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Diagnosis, clinical course, and 1-year outcome in patients hospitalized for heart failure with preserved ejection fraction (from the Polish Cohort of the European Society of Cardiology Heart Failure Long-Term Registry)

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Compared with heart failure (HF) with reduced ejection fraction (HF-REF), the diagnosis of HF with preserved EF (HF-PEF) is more challenging. The aim of the study was to assess the prevalence of HF-PEF among patients hospitalized for HF, to evaluate the pertinence of HF-PEF diagnosis and to compare HF-PEF and HF-REF patients with respect to outcomes. The analysis included 661 Polish patients hospitalized for HF, selected from the European Society of Cardiology (ESC)-HF Long-Term Registry. Patients with an EF of ≥50% were included in the HF-PEF group and patients with an EF of <50% - in the HF-REF group. The primary end point was all-cause death at 1 year. The secondary end point was a composite of all-cause death and rehospitalization for HF at 1 year. HF-PEF was present in 187 patients (28%). Of those 187 patients, mitral inflow pattern was echocardiographically assessed in 116 patients (62%) and classified as restrictive/pseudonormal in 37 patients (20%). Compared with HF-REF subjects, patients with HF-PEF were older, more often female, and had a higher prevalence of hypertension, atrial fibrillation and sleep apnea. Despite lower B-type natriuretic peptide concentrations and lower prevalence of moderate-to-severe mitral regurgitation in patients with HF-PEF, congestive symptoms at admission were as severe as in patients with HF-REF. There were no significant differences in in-hospital mortality between the HF groups. One-year mortality was high in both groups (17% in HF-PEF vs 21% in HF-REF, p = 0.22). There was a trend toward a lower frequency of the secondary end point in the HF-PEF group (32% vs 40%, p = 0.07). In conclusion, in clinical practice, even easily obtainable echocardiographic indexes of diastolic dysfunction are relatively rarely acquired. One-year survival rate of patients with HF-PEF is not significantly better than that of patients with HF-REF.

The prevalence of heart failure (HF) with preserved ejection fraction (HF-PEF) has increased over the last years, with a further increase to be anticipated due to aging of the population and a growing incidence of arterial hypertension, obesity, and type 2 diabetes.[1-3] In clinical practice, adequate echocardiographic evaluation of diastolic function tends to be neglected, as it necessitates a comprehensive examination, incorporating all relevant 2-dimensional, pulsed-wave Doppler (PWD) and tissue Doppler imaging (TDI) data.[4,5] Thus, HF-PEF becomes a diagnosis by exclusion, potentially leading to HF misdiagnosis in patients in whom the actual cause of dyspnea or diminished exercise capacity fails to be identified. Another problem in HF-PEF is the choice of optimal pharmacotherapy, as - so far - no treatment has been shown to improve survival in HF-PEF.[3,6,7,8] The aim of the study was to estimate the prevalence of HF-PEF in patients hospitalized for HF decompensation, to validate the pertinence of HF-PEF diagnosis in these patients, and to assess their clinical profile and outcomes in comparison to patients with HF with reduced EF (HF-REF).

Methods

The European Society of Cardiology (ESC) HF Long-Term Registry is an on-going, prospective, international, observational survey, with 211 cardiology centers from 21 European countries participating.[9] The Registry includes both chronic HF patients presenting to ambulatory care clinics and patients admitted to hospital for new-onset or worsening HF. All patients with a diagnosis of HF who are aged ≥18 years are eligible for enrollment. The survey was approved by local ethical review boards according to the regulations of each participating country. A signed, informed consent was obtained from each patient after providing him/her with detailed information on the Registry.

During phase I of the Registry, lasting from May 2011 to April 2013, patients were enrolled on 1 specific day of the week for 12 consecutive months in each of the participating centers. In phase II/III of the Registry (currently on-going), patients are enrolled during 5 consecutive days per trimester. Data on clinical characteristics, diagnostic tests performed, and implemented treatment are collected in the Registry. Electronic case report forms (eCRFs) enable to describe echocardiographically evaluated left ventricular (LV) diastolic function by (1) denominating whether LV filling pattern, assessed by PWD, is restrictive/pseudonormal or not (yes vs no); (2) entering the value of the early (E) to late (A) LV filling velocity ratio (E/A ratio); and (3) entering the value of wave E deceleration time. Information on the presence of LV hypertrophy (LVH) is given dichotomically (yes vs no). It is also possible to enter left atrial (LA) dimension (measured in parasternal long-axis view) and LA volume in the Registry's eCRF. All patients are followed for 12 months.

The current analysis included Polish patients hospitalized for HF, enrolled during phase I of the Registry. To discriminate between patients with HF-PEF and patients with HF-REF, the analysis included only those patients who had an echocardiographic examination (with EF assessment) performed during index hospitalization. Patients with an EF of ≥50% were included in the HF-PEF group, and patients with an EF of <50% were included in the HF-REF group.

To verify the pertinence of HF diagnosis in patients with EF ≥50%, we assessed whether they met the echocardiographic criteria for HF-PEF according to the 2012 ESC HF guidelines, that is, the presence of LVH and/or LA enlargement (defined as LA dimension of >40 mm and/or LA volume of >34 ml/m^2) and/or LV diastolic dysfunction (defined, for the sake of the current analysis, as restrictive/pseudonormal LV filling pattern and/or as E/A ratio of ≥2).[6] We also evaluated serum concentrations of B-type natriuretic peptide (BNP) and of N-terminal pro-BNP (NT-proBNP) in these patients, and, after 2012 ESC guidelines, adopted a threshold of ≥100 pg/ml for BNP levels and of ≥300 pg/ml for NT-proBNP as justifying HF suspicion in patients hospitalized for exacerbation of symptoms suggestive of HF.[6] We applied ESC guidelines, as the Registry was conducted in the European population.

The HF-PEF and HF-REF groups were compared with regard to clinical profile, initial presentation, diagnostic tests results, clinical course and management during index hospitalization, as well as in-hospital and 1-year outcomes.

The primary end point was all-cause death at 1 year. The secondary end point was a composite of all-cause death and hospital readmission for HF worsening at 1 year. We assessed the frequency of the primary and the secondary end points in both HF groups. In addition, we sought to determine predictors of the primary and the secondary end points separately for the HF-PEF and for the HF-REF group.

All statistical analyses were conducted using the SAS software, version 9.2 (SAS Institute Inc., Cary, NC). Normally distributed continuous variables were presented as mean (±SD), whereas ordinal variables and nonnormally distributed continuous variables were presented as median (interquartile range). The HF-PEF and HF-REF groups were compared using the Fisher's exact test for categorical variables and the Mann–Whitney test for continuous and ordinal variables. Kaplan–Meier curves were plotted for the primary and the secondary end points in both groups. To identify the predictors of the primary and the secondary end points, Cox proportional hazards regression analyses were performed. All variables predictive of the primary or the secondary end points in univariate analyses were consequently included in multivariate models. All tests were 2 tailed. For all tests, a p value of <0.05 was deemed significant.

Results

The final analysis included 661 Polish in-hospital patients with echocardiography performed during index hospitalization: 187 patients (28%) with EF of ≥50% (HF-PEF group) and 474 patients (72%) with EF of <50% (HF-REF group), as shown in Figure 1. In the studied cohort of 661 patients with HF, 229 subjects (35%) had EF of ≥45%, and 292 patients (44%) had EF of ≥40%.

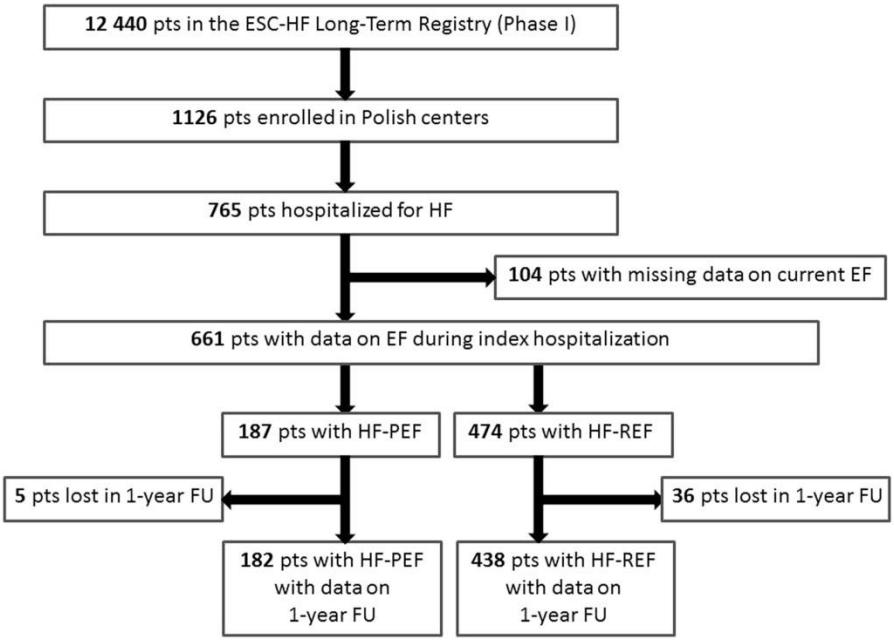

Figure 1. Flow chart of patient selection for the current analysis. FU = follow-up; pts = patients.

Baseline characteristics, clinical course of index hospitalization, management and diagnostic tests performed during hospitalization, as well as in-hospital and 1-year outcomes of patients with HF-PEF and HF-REF are presented in Table 1, Table 2, Table 3.

Detailed echocardiographic and laboratory characteristics of patients with HF-PEF are presented in Table 2. Of 187 patients in the HF-PEF group, 144 patients (77%) met the echocardiographic criteria for HF-PEF, as defined in the Methods section (i.e., the presence of LVH, LA dilation, restrictive/pseudonormal LV filling pattern, and/or E/A ratio of ≥2). This was mostly due to the presence of LVH (assessed in 183 patients [98%] and confirmed in 96 patients [51% of the whole HF-PEF group]) and LA dilation (assessed in 137 patients [73%] and confirmed in 94 patients [50% of the whole HF-PEF group]). The PWD mitral inflow velocity pattern was assessed in 116 (62%) of 187 patients in the HF-PEF group, with exact values of E/A ratio given only in 52 (28%) of 187 patients. Merely 37 patients (20% of the whole HF-PEF group) were classified as demonstrating a restrictive/pseudonormal LV filling pattern by the Registry's investigators. Deceleration time of the E wave was assessed only in 27 (14%) of the 187 patients.

Serum concentrations of NT-proBNP were measured in 62 (33%) of 187 patients with HF-PEF. Of those 62 patients, 57 patients (92%) had an NT-proBNP level of ≥300 pg/ml. Serum concentrations of BNP were evaluated in 33 (18%) of 187 patients with HF-PEF, all of them had a BNP level of ≥100 pg/ml. Of 187 patients from the HF-PEF group, 162 patients (87%) either met the prespecified echocardiographic criteria for HF-PEF or had an NT-proBNP level of ≥300 pg/ml or a BNP level of ≥100 pg/ml.

Of 620 patients with data on 1-year follow-up, 122 patients (20%) reached the primary end point: 30 patients in the HF-PEF group (including 3 patients who died during index hospitalization) and 92 patients in the HF-REF group (including 16 patients who died during index hospitalization), as presented in Table 3. The secondary end point was reached by 233 patients (38%; Table 3). Kaplan–Meier curves for the primary and the secondary end points in both HF groups are plotted in Figures 2 and 3, respectively. Univariate analyses of predictors of the primary and the secondary end points in both groups are presented in the Supplementary Material (Tables S1 and S2). Multivariate analyses of predictors of the primary and the secondary end points for the HF-PEF and the HF-REF group are presented in Table 4. Due to the lack of complete data for some of the patients in the Registry, multivariate models included only those patients for whom all required parameters were available, that is, 177 patients from the HF-PEF group and 420 patients from the HF-REF group for the primary end point analyses, and 176 patients from the HF-PEF group and 421 patients from the HF-REF group for the secondary end point analyses.

Table 1. Baseline clinical characteristics and previous pharmacotherapy in patients with heart failure with preserved ejection fraction (HF-PEF) and in patients with heart failure with reduced ejection fraction (HF-REF)

Variable	HF-PEF *(n=187)*	HF-REF *(n=474)*	*P*
Age (years)	77 (69-84)	67 (58-76)	**<0.0001**
Women	111 (59%)	110 (23%)	**<0.0001**
BMI (kg/m^2)	28.0 (25.4-32.4); n=186	27.6 (24.9-30.8); n=472	0.08
Last known EF before index hospitalization (%)	56 (50-60); n=102	30 (20-38); n=344	**<0.0001**
Last known EF (before index hospitalization) ≥50%	83/102 (81%)	14/344 (4%)	**<0.0001**
Primary described as HF-PEF	20 (11%)	0 (0%)	**<0.0001**
Primary ischemic etiology of HF	62 (33%)	304 (64%)	**<0.0001**
Dilated cardiomyopathy	2 (1%)	96 (20%)	**<0.0001**
Tachycardia-related cardiomyopathy	6 (3%)	14 (3%)	0.81
Previous HF diagnosis	148/186 (80%)	406/473 (86%)	0.06
Previous HF hospitalization	78/186 (42%)	265/473 (56%)	**0.001**
Hypertension	149 (80%)	325/472 (69%)	**0.005**
Coronary artery disease	69 (37%)	293 (62%)	**<0.0001**
Prior PCI or CABG	31 (17%)	201/472 (43%)	**<0.0001**
Previously implanted ICD	3 (2%)	87 (18%)	**<0.0001**
Previously implanted CRT	1 (0.5%)	37 (8%)	**<0.0001**
Pacemaker	16 (9%)	23 (5%)	0.10
History of atrial fibrillation	101 (54%)	204 (43%)	**0.01**
Prior stroke or TIA	24 (13%)	43 (9%)	0.15
Peripheral artery disease	32/186 (17%)	70/473 (15%)	0.47
Diabetes	61 (33%)	170 (36%)	0.47
Chronic kidney disease	52 (28%)	143 (30%)	0.57
Sleep apnea	21/185 (11%)	15/466 (3%)	**<0.0001**
Chronic obstructive pulmonary disease	27 (14%)	70/473 (15%)	1.00
Current smoker	8 (4%)	77 (16%)	**<0.0001**
Current or former smoking	69 (37%)	307 (65%)	**<0.0001**
Loop diuretic	100 (54%)	319 (67%)	**0.001**
Thiazide diuretic	21 (11%)	23 (5%)	**0.005**
Aldosterone antagonist	57 (31%)	250 (53%)	**<0.0001**
ACE-I	100 (54%)	317 (67%)	**0.002**
ARB	24 (13%)	32 (7%)	**0.02**
Nitrates	22 (12%)	54 (11%)	0.89
β-blocker	133 (71%)	366 (77%)	0.11
Calcium channel blocker	41 (22%)	55 (12%)	**0.001**
Ivabradine	0 (0%)	3 (0.6%)	0.56
Digoxin	26 (14%)	97 (21%)	0.06
Amiodarone	11 (6%)	51 (11%)	0.06
Statin	97 (52%)	271 (57%)	0.23
Antiplatelets	90 (48%)	271 (57%)	**0.04**
Anticoagulants	60 (32%)	156 (33%)	0.86
Insulin	28 (15%)	67 (14%)	0.81

Bold indicates p values of <0.05.
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; CRT = cardiac resynchronization therapy; EF = ejection fraction; HF = heart failure; ICD = implantable cardioverter–defibrillator; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

Table 2. Clinical and laboratory status at hospital admission, and echocardiographic findings during index hospitalization in patients with heart failure with preserved ejection fraction (HF-PEF) and in patients with heart failure with reduced ejection fraction (HF-REF)

	HF-PEF *(n=187)*	HF-REF *(n=474)*	*P*
Cardiogenic shock	2 (1%)	14 (3%)	0.26
NYHA class	3 (3-4)	3 (3-4); n=471	
I	0 (0%)	0 (0%)	
II	41 (22%)	103/471 (22%)	0.93
III	83 (44%)	212/471 (45%)	
IV	63 (34%)	156/471 (33%)	
Pulmonary rales	126 (67%)	298 (63%)	0.28
Pulmonary congestion/alveolar oedema on chest X-ray	59/97 (61%)	136/222 (61%)	1.00
Right ventricular HF	17 (9%)	14 (3%)	**0.002**
Peripheral oedema	101 (54%)	239 (50%)	0.44
Systolic blood pressure (mmHg)	135 (120-160)	120 (110-140)	**<0.0001**
Diastolic blood pressure (mmHg)	80 (70-90)	75 (70-80); n=473	**0.0009**
Heart rate (b.p.m.)	80 (70-100)	80 (70-100)	0.72
Paced heart rhythm (ECG)	11/186 (6%)	56/469 (12%)	**0.02**
AF (ECG)	70/186 (38%)	111/469 (24%)	**<0.0001**
AF as a cause of admission	64 (34%)	139 (29%)	0.23
VF or VT as a cause of admission	10 (5%)	55 (12%)	**0.01**
ACS as a cause of admission	6 (3%)	71 (15%)	**<0.0001**
Uncontrolled hypertension as a cause of admission	44 (24%)	38 (8%)	**<0.0001**
Renal dysfunction as a cause of admission	20 (11%)	62 (13%)	0.44
NT-proBNP (pg/ml)	1852 (722-5286); n=62	4085 (1691-8675); n=203	**0.0001**
BNP (pg/ml)	217 (116-479); n=33	656 (249-1337); n=64	**0.0004**
Serum sodium (mmol/l)	140 (137-142); n=185	139 (137-141); n=472	**0.005**
Serum creatinine (mg/dl)	1.02 (0.84-1.27); n=185	1.14 (0.91- 1.43); n=472	**0.0003**
Hemoglobin (g/dl)	13.3 (11.8-14.3); n=185	13.5 (12.2-14.6); n=469	**0.03**
Echocardiography			
Ejection fraction (%)	55 (50-60)	30 (21-38)	**<0.0001**
LVEDD (mm)	48 (43-52); n=173	60 (54-70); n=444	**<0.0001**
Left ventricular hypertrophy	96/183 (53%)	165/446 (37%)	**0.0005**
E/A ≥2	2/52 (4%)	42/135 (31%)	**<0.0001**
E/A <1	33/52 (64%)	64/135 (47%)	0.05
E/A [1-2)	17/52 (33%)	29/135 (22%)	0.13
Restrictive/pseudonormal pattern*	37/116 (32%)	150/319 (47%)	**0.006**
Deceleration time (ms)†	203 (140-290); n=27	149 (108-218); n=64	**0.04**
LA dimension (mm)	47 (40-54); n=94	48 (43-52); n=229	0.71
LA dimension >40 mm	70/94 (75%)	193/229 (84%)	0.71
LA volume (ml)	73 (45-110); n=43	55 (45-90); n=66	0.36
LA volume >34 ml/m^2	24/43 (56%)	26/65 (40%)	0.12
Aortic stenosis‡	25/185 (14%)	31/466 (7%)	**0.008**
Aortic regurgitation‡	13/186 (7%)	43/465 (9%)	0.44
Mitral regurgitation‡	79/185 (43%)	272/466 (58%)	**<0.0001**
Tricuspid regurgitation‡	72/186 (39%)	199/466 (43%)	0.38

Bold indicates p values of <0.05.
ACS = acute coronary syndrome; AF = atrial fibrillation; BNP = B-type natriuretic peptide; E/A = early to late left ventricular filling velocity ratio; ECG = electrocardiogram; LA = left atrium; LVEDD = left ventricular end-diastolic diameter; NTproBNP = N-terminal proBNP; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.
* Of mitral inflow.
† Of the E wave.
‡ Moderate or severe.

Table 3. Management during index hospitalization, clinical status, laboratory findings and pharmacotherapy at discharge, as well as in-hospital and long-term outcomes of patients with heart failure with preserved ejection fraction (HF-PEF) and of patients with heart failure with reduced ejection fraction (HF-REF)

Variable	HF-PEF *(n=187)*	HF-REF *(n=474)*	*P*
Inotropic support	9 (5%)	82/472 (17%)	**<0.0001**
Intravenous nitrates	25 (13%)	56/471 (12%)	0.60
Intravenous diuretics	106 (57%)	289/472 (61%)	0.29
Coronary angiography	24 (13%)	160/471 (34%)	**<0.0001**
PCI/CABG	10 (5%)	75/472 (16%)	**<0.0001**
Holter-ECG	67 (36%)	164/470 (35%)	0.86
Exercise test	18/176 (10%)	63/463 (14%)	0.29
Heart rate (b.p.m.) *	70 (65-80)	70 (65-80)	0.89
Systolic blood pressure (mmHg)*	120 (110-130)	115 (105-125)	**<0.0001**
NYHA class*	2 (2-3)	2 (2-3)	**0.002**
I	11 (6%)	16 (4%)	
II	126 (69%)	268 (59%)	
III	45 (25%)	165 (36%)	
IV	2 (1%)	9 (2%)	
Serum creatinine (mg/dl)*	1.05 (0.88-1.31); n=137	1.12 (0.94-1.41); n=354	**0.04**
Loop diuretic*	134 (73%)	390 (85%)	**0.0004**
Thiazide diuretic*	16 (9%)	18 (4%)	**0.02**
Aldosterone antagonist*	92 (50%)	345 (75%)	**<0.0001**
ACE-I*	114 (62%)	377 (82%)	**<0.0001**
ARB*	30 (16%)	33 (7%)	**0.001**
Nitrates*	16 (9%)	49 (11%)	0.56
β-blocker*	151 (82%)	428 (94%)	**<0.0001**
Bisoprolol*	58 (32%)	143 (31%)	1.00
Carvedilol*	29 (16%)	193 (42%)	**<0.0001**
Metoprolol*	41 (22%)	55 (12%)	**0.001**
Nebivolol*	14 (8%)	34 (7%)	1.00
Target β-blocker dose reached†	10 (5%)	38 (8%)	0.25
Calcium channel blocker*	51 (28%)	51 (11%)	**<0.0001**
Ivabradine*	0 (0%)	6 (1%)	0.19
Digoxin*	33 (18%)	119 (26%)	**0.03**
Amiodarone*	11 (6%)	69 (15%)	**0.001**
Statin*	111 (60%)	332 (73%)	**0.003**
Antiplatelets*	91 (50%)	304 (66%)	**0.0001**
Anticoagulants*	90 (49%)	202 (44%)	0.29
Insulin*	29 (16%)	76 (17%)	0.91
Hospitalization length (days)	7 (4-10)	7 (4-12)	0.26
Death during hospitalization	3 (1.6%)	16 (3.4%)	0.30
Death at 1 year	30/182 (17%)	92/438 (21%)	0.22
Death or rehospitalization at 1 year	58/182 (32%)	175/438 (40%)	0.07

Bold indicates p values of <0.05.
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; ECG = electrocardiogram; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.
∗ At discharge (in patients who survived to hospital discharge, i.e., in 184 patients with HF-PEF, and in 458 patients with HF-REFs).
† That is: bisoprolol ≥10 mg daily, carvedilol ≥50 mg daily, metoprolol ≥200 mg daily, or nebivolol ≥10 mg daily.

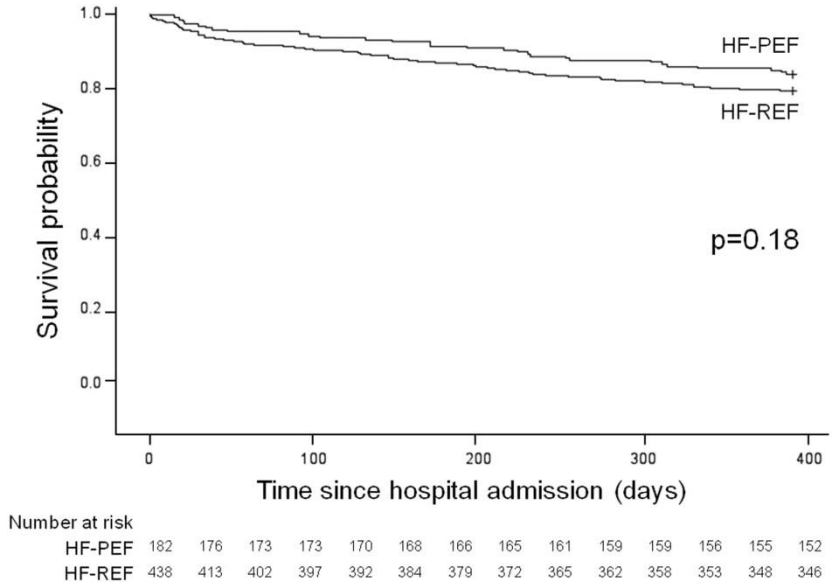

Figure 2. Kaplan–Meier curves for the primary end point in patients with HF-PEF and in patients with HF-REF.

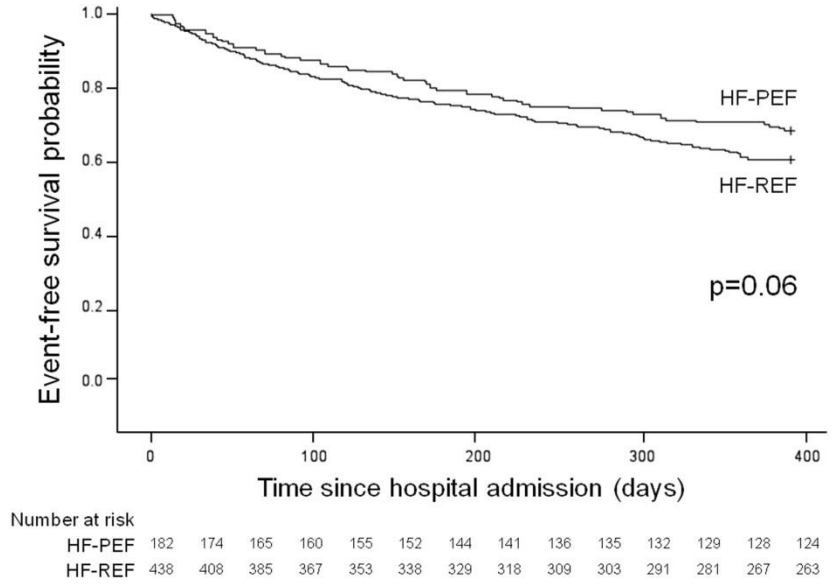

Figure 3. Kaplan–Meier curves for the secondary end point in patients with HF-PEF and in patients with HF-REF.

Table 4. Multivariate analyses of predictors of the primary and the secondary end points in patients with heart failure with preserved ejection fraction and in patients with heart failure with reduced ejection fraction

	Primary endpoint		Secondary endpoint	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Heart failure with preserved ejection fraction				
Age (per 10 years)	**2.04 (1.09-3.81)**	**0.03**	1.37 (0.91-2.04)	0.13
History of atrial fibrillation	-	-	2.22 (0.87-5.65)	0.096
NYHA class* (per 1 class)	**2.91 (1.31-6.47)**	**0.009**	**2.35 (1.32-4.18)**	**0.004**
Heart rate* (per 10 b.p.m.)	-	-	0.96 (0.83-1.13)	0.65
Aortic stenosis†	**3.73 (1.10-12.62)**	**0.04**	**3.44 (1.18-9.98)**	**0.02**
Tricuspid regurgitation†	2.49 (0.91-6.78)	0.07	1.13 (0.46-2.75)	0.80
Serum sodium* (per 1 mmol/l)	-	-	**0.91 (0.84-0.999)**	**0.047**
Serum creatinine* (per 1 mg/dl)	1.68 (0.74-3.82)	0.22	2.02 (0.88-4.63)	0.096
Hemoglobin* (per 1 g/dl)	0.84 (0.66-1.08)	0.17	0.93 (0.75-1.15)	0.49
Heart failure with reduced ejection fraction				
Age (per 10 years)	**1.45 (1.15-1.83)**	**0.002**	-	-
Women	-	-	**1.95 (1.17-3.25)**	**0.01**
Peripheral artery disease	1.69 (0.85-3.33)	0.13	**2.22 (1.19-4.15)**	**0.01**
Chronic obstructive pulmonary disease	-	-	1.37 (0.76-2.47)	0.30
NYHA class* (per 1 class)	**1.89 (1.26-2.85)**	**0.002**	**1.60 (1.15-2.22)**	**0.005**
Systolic blood pressure* (per 10 mmHg)	0.96 (0.87-1.07)	0.47	0.98 (0.89-1.07)	0.65
Heart rate* (per 10 b.p.m.)	-	-	1.06 (0.98-1.15)	0.17
Ejection fraction (per 5%)	**0.85 (0.73-0.99)**	**0.04**	**0.87 (0.77-0.98)**	**0.02**
Aortic regurgitation†	1.90 (0.87-4.12)	0.11	1.72 (0.82-3.60)	0.15
Mitral regurgitation†	1.19 (0.67-2.11)	0.56	1.18 (0.73-1.88)	0.50
Tricuspid regurgitation†	0.92 (0.52-1.63)	0.78	1.02 (0.63-1.64)	0.94
Serum sodium* (per 1 mmol/l)	**0.92 (0.86-0.97)**	**0.004**	0.99 (0.94-1.04)	0.64
Serum creatinine* (per 1 mg/dl)	1.11 (0.80-1.54)	0.54	-	-
Hemoglobin* (per 1 g/dl)	0.94 (0.82-1.08)	0.39	-	-
PCI/CABG during hospitalization	-	-	0.61 (0.30-1.23)	0.17
ACE-I or ARB‡	-	-	**0.40 (0.21-0.76)**	**0.006**

Bold indicates p values of <0.05.
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.
∗ At hospital admission.
† Moderate or severe.
‡ At hospital discharge.

Discussion

In the presented analysis, the prevalence of HF-PEF among hospitalized HF patients was 28%, 35%, and 44%, depending on the cut-off value for "preserved" EF (≥50%, ≥45%, and ≥40%, respectively). This is similar to HF-PEF prevalence observed in the whole population of hospitalized ESC-HF Long-Term Registry patients (31% for "preserved" EF threshold of >45%).[9] Data from previously published studies demonstrate that the proportion of patients with HF-PEF among all patients with HF varies widely from 25% to 71%, depending on the adopted threshold for "preserved" EF, as well as on the clinical setting and study type.[1,2,3,10,11,12] In previous large, prospective registries, patients with preserved EF constituted approximately half of patients hospitalized for acute HF.[13,14,15]

The echocardiographic criteria for HF-PEF we adopted in the current analysis were fairly mild, that is, required the presence of only one of the abnormalities suggestive of LV diastolic dysfunction, including the presence of LA dilation, which is very unspecific for LV diastolic dysfunction and might be attributable to a number of other conditions, such as hypertension or atrial fibrillation (both highly prevalent in the population studied).[4,5,16,17] Still, almost one quarter of the HF-PEF group in our study did not fulfill those mild echocardiographic criteria. Furthermore, the diagnosis of HF-PEF was actually confirmed by the presence of restrictive/pseudonormal mitral inflow pattern in merely 20% of patients. Thus, the remaining 80% of patients with EF ≥50% and no convincing evidence for significant LV diastolic dysfunction might have been misdiagnosed with HF. Possibly, some of those patients were classified as HF-PEF based on the E/A ratio of <1, which may be indicative of impaired LV relaxation.[4,5] However, it has been well established that in healthy persons aged >60 years, the E/A ratio decreases below 1 (together with a prolongation of the E wave deceleration time).[4,5,18] Therefore, the diagnosis of HF-PEF based solely on the value of E/A ratio <1 in patients more than 60 years old is not justified (median age in the studied HF-PEF group was 77 years). According to the present guidelines, evaluation of LV diastolic function in patients with suspected HF-PEF should be largely based on the estimation of TDI-assessed early diastolic velocities of mitral annulus (e') and the E/e' ratio.[4,5,6] Unfortunately, the eCRF of the ESC-HF Long-Term Registry did not allow entering TDI-derived measurements.

The clinical profile of patients with preserved EF in our analysis corresponds to the previously described characteristics of HF-PEF population, with a higher prevalence of hypertension, atrial fibrillation, obesity, and female gender, and patients being older compared with HF-REF population.[2,3,10,11,12,13,14,15,19,20] Interestingly, although coronary artery disease (CAD) is a risk factor for the development of diastolic dysfunction, this ultimately progresses to systolic dysfunction in a vast number of patients with CAD; thus, the observed prevalence of CAD is higher in patients with HF-REF than in patients with HF-PEF.[2,12,13,14,21,22] Of note, many patients with HF-PEF may in fact exhibit impaired longitudinal and circumferential systolic LV function, despite preserved global EF.[20,23] Importantly, HF-PEF is typically accompanied by a number of noncardiac co-morbidities (including diabetes, sleep apnea, chronic obstructive pulmonary disease, chronic kidney disease, and anemia), which - on one hand - might be involved in its development, and - on the other hand - deteriorate prognosis in HF.[2,10,12,21,24,25]

Despite preserved EF, lower prevalence of moderate-to-severe mitral regurgitation and lower BNP/NT-proBNP concentrations on hospital admission, the severity of congestive symptoms in patients presenting with HF-PEF was similar to that observed in HF-REF. Consequently, the proportion of patients receiving intravenous nitrate or diuretic treatment was comparable in both HF groups. Nevertheless, patients with HF-REF more often required inotropic support.

In-hospital mortality rate of patients with HF-PEF was twice as low as of patients with HF-REF, but due to the low number of events, the difference did not reach statistical significance. Among patients who survived to hospital discharge, subjects with HF-PEF were characterized by a better functional status at discharge than those with HF-REF. However, no evident benefit in terms of 1-year mortality was demonstrated for the HF-PEF group. Previous studies have brought inconsistent results on survival in patients with HF-PEF compared with HF-REF, with similar prognosis in both HF groups demonstrated predominantly in epidemiological studies and registries, and with a 32% lower risk of death in HF-PEF in

a meta-analysis including randomized clinical trials.[2,3,10,11,12,13,14,15,21,26,27] According to previously published analyses, the most important risk factors for reduced survival in HF-PEF include advanced age, male gender, CAD, a greater noncardiac co-morbidity burden, renal impairment, hyponatremia, and both very high (≥35 kg/m^2) and normal-to-low (<23.5 kg/m^2) body mass index.[14,26,28,29,30] To date, none of the medications routinely used in HF-REF has shown efficacy in improving prognosis of patients with HF-PEF.[3,6,7,8]

The limitations of our study arise largely from the type of data (i.e., registry derived) we analyzed. First, there was a certain proportion of data missing for some of the patients. Second, the eCRF enabled investigators to enter only data predefined by the coordinators of the registry. In terms of evaluation of diastolic function, those were limited to PWD-assessed parameters of mitral inflow. Regretfully, no data on other important indexes of diastolic function were gathered in the registry. Therefore, definitive verification of the pertinence of HF-PEF diagnosis was not possible. Moreover, we were not able to assess how often each of those parameters is actually implemented in everyday clinical practice.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data related with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2016.05.046.

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