered in these studies of sudden cardiac arrest, so comparison of rhythm events in our collective to general population is limited; patients should be differentiated cleared up. In secondary prevention ICD indication, patients can be calmed having fewer rhythm events, but ICD therapy would be further indicated.

The group of patients with HFuEF in our investigation was small with 21 participants. These subjects had similar rates of re-hospitalization due to congestive heart failure and adequate electrical therapies compared to HFrEF, but lower rates of mortality, so HFuEF seem to have an intermediate position with regard to prognosis between HFrEF and HFrecEF in our collective. So far, the entity of HFuEF has not been described in literature, but in our opinion, a differentiation to HFrEF and HFrecEF would be useful with the need of an investigation in a larger collective to determine the prognostic value. Moon et al. described a recurrence of 19% of initially recovered HF patients with DCM to LV dysfunction in a small collective of 42 participants,[16] which is higher than our group of HFuEF (8.1%), but in this mentioned collective recurrence of LV dysfunction was significantly associated to discontinuation of heart failure drugs.[16]

Strength of our study is the clear differentiation between HFrecEF and HFuEF, which is mainly not done in earlier investigations.

4.1 | Study limitations

Our study has several limitations. First, event rates could be underestimated, if patients were not treated at our university hospital for re-hospitalization of congestive heart failure or rhythm events, although the primary care physician was contacted to include these cases. Second, numbers of cases in the subgroups were partly small, however results were similar to the whole study population and therefore some deviation is possible responsible to the small case numbers. Third, patients with an early recovery of LV-EF were not included in the group of primary prevention ICD-indication, all of these patients had at least three months of stable EF $\leq$ 35% and recovery was at least after this period.

Nevertheless, we can describe two further classes of HF with different prognosis to the common ones, so further prospective studies have to be done for better understanding of HFrecEF and HFuEF in order to establish new HF entities.

5 | CONCLUSION

In conclusion, HFrecEF indicates as a new entity of HF with similar prognosis as pEF and HFmrEF with regard to re-hospitalization due to congestive heart failure and all-cause mortality and even better prognosis with regard to adequate electrical therapies. HFuEF has an intermediate position with similar rates of re-hospitalization due to congestive heart failure and adequate electrical therapies compared to HFrEF, but lower rates of all-cause mortality.

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AUTHOR CONTRIBUTIONS

Judith Zeller was engaged in study design, data collection, data analysis and interpretation, statistics and drafting the article. Ute Hubauer was involved in data collection and interpretation. Andreas Schober and Alexander Schober were engaged in data collection. Andreas Keyser

did data collection and critical revision of the manuscript. Sabine Fredersdorf and Ekrem Uecer were involved in study design and data collection. Lars S. Maier critically revised the manuscript. Carsten Jungbauer was engaged in study design, data collection, analysis and interpretation, statistics and critical revision of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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