Differences in risk profiles and long-term outcomes in acute heart failure patients with preserved and reduced left ventricular ejection fraction in the Czech Republic: The AHEAD registry sub-analysis

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Background. The latest European heart failure guidelines define patients as those with reduced (HFrEF), mid-range, and preserved (HFpEF) left ventricular ejection fraction (LVEF; <40%, 40%-49%, and ≥50%, respectively). We investigated the causes of rehospitalizations/deaths in our institution's heart failure patients and focused on differences in the clinical presentation, risk profile, and long-term outcomes between the HFrEF and HFpEF groups in a real-life scenario.
Methods and Results. We followed 1274 patients discharged from heart failure hospitalization in 2 centres. The mean patient age was 75.9 years, and men and women were represented equally. During the minimal follow-up of 2 years, 57% of patients were hospitalised for any cause, 24.9% for decompensated heart failure, and 43.3% for any cardiovascular cause. A total of 36.1% of patients died, either with prior (11.8%) or without prior (24.3%) heart failure rehospitalization. Heart failure was also the most frequent cause of cardiovascular hospitalization, followed by gastrointestinal problems, infections, and tumours for noncardiovascular hospitalizations. Patients with HFrEF had different baseline characteristics and risk profiles, experienced more hospitalizations for acute heart failure (28.6% vs 20.2%, P=0.012), and had higher cardiovascular mortality (82.4% vs 63.5%, P<0.001) when compared with HFpEF patients. Overall mortality and rehospitalization rates were similar.
Conclusion. Within 2 years, half of the patients died and/or were hospitalised for acute decompensation of heart failure, and only one-third of the patients survived without any hospitalization. HFrEF and HFpEF patients were confirmed to be different entities with diverse characteristics, risk profiles, and cardiovascular event rates.

Key words: acute heart failure, left ventricular ejection fraction, rehospitalization, AHEAD, mortality

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INTRODUCTION

The prognosis of patients hospitalised for acute heart failure (AHF) is unfavourable, with a hospitalization mortality rate of 4% to 12.7% (ref.[1-4]) and annual mortality of 17% to 32.3% (ref.[5]) in an unselected population. The most frequent causes of death are sudden cardiac death and terminal progression of heart failure.

Heart failure is a global problem with a rapidly increasing number of diagnosed patients; in 2012, the estimated number of patients worldwide was 26 million. Hospitalization for heart failure is the major cause of hospitalizations in the United States and Europe. There are more than 1 million AHF hospitalizations per year, accounting for 1% to 2% of all hospitalizations[6-13] and consuming as much as 7.7% of all annual in-hospital expenses and 2.7% of total healthcare expenditure[14].

Systolic function of the left ventricle plays an important role in a patient's prognosis. New guidelines from the European Society of Cardiology for the Diagnosis and Treatment of Heart Failure were published in 2016 (ref.[2]). Compared with previous guidelines, a new group of patients with mid-range left ventricular ejection fraction (LVEF; from 40 to 49%) was defined as a transition group between those with preserved (HFpEF; LVEF ≥50%) and reduced systolic function (HFrEF; LVEF <40%).

To our knowledge, no article has been published to date comparing long-term outcomes of patients with preserved and reduced LVEF according to the new guidelines who were discharged in a stable condition from an AHF hospitalization. The primary objective of our study was to describe the combined incidence of rehospitalizations for acute decompensation of heart failure and overall mortality during a 2-year follow-up. The secondary ob-
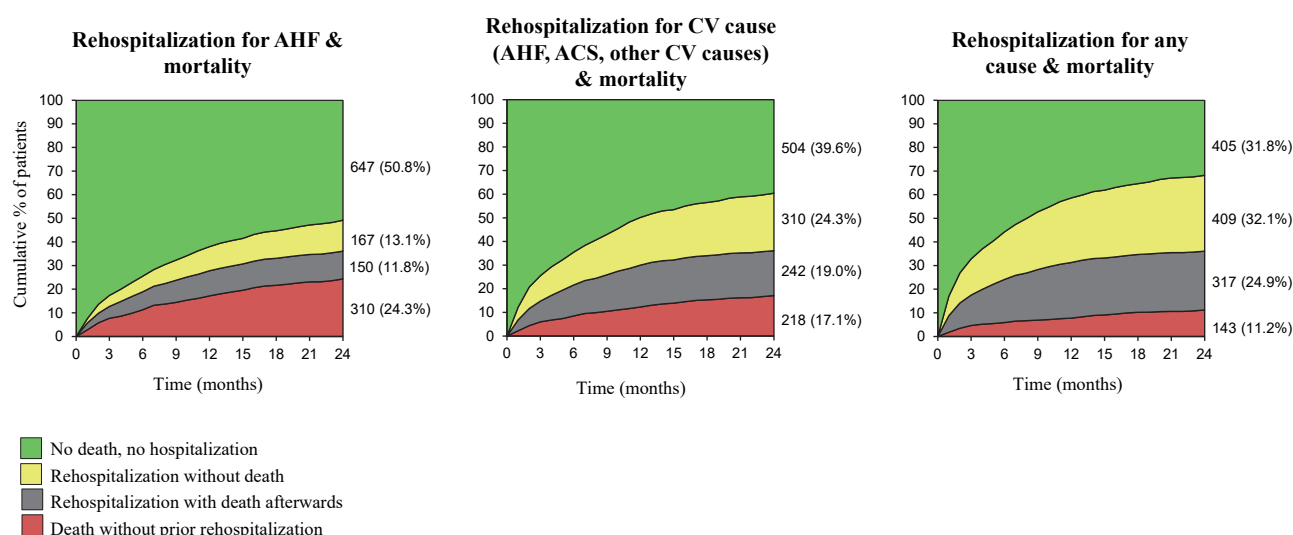
Fig. 1. Rehospitalization & mortality within 2 years after discharge from index acute heart failure hospitalization (n = 1274). ACS – acute coronary syndrome; AHF – acute heart failure; CV – cardiovascular

jectives were the number of cardiovascular and all-cause hospitalizations, mortality rates, and causes of death. Furthermore, we focused in detail on the comparison between characteristics, risk profiles, and outcomes of patients with HFrEF and HFpEF.

METHODS

Our study was a retrospective analysis of a set of 1,274 consecutive patients enrolled in the AHEAD registry (Czech Acute Heart Failure Database) who were discharged to home in a stable condition from a hospitalization for AHF. These patients were considered as chronic heart failure patients and the hospitalization hereinafter referred to as the index hospitalization. The Acute Heart Failure Database included patients enrolled from 2006-2012 in 15 participating centres; the methodology has been described in detail elsewhere[15,16]. Briefly, the exclusion criteria were advanced stage of malignancy (life expectancy less than 2 years) and refusal to participate in the registry. Nearly all consecutive patients with a final diagnosis of AHF according to the European Acute Heart Failure Guidelines issued in 2005 (ref.[10]) were enrolled during the index hospitalization. In this subanalysis, we evaluated consecutive patients from two centres only. These centres had collected more extensive follow-up data of enrolled patients than the other sites. As one centre is a major district hospital with a cath lab (Brno University Hospital) and the other is a regional referring hospital without a cath lab (Frydek-Mistek Hospital), our study cohort can be considered as a representative sample of the entire population.

The minimal follow-up was 2 years and was based on regular outpatient check-ups, evaluation of hospitalization records, and phone consultations with a patient or his or her relative. Causes of death were identified from the Institute of Health Information and Statistics of the

Czech Republic. We assume to have captured more than 95% of all hospitalization events.

The study was approved by the Ethics Committee of Brno University Hospital and was conducted in accordance with the provisions of the Declaration of Helsinki. All patients signed an informed consent to participate in the registry.

Subsequent hospitalizations were divided into 4 categories: (1) AHF hospitalization, (2) acute coronary syndrome (ACS) hospitalization, (3) hospitalization for other cardiovascular cause, and (4) noncardiovascular hospitalization.

The patients were also divided into 4 groups by their outcome: (1) no death, no hospitalization; (2) rehospitalization without death; (3) rehospitalization with death afterwards; (4) death without prior rehospitalization.

To provide a detailed analysis of patient outcomes based on LVEF, the patients were divided into 3 groups: (1) HFrEF (LVEF <40%), (2) mid-range (LVEF 40%-49%), and (3) HFpEF (LVEF >50%).

Statistical analysis

Standard descriptive statistics were used to analyse the data. Categorical variables were described by absolute and relative frequencies and continuous variables by median and 5th-95th percentile range or by average with standard deviation. A statistical significance of differences between patient groups was tested by the Kruskal-Wallis test and post hoc tests for continuous variables and by chi-square test or Fisher's exact test for categorical variables. Survival (time-to-event) analysis was used to evaluate the likelihood of hospitalizations and deaths at certain time points; Kaplan-Meyer curves were used for graphical visualisation. Binary logistic regression models and subsequently multivariate logistic regression models using backward stepwise algorithm for selection of independent predictors were used to calculate the odds of 2-year outcomes for different variables stratified by the

Table 1. Basic characteristics of 1274 consecutive patients discharged from hospitalization for acute heart failure in a stabilized condition. A total of 1166 (91.5%) patients had echocardiography performed during index hospitalization.

	Patients in total (n = 1 274)	LVEF < 40% (n = 482)	LVEF 40–49% (n = 244)	LVEF ≥ 50% (n = 440)	P
Gender - male	647 (50.8%)	311 (64.5%)	137 (56.1%)	157 (35.7%)	**< 0.001**
Age (years)	75.9 (54.3; 88.4)	73.8 (50.8; 87.2)	75.0 (54.8; 88.4)	76.9 (55.3; 87.7)	**< 0.001**
BMI (kg/m^2)	n = 1 005; 27.9 (21.1; 39.8)	n = 389; 27.7 (21.1; 38.9)	n = 203; 27.9 (21.3; 40.1)	n = 347; 28.4 (21.0; 41.1)	0.246
Systolic pressure (mmHg)	n = 1 259; 140.0 (95.0; 200.0)	n = 475; 140.0 (90.0; 190.0)	n = 244; 150.0 (100.0; 220.0)	n = 434; 145.0 (95.0; 210.0)	**< 0.001**
Diastolic pressure (mmHg)	n = 1 257; 80.0 (60.0; 110.0)	n = 475; 80.0 (60.0; 110.0)	n = 244; 80.0 (60.0; 120.0)	n = 433; 80.0 (60.0; 115.0)	0.309
Heart rate (per min)	n = 1 266; 95.0 (60.0; 150.0)	n = 478; 100.0 (60.0; 160.0)	n = 242; 90.0 (57.0; 135.0)	n = 438; 90.0 (54.0; 150.0)	**< 0.001**
NYHA class dyspnea					
1	205 (16.2%)	73 (15.2%)	50 (20.6%)	76 (17.4%)	
2	880 (69.4%)	317 (65.9%)	161 (66.3%)	313 (71.6%)	**0.006**
3	183 (14.4%)	91 (18.9%)	32 (13.2%)	48 (11.0%)	
Hypertension	1 001 (79.1%)	370 (76.8%)	189 (77.5%)	357 (81.1%)	0.243
Diabetes mellitus	551 (43.5%)	203 (42.1%)	101 (41.4%)	195 (44.3%)	0.703
Prior myocardial infarction	395 (31.2%)	191 (39.6%)	88 (36.1%)	85 (19.3%)	**< 0.001**
Prior PCI/CABG	208 (16.4%)	97 (20.1%)	47 (19.3%)	43 (9.8%)	**< 0.001**
Stroke/TIA	323 (25.5%)	107 (22.2%)	57 (23.4%)	119 (27.0%)	0.215
Peripheral artery disease	302 (23.8%)	125 (25.9%)	48 (19.7%)	95 (21.6%)	0.113
COPD	309 (24.4%)	117 (24.3%)	62 (25.4%)	107 (24.3%)	0.937
Atrial fibrillation	443 (34.9%)	160 (33.2%)	68 (27.9%)	173 (39.3%)	**0.008**
BNP (pg/ml; baseline)	(n = 234) 788 (86; 4 559)	n = 96; 1 187.9 (147.9; 5 000.0)	n = 37; 576.5 (180.0; 2 908.2)	n = 76; 536.8 (44.7; 3 907.0)	**< 0.001**
eGFR (mL/min/1.73m^2)	52.7 (21.2; 96.6)	52.7 (22.8; 95.3)	56.2 (23.9; 101.3)	51.6 (18.0; 89.4)	**0.007**
LVEF (%)	42 (20; 65)	-	-	-	-
Acute heart failure de-novo	621 (48.7%)	196 (40.7%)	124 (50.8%)	268 (60.9%)	**< 0.001**
Acute heart failure etiology					
Acute coronary syndrome	285 (22.4%)	111 (23.0%)	78 (32.0%)	82 (18.6%)	**< 0.001**
Ischemic heart disease	348 (27.3%)	188 (39.0%)	73 (29.9%)	40 (9.1%)	
Valve defects	178 (14.0%)	43 (8.9%)	34 (13.9%)	91 (20.7%)	
Arrhythmia	166 (13.0%)	47 (9.8%)	20 (8.2%)	83 (18.9%)	
Hypertension	79 (6.2%)	6 (1.2%)	19 (7.8%)	46 (10.5%)	
Other	218 (17.1%)	87 (18.0%)	20 (8.2%)	98 (22.3%)	
Hospitalization procedures					
Pacemaker	39 (3.1%)	15 (3.1%)	9 (3.7%)	12 (2.7%)	0.784
PCI	143 (11.2%)	57 (11.8%)	41 (16.8%)	44 (10.0%)	**0.032**
CABG	38 (3.0%)	19 (3.9%)	15 (6.1%)	4 (0.9%)	**< 0.001**
ICD	24 (1.9%)	7 (1.5%)	1 (0.4%)	3 (0.7%)	0.301
CRT	11 (0.9%)	9 (1.9%)	0 (0.0%)	0 (0.0%)	**0.002**
Medication at discharge					
Antiaggregation	905 (71.3%)	342 (71.0 %)	196 (80.3%)	285 (64.8%)	**< 0.001**
Anticoagulation	312 (24.6%)	122 (25.3 %)	51 (20.9%)	124 (28.2%)	0.111
ACE-inhibitors/sartans	1 064 (83.8%)	416 (86.3 %)	207 (84.8%)	355 (80.7%)	0.061
Beta-blockers	954 (75.2%)	394 (81.7 %)	195 (79.9%)	297 (67.5%)	**< 0.001**
Calcium channel blockers	286 (22.5%)	61 (12.7 %)	53 (21.7%)	146 (33.2%)	**< 0.001**
Diuretics	1 127 (88.8%)	452 (93.8 %)	210 (86.1%)	368 (83.6%)	**< 0.001**
Verospirone	578 (45.5%)	318 (66.0 %)	98 (40.2%)	120 (27.3%)	**< 0.001**
Digoxin	310 (24.4%)	143 (29.7%)	51 (20.9%)	84 (19.1%)	**< 0.001**

Categorical variables are described by absolute (relative) frequencies. Continuous variables are described by n, median (5th-95th percentile). BNP - B-type natriuretic peptide; CABG –coronary bypass graft; COPD - chronic obstructive pulmonary disease; CRT – resynchronization therapy; eGFR - estimated glomerular filtration rate by Modification of Diet in Renal Disease study equation; ICD – implantable cardioverter defibrillator; LVEF – left ventricular ejection fraction; PCI – percutaneous coronary intervention; PM – pacemaker; TIA – transient ischemic attack
* Reported % are related to total number of hospitalizations in the 1st year (n=1193), in the 2nd year (n=318) and the sum of both years (n=1511). The column totals can exceed 100% as there could have been 2 major causes for one hospitalization.

Table 2. Number of hospitalizations during the first two years following discharge from index hospitalization (n = 1274).

Number of hospitalizations	Cause of hospitalization				
	AHF	ACS	Other CV	Non-CV	Any
0. n (%)	957 (75.1 %)	1 209 (94.9 %)	921 (72.3 %)	722 (56.7 %)	548 (43.0 %)
1. n (%)	225 (17.7 %)	50 (3.9 %)	233 (18.3 %)	349 (27.4 %)	362 (28.4 %)
2. n (%)	57 (4.5 %)	12 (0.9 %)	75 (5.9 %)	112 (8.8 %)	182 (14.3 %)
3. n (%)	22 (1.7 %)	3 (0.2 %)	19 (1.5 %)	53 (4.2 %)	89 (7.0 %)
> 3. n (%)	13 (1.0 %)	0 (0.0 %)	26 (2.0 %)	38 (3.0 %)	93 (7.3 %)
Average (SD)	0.4 (0.8)	0.1 (0.3)	0.5 (1.0)	0.7 (1.1)	1.2 (1.6)
Median (min.–max.)	0 (0; 11)	0 (0; 3)	0 (0; 14)	0 (0; 11)	1 (0; 15)

ACS – acute coronary syndrome; AHF – acute heart failure; CV – cardiovascular; SD – standard deviation

Table 3. The causes for hospitalizations during the first and the second year of follow-up and cumulative summary of all events during the follow-up period of 2 years after index hospital discharge.

Cause for hospitalization n = 1 274	Number of hospitalizations in 1st year		Number of hospitalizations in 2nd year		Cumulative number of all hospitalizations	
	Total*	Per 1000 patients	Total*	Per 1000 patients	Total*	Per 1000 patients
CV AHF	364 (30.5%)	286	108 (34.0%)	85	472 (31.2%)	370
ACS	72 (6.0%)	57	21 (6.6%)	16	93 (6.2%)	73
Other						
Arrhythmia	124 (10.4%)	97	33 (10.4%)	26	157 (10.4%)	123
CVD	58 (4.9%)	46	20 (6.3%)	16	78 (5.2%)	61
PAD	41 (3.4%)	32	9 (2.8%)	7	50 (3.3%)	39
Hypertension	20 (1.7%)	16	7 (2.2%)	5	27 (1.8%)	21
Valve disease	20 (1.7%)	16	1 (0.3%)	1	21 (1.4%)	16
CAD	16 (1.3%)	13	1 (0.3%)	1	17 (1.1%)	13
PM/ICD implantation	14 (1.2%)	11	9 (2.8%)	7	23 (1.5%)	18
Pulmonary embolism	13 (1.1%)	10	1 (0.3%)	1	14 (0.9%)	11
Deep venous thrombosis	9 (0.8%)	7	0 (0.0%)	0	9 (0.6%)	7
Systemic embolism	4 (0.3%)	3	1 (0.3%)	1	5 (0.3%)	4
PCI	3 (0.3%)	2	3 (0.9%)	2	6 (0.4%)	5
Other	3 (0.3%)	2	4 (1.3%)	3	7 (0.5%)	5
Non CV						
GIT disease	90 (7.5%)	71	9 (2.8%)	7	99 (6.6%)	78
Respiratory infection	57 (4.8%)	45	17 (5.3%)	13	74 (4.9%)	58
Tumor	55 (4.6%)	43	19 (6.0%)	15	74 (4.9%)	58
Diabetes mellitus	40 (3.4%)	31	16 (5.0%)	13	56 (3.7%)	44
Bleeding	38 (3.2%)	30	6 (1.9%)	5	44 (2.9%)	35
Renal failure/disease	30 (2.5%)	24	9 (2.8%)	7	39 (2.6%)	31
Non-respiratory infection	27 (2.3%)	21	8 (2.5%)	6	35 (2.3%)	27
Dehydratation	19 (1.6%)	15	2 (0.6%)	2	21 (1.4%)	16
COPD	19 (1.6%)	15	6 (1.9%)	5	25 (1.7%)	20
Urinary infection	15 (1.3%)	12	7 (2.2%)	5	22 (1.5%)	17
Anemia	14 (1.2%)	11	1 (0.3%)	1	15 (1.0%)	12
Syncope	14 (1.2%)	11	6 (1.9%)	5	20 (1.3%)	16
Thoracic syndrome	11 (0.9%)	9	1 (0.3%)	1	12 (0.8%)	9
Musculoskeletal pain	10 (0.8%)	8	2 (0.6%)	2	12 (0.8%)	9
Neurological disease	10 (0.8%)	8	1 (0.3%)	1	11 (0.7%)	9
Fracture	7 (0.6%)	5	0 (0.0%)	0	7 (0.5%)	5
Collapse	5 (0.4%)	4	0 (0.0%)	0	5 (0.3%)	4
Diagnostic hospitalization	0 (0.0%)	0	1 (0.3%)	1	1 (0.1%)	1
Other	56 (4.7%)	44	23 (7.2%)	18	79 (6.0%)	62
Total	1 193 (100.0%)	936	318 (100.0%)	250	1 511 (100.0%)	1 186

ACS –acute coronary syndrome; AHF – acute heart failure; CAD – chronic coronary artery disease; COPD – chronic obstructive pulmonary disease; CV – cardiovascular; CVD – cerebrovascular disease; GIT – gastrointestinal tract; PCI – percutaneous coronary intervention; PM/ICD – pacemaker / implantable cardioverter-defibrillator.
* Reported % are related to total number of hospitalizations in the 1st year (n = 1193), in the 2nd year (n = 318) and the sum of both years (n = 1511). The column totals can exceed 100% as there could have been 2 major causes for one hospitalization.

Table 4. Echocardiographical findings - diastolic function and valvular defects by LVEF groups.
Only moderate-severe defects are reported.

	LVEF < 40% (n = 482)	LVEF 40–49% (n = 244)	LVEF ≥ 50% (n = 440)	P
Diastolic function				
Normal	29 (6.0%)	25 (10.2%)	29 (6.6%)	
Relaxation failure	80 (16.6%)	76 (31.1%)	190 (43.2%)	
Pseudonormalisation	29 (6.0%)	11 (4.5%)	19 (4.3%)	**< 0.001**
Restriction	69 (14.3%)	10 (4.1%)	18 (4.1%)	
Unknown	275 (57.1%)	122 (50.0%)	184 (41.8%)	
Valvular defects				
Mitral regurgitation	279 (57.9%)	95 (38.9%)	142 (32.3%)	**< 0.001**
Mitral stenosis	4 (0.8%)	3 (1.2%)	14 (3.2%)	**0.031**
Aortic stenosis	41 (8.5%)	18 (7.4%)	39 (8.9%)	0.831
Aortic regurgitation	19 (3.9%)	12 (4.9%)	35 (8.0%)	**0.030**
Tricuspid regurgitation	204 (42.3%)	62 (25.4%)	142 (32.3%)	**< 0.001**
Other valvular disease	5 (1.0%)	6 (2.5%)	8 (1.8%)	0.309

LVEF – left ventricular ejection fraction
P-value of Fisher Exact Test is reported.

Table 5. Rehospitalization & mortality within 2 years after discharge from index acute heart failure hospitalization, stratified by LVEF.

2-year outcome	LVEF < 40% (n = 482)	LVEF 40–49% (n = 244)	LVEF ≥ 50% (n = 440)	P	
Rehospitalizations					
Rehospitalization for any cause	269 (55.8%)	132 (54.1%)	270 (61.4%)	0.110	
Rehospitalization for CV cause	220 (45.6%)	99 (40.6%)	190 (43.2%)	0.418	
Rehospitalization for AHF	138 (28.6%)	62 (25.4%)	89 (20.2%)	**0.012**	a/ab/b
Rehospitalizations and mortality	182 (37.8%)	74 (30.3%)	148 (33.6%)	0.120	
Rehospitalization for any cause or mortality	328 (68.0%)	151 (61.9%)	311 (70.7%)	0.063	
Rehospitalization for CV cause or mortality	301 (62.4%)	127 (52.0%)	267 (60.7%)	**0.023**	a/b/a
Rehospitalization for AHF or mortality	256 (53.1%)	109 (44.7%)	195 (44.3%)	**0.014**	a/b/b

LVEF – left ventricular ejection fraction, CV – cardiovascular, AHF – acute heart failure
P-value of Fisher Exact Test is reported; post hoc – same letters denote groups which do not differ statistically from each other.

patients' LVEF. The level of significance was set at α = 0.05 for all analyses.

RESULTS

Entire cohort (1274 patients with AHF)

Baseline characteristics, course of hospitalization, medication

The patients' baseline characteristics are shown in Table 1 (left column). The mean patient age was 75.9 years, and half of the patients were men. The most frequent comorbidities included hypertension (79.1%), diabetes mellitus (43.5%), and prior myocardial infarction (31.2%). A quarter of the patients had previous stroke, chronic obstructive pulmonary disease, and peripheral ischemic disease; one-third had any form of atrial fibrillation. ACS (22.4%) and chronic coronary artery disease (27.3%) were the most common causes of AHF hospitalizations, followed by valvular defects (14%) and arrhythmias (13%). At discharge from the index hospitalization,

most patients had their heart failure medication well established.

Outcome

During the course of the 2-year follow-up, the primary combined endpoint (AHF rehospitalization/all-cause death) occurred in 49.2% of the patients. Fifty-seven percent of the patients were hospitalised for any cause, 24.9% for acute decompensation of heart failure and 43.3% for any cardiovascular cause; only 31.8% of the patients survived without any rehospitalization. The overall mortality rate was 36.1% (11.8% with prior and 24.3% without prior heart failure rehospitalization; Fig 1).

Table 2 clearly shows that some patients experienced multiple rehospitalizations. More than 3 rehospitalizations for heart failure decompensation were recorded in 1% of the patients, 3 rehospitalizations in 1.7%, and 2 rehospitalizations in 4.5%. The mean number of rehospitalizations for acute decompensation of heart failure was 0.4 ± 0.8 per patient, for a cardiovascular cause 0.5 ± 1.0, and for any cause 1.2 ± 1.6 per patient over the period of 2 years.

Table 6. Causes of death by LVEF, as reported in hospitalization records or in the Institute of Health Information and Statistics of the Czech Republic.

	EF < 40% (n = 482)	EF 40–49% (n = 244)	EF ≥ 50% (n = 440)	P
No. of deaths within the first two years of follow-up	182 (37.8%)	74 (30.3%)	148 (33.6%)	
% and P-values related to patients who died:				
Diseases of the circulatory system (I00–I99)	150 (82.4%)	54 (73.0%)	94 (63.5%)	**0.001**
Neoplasms (C00–D49)	12 (6.6%)	7 (9.5%)	21 (14.2%)	0.073
Diseases of the respiratory system (J00–J99)	6 (3.3%)	6 (8.1%)	8 (5.4%)	0.252
Endocrine, nutritional and metabolic diseases (E00–E89)	6 (3.3%)	1 (1.4%)	9 (6.1%)	0.237
Diseases of the digestive system (K00–K95)	2 (2.2%)	2 (4.1%)	5 (4.1%)	0.365
Injury, poisoning and certain other consequences of external causes (S00–T88)	2 (1.1%)	1 (2.7%)	5 (3.4%)	0.370
Other cause of death	4 (1.1%)	3 (1.4%)	6 (3.4%)	0.571
% and P-values related to all patients:				
Diseases of the circulatory system (I00–I99)	150 (31.1%)	54 (22.1%)	94 (21.4%)	**0.001**
Neoplasms (C00–D49)	12 (2.5%)	7 (2.9%)	21 (4.8%)	0.150
Diseases of the respiratory system (J00–J99)	6 (1.2%)	6 (2.5%)	8 (1.8%)	0.434
Endocrine, nutritional and metabolic diseases (E00–E89)	6 (1.2%)	1 (0.4%)	9 (2.0%)	0.209
Diseases of the digestive system (K00–K95)	2 (0.8%)	2 (1.2%)	5 (1.4%)	0.465
Injury, poisoning and certain other consequences of external causes (S00–T88)	2 (0.4%)	1 (0.8%)	5 (1.1%)	0.429
Other cause of death	4 (0.4%)	3 (0.4%)	6 (1.1%)	0.718

LVEF – left ventricular ejection fraction
P-value of Fisher Exact Test is reported. Codes in brackets express causes of death by International Classification of Disease-10.

Table 7. Multivariant logistic regression analysis for prediction of 2-year all-cause rehospitalization/mortality of acute heart failure patients after dismissal from the index hospitalization; stratified by the value of left ventricular ejection fraction (HFrEF and HFpEF patients).

Predictor		LVEF < 40% (n = 482)	
		OR (95% IS)	P
Age (+10 years)		1.38 (1.15; 1.66)	< 0.001
Diastolic pressure (+10 mmHg)		0.87 (0.77; 1.00)	0.045
NYHA class at admission			
	3 vs 1+2	2.49 (1.36; 4.56)	0.003
eGFR (+10 mL/min)		0.89 (0.81; 0.98)	0.020
Peripheral artery disease		2.07 (1.21; 3.52)	0.008

AUC (95% IS): 0.702 (0.654; 0.750), P-value: < 0.001

Predictor		LVEF ≥ 50% (n = 440)	
		OR (95% IS)	P
NYHA class at admission			
	2 vs 1	2.04 (1.19; 3.52)	0.010
	3 vs 1	4.30 (1.72; 10.72)	0.002
eGFR (+10 mL/min)		0.80 (0.72; 0.88)	< 0.001
Diabetes mellitus		1.69 (1.07; 2.68)	0.024
Peripheral artery disease		2.04 (1.10; 3.78)	0.023

AUC (95% IS): 0.715 (0.663; 0.767), P-value: < 0.001

For the list of all included variables see Appendix Table 2; only statistically significant predictors are shown.
AUC – Area Under Curve; eGFR - estimated glomerular filtration rate by Modification of Diet in Renal Disease study equation;
LVEF – left ventricular ejection fraction

Table 3 presents major causes of hospitalizations. The most frequent cardiovascular cause was acute decompensation of heart failure (31.2% of all hospitalizations), followed by arrhythmias, ACS, and cerebrovascular disease. Noncardiovascular hospitalizations were mostly due to gastrointestinal problems, infections, tumours, diabetes mellitus, bleeding events, and renal disease.

Stratification of patients by LVEF: comparison of HFrEF and HFpEF groups

Baseline characteristics, course of hospitalization, medication

Focusing on prespecified groups of patients with HFrEF and HFpEF (Table 1, right side), the patients with low LVEF were much more often men (64.5% vs 35.7%) and on average 3 years younger (73.8 vs 76.9 years) than the patients with LVEF ≥50% (both P<0.001). These findings reflect the fact that the HFrEF group consisted of patients mostly with ischemic heart disease, with prior myocardial infarction and coronary intervention. These patients also presented dominantly with acutely decompensated chronic heart failure and not with de novo heart failure (59.3% and 40.7% in HFrEF vs 39.1% and 60.9% in HFpEF, P<0.001). Hypertensive crisis as the cause of heart failure was identified in 10.5% of the HFpEF group but in only 1.2% in the HFrEF group (P<0.001). Pharmacological treatment at discharge was in accordance with heart failure guidelines, with a higher prevalence of beta-blockers, spironolactone, loop diuretics, and digoxin in the HFrEF (all P<0.001).

Echocardiographic pictures were also different. Advanced grades of diastolic dysfunction with secondary mitral and tricuspid regurgitation were frequently found in HFrEF patients, while in the HFpEF group, other valvular defects were more often stated as the primary aetiology of AHF (Table 1, right side; Table 4).

Outcome

Table 5 shows clearly that we found a significant difference in the occurrence of the primary combined endpoint between the HFrEF and HFpEF groups (53.1% vs 44.3%, P=0.014) which was mostly driven by a higher AHF rehospitalization rate in the group with severe systolic dysfunction. All-cause hospitalizations and hospitalizations for cardiovascular causes were similar between the groups. The all-cause mortality also did not differ between groups (37.8% vs 33.6%). Notably, the incidence of cardiovascular deaths was significantly related to the LVEF value, reaching the highest percentage in the HFrEF group, followed by the mid-range group, and with the lowest death rate in the HFpEF group (82.4% vs 73.0% vs 63.5%, respectively, P<0.001). More patients with preserved LVEF died from a noncardiac disease, particularly tumours or respiratory system failure (Table 6).

To express differences in patient characteristics and risk profiles between the two groups in terms of 2-year mortality risk/all-cause rehospitalization, we selected more than 30 variables (demographic, laboratory, echocardiographic, and hemodynamic parameters, medica-tions and concomitant cardiovascular comorbidities recorded during the index AHF hospitalization) and calculated the odds ratios (ORs). A multivariate regression analysis revealed that only glomerular filtration rate and the presence of peripheral artery disease were independent predictors of the combined endpoint identically for HFrEF and HFpEF patients (Table 7).

DISCUSSION

Our paper evaluated the 2-year prognosis of an unselected group of consecutive patients released in stable condition from hospitalization for AHF. Our patients were well treated according to the guidelines. Somewhat misleading is the number of revascularisation procedures (percutaneous coronary intervention [PCI]/coronary artery bypass graft [CABG]) that were performed in only 14.2% of patients during the index hospitalization. The reason for this finding is that many patients underwent elective coronarography/PCI/CABG shortly after discharge. This is a common practice in our region for reimbursement purposes.

In this study, we found the prognosis of heart failure patients to be very poor. Approximately one-third of all patients died, a quarter of the patients were hospitalised for AHF, and only about a third of the patients survived without any further hospitalization over 2 years. These unfavourable outcomes were much worse than those reported in recent randomised clinical trials[6-9] that focused on only stable chronic heart failure patients with either systolic dysfunction (different LVEF cutoffs) or preserved LVEF >45%. These trials (median patient follow-up 23-40 months), compared with our registry, reported significantly lower mortality rates (15.5%-19.8% vs 36.1%), fewer rehospitalizations for acute decompensation of heart failure (14.2%-18.4% vs 24.9%), and fewer all-cause hospitalizations (35.8%-45% vs 57%). The primary composite endpoint in these trials, comprising hospitalizations for heart failure and/or cardiovascular mortality, occurred in 20.4% to 29% of the patients[8-10,13], while in our real-world registry, the incidence reached 41.3%. These variances are due to different characteristics of the enrolled patients. Our registry patients were older (60-69 years vs 75.9 years), had more comorbidities, and, importantly, 48.7% were de novo heart failure patients with no previous experience with heart failure treatment. On the contrary, the clinical trials mentioned above with a long-term follow-up enrolled chronic heart failure patients with varied histories and therapies. In a meta-analysis by Pocock et al. (ref.[5]), evaluating 6 randomised studies and 24 observational registries, the overall mortality was 40.2% during the 2.5-year follow-up, which is comparable with our cohort. Our results provide more complex information in addition to overall mortality (i.e., numbers and causes of subsequent rehospitalizations and deaths). This information may help place the focus on and manage the comorbidities of heart failure patients that potentially lead to subsequent events.

One has to point out that the patients were at the highest risk of hospitalization or death during the first year

(particularly during the first 3-6 months) after discharge. Later on, the cumulative incidence of events declined (the number of hospitalizations from any cause in the 1st year was 1193 and in the 2nd year 318 cases).

Recently, much has been discussed about the differences in the characteristics and outcomes of patients with reduced and preserved LVEF. Many previous heart failure trials or registries had excluded patients with preserved LVEF. Low LVEF (various cutoffs of <35% to <50%) had been found to be a strong negative predictor of mortality[17,18], and patients with preserved LVEF were believed to have a better survival. Today, we perceive HFrEF and HFpEF as different entities with various patient characteristics but with very similar outcomes. Previous studies found that chronic obstructive pulmonary disease (COPD), anaemia, diabetes mellitus, and obesity were more prevalent in HFpEF patients than in those with HFrEF. In our study, we did not observe a different prevalence of the above-mentioned comorbidities between the patient groups but the HFpEF patients were older, more often women and with significantly less frequent ischemic heart disease. In most trials and registries, COPD was associated with a higher mortality in HFpEF subjects[19]. Pocock et al. identified 13 major variables associated with long-term mortality (LVEF value being one of them), but only systolic blood pressure and age had different prognostic impacts on patients with reduced (<40%) and preserved (>40%) LVEF. All other variables (particularly creatinine, New York Heart Association class, diabetes mellitus, etc.) demonstrated comparable negative predictive values for both groups[5]. Similarly in our study, we identified the decrease in glomerular filtration rate, concomitant peripheral artery disease and advanced chronic dyspnoea (NYHA class III) to be negatively associated with increased 2-year rehospitalization/mortality rates of our AHF patients. Specifically for each patient group, higher diastolic blood pressure was protective in HFrEF patients, unlike their higher age, and concomitant diabetes mellitus was significantly and independently associated with adverse outcomes in the HFpEF group. The effect of different doses of loop diuretics on the long-term mortality of the same cohort of patients was described elsewhere[20].

We demonstrated that there were differences between heart failure patients with low and preserved LVEF. Consequently, there were more AHF rehospitalizations and cardiovascular deaths in the HFrEF group during the 2-year follow-up and numerically more noncardiovascular deaths and rehospitalizations in the HFpEF group. Similar differences had been described previously[21]. The results suggest that we should wisely consider our treatment and management plans in order to focus more on noncardiovascular comorbidities of HFpEF patients in particular ("triggers" of heart failure), possibly limit the use of loop diuretics in HFpEF patients, carefully follow all heart failure patients during initial "critical" months after discharge, and perform more revascularisation procedures during the same hospitalization in patients with HFrEF of ischemic origin. Specially designed observational studies using advanced echocardiographic parameters, stress tests, and biomarkers as well as studies performing close follow-up of the patients are needed to determine the best management of care of patients with HFpEF.

There are limitations of our study. (1) We evaluated patients from only 2 hospital centres. Nevertheless, as one site has a 24/7 operating cath lab (a district hospital) and the other site does not (regional referring hospital), and both centres enrolled all consecutive patients, we consider our patient cohort to be a representative sample of the entire population. (2) We collected data about numbers of hospitalizations, causes of hospitalizations, and deaths but not subsequent interventions, laboratory tests, echocardiographic parameters, and so forth. All characteristics and results of individual patients originated from the index hospitalization only. (3) We are aware of the fact that there are other prognostic variables identified in previous registries (hyponatremia, anaemia, novel biomarkers, etc) that were not included in our analysis. (4) In the analysis by LVEF value, some patients might have had right ventricular dysfunction causing right heart failure with preserved LVEF but with much worse outcome than other patients with preserved LVEF. Similar controversies could have been found in other AHF patients with malign arrhythmias or high-output heart failure (sepsis, anaemia). All of these patients were included in the registry.

CONCLUSION

Despite advanced therapies, the prognosis of patients released from hospitalization for heart failure remains poor. Within 2 years, half of these patients die and/or are hospitalised for acute decompensation of heart failure, and only about a third of the patients survive without any hospitalization. Unselected heart failure patients from real clinical practice have worse prognosis than those enrolled (selected) in clinical trials. Patients with reduced LVEF (<40%), when compared with those with preserved LVEF (≥50%), have different characteristics and risk profiles. HFrEF patients experience more rehospitalizations for heart failure and die more often of a cardiovascular cause than HFpEF patients, but overall mortality and rehospitalization rates do not differ between the groups. More detailed investigations are needed to determine an association of noncardiovascular comorbidities and mortality of HFpEF patients.

ABBREVIATIONS

ACEIs/ARBs: Angiotensin-converting-enzyme inhibitors/angiotension receptor blockers; ACS: Acute coronary syndrome; AHF: Acute heart failure; CHF, Chronic heart failure; CV: Cardiovascular; GFR: Glomerular filtration rate; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; LVEF: Left ventricular ejection fraction; NYHA: Dyspnea degree according to New York Heart Association; OR: Odds ratio.

velopment of research organisations (FNBr, 65269705) and by the research project No. MUNI/A/1250/2017 of Masaryk University (Brno, Czech Republic, principal investigator Petr Lokaj). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author contributions: MM, RM, JS: manuscript writing; MM, RM, RS, KZ, MF, LP: data collection and revision; JS, PL: scientific revision and consultations; KB, LD, JJ: statistics, graphical visualisation and table design.

Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

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