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ORIGINAL ARTICLE

Baseline characteristics of 547 new onset heart failure patients in the PREFERS heart failure study

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Abstract

Aim We present the baseline characteristics of the PREFERS Stockholm epidemiological study on the natural history and course of new onset heart failure (HF) aiming to improve phenotyping focusing on HF with preserved left ventricular ejection fraction (HFpEF) pathophysiology.

Methods and results *New onset* HF patients diagnosed in hospital or at outpatient HF clinics were included at five Stockholm hospitals 2015–2018 and characterized by N-terminal pro brain natriuretic peptide (NT-proBNP), biomarkers, echocardiography, and cardiac magnetic resonance imaging (subset). HFpEF [left ventricular ejection fraction (LVEF) $\geq$ 50%] was compared with HF with mildly reduced LVEF (HFmrEF; LVEF 41–49%) and with HF with reduced LVEF (HFrEF; LVEF $\leq$ 40%). We included 547 patients whereof HFpEF (n = 137; 25%), HFmrEF (n = 61; 11%), and HFrEF (n = 349; 64%). HFpEF patients were older (76; 70–81 years; median; interquartile range) than HFrEF (67; 58–74; $P < 0.001$), more often women (49% vs. 30%; $P < 0.001$), and had significantly higher comorbidity burden. They more often had atrial fibrillation, hypertension, and renal dysfunction. NT-proBNP was lower in HFpEF (896; 462–1645 ng/L) than in HFrEF (1160; 563–2370; P = 0.005). In HFpEF, left ventricular (LV) diameters and volumes were smaller ($P < 0.001$) and septal and posterior wall thickness and relative wall thickness higher ($P < 0.001$). E/é $\geq$ 14 was present in 26% of HFpEF vs. 32% of HFrEF (P = 0.017) and left atrial volume index $>$ 34 mL/m^2 in 57% vs. 61% (P = 0.040). HFmrEF patients were intermediary between HFpEF and HFrEF for LV mass, LV volumes, and RV volumes but had the highest proportion of left ventricular hypertrophy and the lowest proportion of elevated E/é.

Conclusions Phenotype data in *new onset* HF patients recruited in a broad clinical setting showed that 25% had HFpEF, were older, more often women, and had greater comorbidity burden. PREFERS is well suited to further explore biomarker and imaging components of HFpEF pathophysiology and may contribute to the emerging knowledge of HF epidemiology.
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Keywords Heart failure; Preserved ejection fraction; Epidemiology; Diastolic function

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Introduction

The prevalence of heart failure (HF) remains high and is associated with high morbidity and mortality and with poor quality of life (QoL). HF is classified according to left ventricular ejection fraction (LVEF) as preserved (≥50%; HFpEF), mildly reduced (HFmrEF; 41–49%[1] or 40–49%),[2] and reduced (HFrEF; ≤40%[1] or <40%[2]). The relative proportion of HFpEF is increasing, lacks evidence-based therapy[2] but carries similar high risks for HF readmissions and all-cause mortality as HFrEF. It has been suggested that the pathophysiology for HFpEF differs from that of HFrEF, explaining why drugs to decrease neurohormonal activation have not been proven beneficial. In HFrEF, HF disease is initiated in the myocardium and inflammation develops as HF progresses. In contrast, HFpEF may be initiated and driven by comorbidity induced systemic, chronic inflammation, and metabolic factors leading to microvascular and endothelial dysfunction in turn resulting in cardiac fibrosis.[3] Thus, the unique pathophysiological features of HFpEF need to be identified to design effective therapies in HFpEF.[4]

We have previously characterized HFpEF patients in stable condition.[5] Because few studies focused on *new onset* HF with respect to HF phenotype, we initiated this phenotyping study, the PREFERS study.[6] The aim was to combine detailed phenotyping with comprehensive studies of circulating biomarkers, including proteomics and metabolomics reflecting different pathways, as well as genetic studies to help find pathophysiologic mechanisms of new onset HF over the full range of LVEF and to contribute to the identification of novel drug targets for HFpEF.

The aim of this paper was to describe patient characteristics of new onset HF with respect to LVEF category.

Methods

Between 2015 and 2018, new onset HF patients diagnosed in hospital or at outpatient HF clinics at all five major hospitals in Stockholm were offered to participate in the PREFERS Stockholm study (Preserved and Reduced Ejection Fraction Epidemiological Regional Study) following written informed consent.[6] The study protocol was approved by the Regional Ethics Review Board, Stockholm, was descriptive and did not include treatments or interventions outside of ordinary care. In short, patients were included if they had previously undiagnosed HF and had symptoms of HF and an elevated NT-proBNP, that is, of >300 ng/L for patients hospitalized with acute HF and >125 ng/L for patients with new onset HF in the outpatient setting. Among exclusion criteria were HF primarily due to valvular disease, hypertrophic obstructive cardiomyopathy, infiltrative cardiomyopathy (eGFR < 30 mL/min/1.73 m^2), or moderate–severe anaemia (haemoglobin level < 90 g/L).

Clinical care and measurements

The patients were treated according to a structured regional guideline.[2,7] All clinical assessments and data entry were made by an HF physician and an HF nurse on the average 2–4 weeks after a de novo HF hospital admission or at the first outpatient visit for new onset HF in the HF outpatient clinics. All variables were developed for a clinical HF improvement programme and extracted in a standardized format from the electronic patient data files.[7] Cardiac magnetic resonance imaging (cMRI) was performed in a pre-specified subset of 10%.[6]

Doppler-echocardiographic and cardiac magnetic resonance imaging measurements

We present results according to the recently proposed *Universal definition and classification of heart failure* (HFmrEF; LVEF 41–49% and HFrEF ≤ 40%)[1] and the *2016 ESC HF guidelines* (HFmrEF; LVEF 40–49% and HFrEF < 40%)[2] although our original study design[6] used LVEF < 45% defined HFrEF and ≥45% HFpEF. Left ventricular hypertrophy (LVH) was defined as left ventricular mass index > 95 g/m^2 in women and >115 g/m^2 in men. E/é ratio was calculated using the average between septal and lateral é as ≥ 13[2] and as > 14 according to more recent recommendations.

Cardiac magnetic resonance imaging used late gadolinium enhancement for myocardial scar detection and quantitative myocardial tissue characterization (T1-mapping; ms), and extracellular volume (ECV, %) to differentiate between focal scar, diffuse myocardial fibrosis, and presence or absence of focal or global inflammation/oedema.[6] We report myocardial scar or diffuse myocardial fibrosis by measuring T1 and ECV in remote myocardium.

Quality of life measurements, blood tests, and biobank

We used a generic QoL questionnaire the EQ-5D[8] and an HF disease-specific MLHFQ (Minnesota Living with heart failure questionnaire).[9] EQ-5D has five subscales (the higher the score the worse QoL) and visual analogue scale, rating 0–100 mm (the higher the score the better QoL). Blood sampling procedures were described in the design paper.[6] In short, blood was biobanked for analyses of proteomic, metabolomic, as well as genetic studies. In this report, we present routine laboratory results and will reveal full biomarker data at a later stage.

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Comparison with other new onset heart failure cohorts Swedish and international

We compared our data with a cohort of patients from Swedish National Heart Failure registry (SwedeHF) that enrols patients with clinician-judged HF. This comparative cohort had a recent onset HF defined as onset $<$ 6 months and were registered at hospital clinics during the same time-period as PREFERS (1 January 2015 to 31 December 2018).

Statistical analysis

The pre-specified calculation of study power and sample size for PREFERS has been previously described.[6] In brief, we hypothesized that HFpEF is characterized by collagen synthesis reflected by procollagen type 1 (PICP) and HFrEF by collagen degradation reflected by carboxytermal telopeptide collagen type I (CITP). To detect a 20% difference between phenotypes (at the time of study design defined as HFpEF $\geq$ 45%, HFrEF $<$ 45%) with 80% power, we needed 250 patients in each group to obtain samples from 200 per group allowing dropouts. A recalculation to a LVEF cut-off of 50% was performed. With an objective to detect a difference of mean PICP by 10 ng/mL and mean CITP by 1 ng/mL between HFpEF (LVEF $\geq$ 50%) (30%) and HFrEF (LVEF $<$ 50%) (70%), the needed number of study participants (*n*) to achieve study power of 90% would be 363 patients (for PICP) and 449 patients (for CITP).

Electronic patient records, echocardiography, 12-lead ECG, and cMRI data[6] were compiled in a common database for analysis. Continuous variables are expressed as median and interquartile range (Q1; Q3) and categorical variables as number (*n*) and percentage (%). A *P* value $<$ 0.05 was considered statistically significant. Comparisons between two groups were performed using Mann–Whitney *U*-test and Fisher's exact test and between three groups using Kruskal–Wallis test and χ^2 test as appropriate. The analyses were carried out in SAS software Version 9.4 (SAS Institute, Cary, NC, USA). Comparisons with SwedeHF were performed by χ^2 and Mann–Whitney *U*-test in R Version 4.0.2 (2020-06-22) (R Core Team 2019).

Results

Flowchart

From December 2015 to June 2019, a total of 564 patients were consented, and 547 were eligible after meeting the inclusion and none of the exclusion criteria (*Figure 1*). Of these, *n* = 137 (25%) were HFpEF, *n* = 61 (11%), HFmrEF (LVEF 41–49%), and 349 (64%) HFrEF (LVEF $\leq$ 40%) (*Figure 1*) Most patients (395/547; 72%) were enrolled at the HF outpatient clinics (*Table 1*) and the remainder (152/547; 28%) during a de novo HF hospital admission or at discharge. Blood sampling was performed on average after 2–4 weeks.

Patient characteristics

Baseline characteristics are given in *Table 1*, whereas the results according to the 2016 ESC HF guidelines[2] are displayed in Supporting Information, *Table S1*.

Heart failure with preserved left ventricular ejection fraction compared with HFrEF patients were older, more commonly women, and with higher body mass index (*Table 1*). More HFpEF patients had a history of atrial fibrillation, diabetes, pulmonary disease, peripheral artery disease, and hypertension. In contrast, few with HFpEF had a history of coronary revascularization. HFpEF and HFmrEF were associated with higher systolic blood pressure and more peripheral oedema and HFrEF with higher heart rate. The majority with HFrEF and HFmrEF were treated with renin angiotensin inhibitors, angiotensin II receptor inhibitors, or angiotensin receptor-neprilysin inhibitor (92% and 93%, respectively) compared with 70% of HFpEF patients. Thiazides, calcium antagonists, and oral anticoagulants were more commonly prescribed in HFpEF.

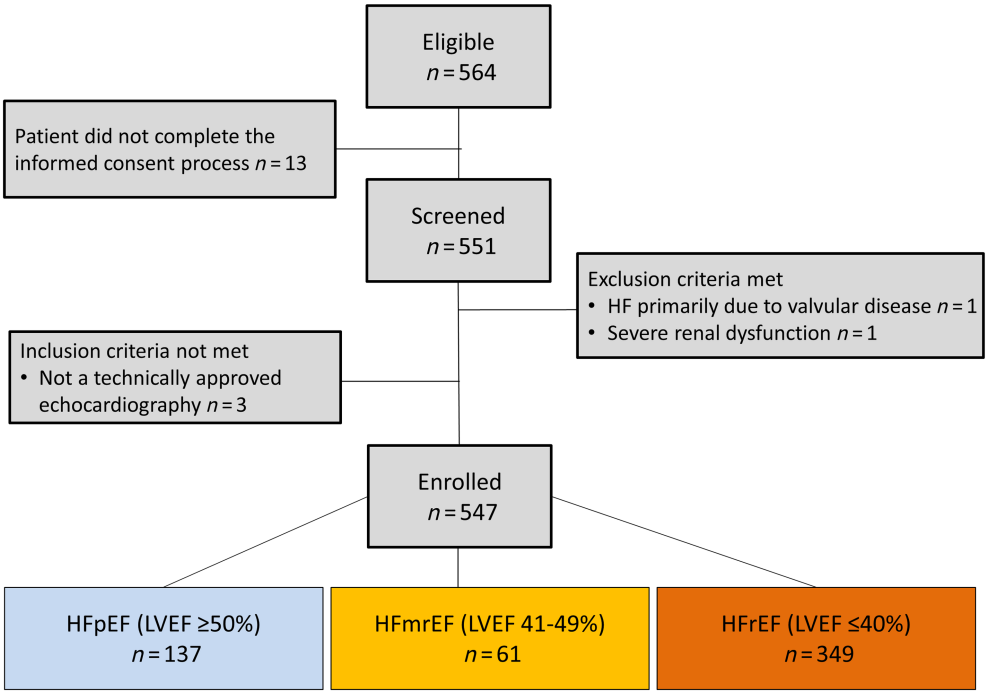
Patients with HFpEF had lower eGFR (*Table 2*) haemoglobin and more commonly had anaemia than HFrEF patients. High-sensitive CRP was higher in HFpEF. ECG revealed (*Table 2*) significantly more AF in 43% in HFpEF and 34% in HFmrEF compared with 29% in HFrEF. QRS width and QTc was significantly longer in HFmrEF and HFrEF patients. Laboratory results and ECG according to the ESC HF guidelines HF definition from 2016 are given in *Table S2*.

When comparing these results with those using the 2016 ESC guidelines definition, a total of 41 patients with LVEF 40% were moved from HFrEF to HFmrEF. With this definition, HFmrEF (*n* = 102) vs. HFpEF patients (*n* = 137)[1] were younger (71 vs. 76 years), less often had a history of AF or hypertension, and had higher haemoglobin and eGFR overall resembling HFrEF (LVEF $\leq$ 40%; *n* = 308). Compared with HFpEF, HFmrEF had slightly higher proportion of CAD and LDL. HFmrEF patients had the lowest NT-proBNP compared with both HFpEF and HFrEF (730 vs. 896 and 1210 ng/L; $P < 0.001$) (*Tables S1–S2*).

Distribution and number of comorbidities

The presence and distribution of common comorbidities by HF type and according to sex (females patients *n* = 191, male patients *n* = 356) is given in the Central Illustration. The total number of comorbidities were higher in HFpEF (31% with more than or equal to four comorbidities) compared with

Figure 1 Flow chart of the patents in the PREFERS study. Distribution by HF type.[1] HF, heart failure; HFmrEF, heart failure with mildly reduced left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; LVEF, left ventricular ejection fraction.



HFmrEF (18%) and HFrEF (11%; $P < 0.001$) (*Figure S1*). Two HFpEF patients (1.5%), compared five HFmrEF (8%), and 50 (14%) of HFrEF patients had none. In HFpEF, 30% of women and 31% of men had more than or equal to four comorbidities ($P = 0.855$). In HFmrEF, the corresponding numbers for women and men were 6% and 23% ($P = 0.150$) and in HFrEF 7% and 12%, respectively ($P = 0.131$).

Doppler-echocardiographic and cardiac magnetic resonance imaging data

Doppler-echocardiographic data were available in all patients and cMRI in 50 patients (*Table 3*). Median LVEF was 55% in HFpEF (Q1; Q3:53; 60%), 45% in HFmrEF (43; 46%) and 30% (25; 35%) in HFrEF. LV end-diastolic and systolic diameter and volumes were smaller in HFpEF than in HFrEF. HFpEF patients had significantly thicker septum and posterior wall, and higher relative wall thickness, but significantly smaller LV size (diameter and volume). Therefore, the HFpEF group had a significantly lower LV mass index than HFrEF, both overall and corrected for sex. LVH was significantly more often present in HFrEF vs. HFpEF and was more often eccentric in HFrEF and concentric in HFpEF. LAVI ≥ 34 was fulfilled in 57% of HFpEF patients and 61% with HFrEF. One-third of both HF phenotypes had elevated E/é ≥ 13 (36% of HFpEF and 37% of HFrEF; $P = 0.023$) or >14 (26% of HFpEF and 32% of HFrEF; $P = 0.017$) (*Table 3*). HFmrEF patients were intermediary between HFpEF and HFrEF for LV mass, LV volumes, and right ventricular (RV) volumes but had the highest proportion of LVH and the lowest proportion of elevated E/é. Among HFpEF patients, 73% thus fulfilled the echocardiographic ESC HFpEF criteria.[2]

Right ventricular size and function (tricuspid annular plane systolic excursion) were preserved in HFpEF and significantly different compared with HFrEF which may suggest higher presence of RV failure in HFrEF. Reflecting our exclusion criteria mitral regurgitation grade ≥ 2 was uncommon especially in HFpEF and HFmrEF, present only in 8% and 10%, respectively, vs. 27% in HFrEF ($P < 0.001$). Tricuspid regurgitation of grade ≥ 2 was found to the same extent in HFpEF (18%), HFmrEF (15%), and HFrEF (17%; $P = 0.863$).

A total of 50 patients underwent cMRI: 14 (10%) of all HFpEF patients, 6 (10%) of HFmrEF, and 30 (9%) of the HFrEF patients (*Table 3*). Small myocardial scars in the LV myocardium indicating a previous myocardial infarction were observed in all phenotypes. Of five HFpEF patients with myocardial scaring, one patient had a history of MI compared with 2 of 4 with HFmrEF and 3 of 8 HFrEF patients. One HFrEF patient had a history of MI but with no scar tissue found on cMRI. Imaging results presented according to the universal classification of HF, the ESC HF guidelines, and our initial study design are given in *Table 3*.

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Table 1 Clinical characteristics HF PREFERS patients categorized according to the proposed universal classification of HF

	HFpEF (LVEF ≥ 50%) *n* = 137		HFmrEF (LVEF 41–49%) *n* = 61		HFrEF (LVEF ≤ 40%) *n* = 349			
Demographics	*n*	%	*n*	%	*n*	%	*P* value overall	*P* value HFpEF vs. HFrEF
Enrolled during HF hospitalization	38	28	10	16	104	30	0.098	0.653
Age (years)	76	[70, 81]	71	[63, 77]	67	[58, 74]	<**0.001**	<**0.001**
Sex (females)	67	49	18	30	106	30	<**0.001**	<**0.001**
Smoking ever	51	37	21	34	126	36	0.234	0.207
Height (cm) median [IQR]	171	[164, 178]	176	[169, 182]	176	[168, 182]	<**0.001**	<**0.001**
Weight (kg) median [IQR]	82	[75, 96]	86	[71, 96]	80	[72, 93]	0.511	0.311
Body mass index (kg/m^2) median [IQR]	28	[25, 32]	27	[24, 31]	27	[24, 29]	**0.008**	**0.002**
Previous medical history								
Atrial fibrillation or flutter	81	59	31	51	136	39	<**0.001**	<**0.001**
Permanent	30	21	3	5	19	5		
Persistent	12	9	8	13	48	14		
Paroxysmal	14	10	5	8	20	6		
Atrial flutter	4	3	2	3	8	2		
Unknown	21	15	13	21	41	12		
Ischaemic heart disease	44	32	23	38	97	28	0.243	0.345
Myocardial infarction	14	10	11	18	31	9	0.094	0.647
Previous CABG	10	7	9	15	11	3	<**0.001**	**0.043**
Previous PCI	16	12	12	20	30	9	0.031	0.296
Peripheral artery disease	10	7	1	2	12	3	0.092	0.066
Stroke/TIA	13	10	5	8	27	8	0.673	0.376
Hypertension	117	85	43	70	188	54	<**0.001**	<**0.001**
COPD	19	14	4	7	29	8	0.121	0.045
Other lung disease	7	5	3	5	11	3	0.539	0.344
Diabetes	38	28	13	21	64	18	0.073	**0.022**
Type 1 or unknown	1	0.5	1	0.2	3	0.8	0.811	0.732
Type 2	37	27	12	19	61	17		
Renal dysfunction (eGFR < 60 mL/kg/min)	45	33	17	28	55	16	<**0.001**	<**0.001**
Anaemia (Hb < 130/120 g/dL)	27	20	5	8	36	10	0.056	**0.021**
Primary HF aetiology								
Ischaemic	6	4	7	11	36	10	0.260	0.087
Non-ischaemic	42	31	16	26	90	26		
Dilated cardiomyopathy	1	1	3	5	45	13	<**0.001**	<**0.001**
Hypertrophic cardiomyopathy	2	1	0	0	4	1		
Clinical findings								
NYHA class							<**0.001**	0.388
I	7	5	14	23	22	6		
II	59	43	29	48	173	50		
III	36	26	12	20	82	23		
IV	0	0	0	0	3	1		
Systolic blood pressure (mmHg) median [IQR]	140	[120, 150]	135	[120, 145]	127	[110, 140]	<**0.001**	<**0.001**
Diastolic blood pressure (mmHg) median [IQR]	80	[70, 85]	80	[72, 86]	80	[70, 85]	0.511	0.780
Heart rate (beats/min) median [IQR]	70	[60, 76]	70	[61, 80]	74	[65, 90]	<**0.001**	<**0.001**
Lung auscultation							0.247	0.273
Absent breath sounds	6	4	2	3	9	3	0.587	0.302
Rales	12	9	4	7	27	8	0.230	0.331
Jugular venous distension	9	7	0	0	10	3	**0.039**	0.058

(*Continues*)

Table 1 (continued)

Demographics	HFpEF (LVEF ≥ 50%) *n* = 137		HFmrEF (LVEF 41–49%) *n* = 61		HFrEF (LVEF ≤ 40%) *n* = 349		*P* value overall	*P* value HFpEF vs. HFrEF
	n	%	*n*	%	*n*	%		
Peripheral oedema	24	18	3	5	21	6	<**0.001**	<**0.001**
Dyspnoea at rest	3	2	0	0	8	2	0.493	0.946
Treatment[a]								
ARB	52	38	18	30	80	23	**0.004**	<**0.001**
ACE inhibitor	43	32	37	61	233	67	<**0.001**	<**0.001**
ARNi	0	0	1	2	6	2	0.305	0.123
Thiazide HTZ	8	6	1	2	4	1	**0.009**	**0.003**
MRA	32	24	15	25	103	30	0.341	0.173
Beta-blocker	108	79	55	90	319	91	<**0.001**	<**0.001**
Calcium antagonist	46	33	13	21	35	10	<**0.001**	<**0.001**
Furosemide	93	68	33	54	208	60	0.120	0.091
Antiplatelet	25	18	16	26	99	28	0.071	**0.021**
Anticoagulant	32	24	8	13	41	12	**0.005**	**0.001**
Nitrates longstanding	7	5	1	2	13	4	0.494	0.489
Statin	61	45	29	48	116	33	**0.017**	**0.020**
Oral hypoglycaemic drug	25	18	9	15	42	12	0.200	0.074
Insulin	16	12	6	10	20	6	0.069	**0.024**
Pacemaker	5	5	1	2	18	5	0.413	0.482
ICD	1	1	1	2	6	2	0.711	0.410
CRT-D	0	0	0	0	2	1	0.566	0.375

ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy-defibrillator; eGFR, estimated glomerular filtration rate; HTZ, hydrochlorothiazide; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack. Continuous variables are presented as median and interquartile range [IQR] and categorical variables as numbers (*n*) and percentages (%).

[a]Treatment may have been instituted at incident heart failure hospitalization estimated to be within previous 4–6 weeks.

Table 2 Laboratory and ECG variables in HF PREFERS patients categorized according to the proposed universal classification of HF

	HFpEF (LVEF ≥ 50%) *n* = 137		HFmrEF (LVEF 41–49%) *n* = 61		HFrEF (LVEF ≤ 40%) *n* = 349			
Laboratory variable	Median	IQR	Median	IQR	Median	IQR	*P* value overall	*P* value HFpEF vs. HFrEF
Creatinine (μmol/L)	89	[77, 108]	90	[77, 104]	87	[77, 100]	0.437	0.288
eGFR (mL/min/1.73 m^2)	68	[54, 78]	71	[59, 86]	74	[65, 85]	**<0.001**	**<0.001**
eGFR (MDRD), *n* (%)							**<0.001**	**<0.001**
≥90	15	11%	7	11%	63	18%		
60–89	68	52%	33	54%	215	62%		
30–59	44	33%	15	25%	55	16%		
<30	1	0.7%	2	3%	0	0%		
Urine albumin/creatinine ratio	2.3	[0.8, 5.5]	2.2	[0.9, 3.9]	1.9	[0.7, 5.1]	0.310	0.669
NT-proBNP (ng/L)	896	[462, 1645]	746	[252, 1420]	1160	[563, 2370]	**<0.001**	**0.005**
hsTroponin T (nanog/L)	16	[11, 25]	17	[9, 23]	14	[9, 23]	0.266	0.105
Potassium (mmol/L)	4.2	[3.9, 4.4]	4.2	[4.0, 4.4]	4.2	[4, 4.5]	0.644	0.348
Sodium (mmol/L)	140	[139, 142]	141	[140, 142]	141	[139, 142]	0.051	**0.020**
hsCRP (ml/L)	2.3	[1.2, 4.2]	2.2	[1.1, 4.8]	1.6	[0.77, 3.6]	0.057	**0.027**
Haemoglobin (g/dL)	133	[125, 142]	138	[132, 148]	143	[132, 154]	**<0.001**	**<0.001**
White blood cells (10E9/L)	6.5	[5.0, 7.9]	6.1	[5.0, 7.2]	6.75	[5.7, 8.3]	0.047	0.153
Platelets (10E9/L)	229	[187, 276]	221	[165, 257]	233	[197, 274]	0.222	0.578
AST (μkat/L)	0.42	[0.36, 0.54]	0.41	[0.30, 0.51]	0.42	[0.35, 0.54]	0.590	0.699
ALT (μkat/L)	0.39	[0.29, 0.49]	0.37	[0.29, 0.47]	0.42	[0.32, 0.61]	**0.030**	**0.022**
HbA1c (mmol/mol)	42	[38, 47]	40	[37, 45]	41	[38, 46]	0.359	0.523
Glucose (mmol/L)	6.1	[5.4, 7.0]	5.9	[5.6, 6.8]	6.0	[5.5, 6.8]	0.938	0.773
TSH (mE/L)	2.3	[1.4, 3.2]	2.3	[1.4, 2.8]	2.0	[1.3, 4.0]	0.978	0.870
Uric acid (μmol/L)	396	[327, 483]	389	[328, 473]	404	[338, 482]	0.835	0.957
Total cholesterol (mmol/L)	4.3	[3.8, 5.2]	4.4	[3.8, 5.0]	4.6	[3.8, 5.6]	0.098	0.075
LDL (mmol/L)	2.3	[1.8, 3.1]	1.4	[1.0, 1.8]	2.7	[2.0, 3.5]	**0.001**	**0.011**
Triglycerides (mmol/L)	1.10	[0.85, 1.60]	1.00	[0.79, 1.30]	1.20	[0.94, 1.60]	0.118	0.196
ECG								
Sinus, *n* (%)	61	52%	27	61%	192	64%	0.074	**0.023**
Atrial fibrillation/flutter, *n* (%)	51	43%	15	34%	87	29%	**0.020**	**0.005**
PQ time (ms)	168	[152, 192]	168	[154, 184]	166	[148, 182]	0.558	0.405
QRS width (ms)	96	[88, 118]	102	[90, 136]	106	[94, 140]	**<0.001**	**<0.001**
QT (ms)	415	[387, 438]	416	[382, 456]	406	[368, 438]	0.097	0.119
QTc (ms)	436	[419, 463]	451	[430, 470]	450	[428, 473]	**0.008**	**0.003**

ALT, alaninaminotransferas; AST, aspartataminotransferas; eGFR, estimated glomerular filtration rate (according to the Modification of Diet in Renal Disease study); HbA1c, haemoglobin A1c; hsCRP, high-sensitivity C-reactive protein; LDL, low density lipoprotein; NT-proBNP, N-terminal pro brain natriuretic peptide; TSH, thyroid-stimulating hormone. Continuous variables are presented as median and interquartile range [IQR] and categorical variables as numbers (*n*) and percentages (%).

Table 3 Imaging measures in HF PREFERS patients categorized according to the proposed universal classification of HF

	HFpEF (LVEF ≥ 50%) *n* = 137		HFmrEF (LVEF 41–49%) *n* = 61		HFrEF (LVEF ≤ 40%) *n* = 349			
Echocardiography	Median	IQR	Median	IQR	Median	IQR	*P* value overall	*P* value HFpEF vs. HFrEF
LV e-d diameter, (mm)	48	[43, 52]	55	[48, 61]	59	[54, 64]	<**0.001**	<**0.001**
Interventricular septum e-d thickness, (mm)	12	[11, 13]	11	[10, 13]	10	[9, 12]	<**0.001**	<**0.001**
LV posterior wall e-d thickness, (mm)	10	[9, 11]	10	[9, 11]	10	[8, 11]	**0.003**	**0.001**
Relative wall thickness	0.43	[0.37, 0.49]	0.35	[0.32, 0.41]	0.32	[0.28, 0.37]	<**0.001**	<**0.001**
Left e-d volume, (mL)	93	[72, 115]	131	[95, 169]	164	[127, 212]	<**0.001**	<**0.001**
LV e-s volume, (mL)	39	[30, 50]	67	[49, 88]	110	[79, 148]	<**0.001**	<**0.001**
LV mass index (g/m^2)	96	[79, 116]	115	[88, 139]	119	[99, 143]	<**0.001**	<**0.001**
LV mass index, (g/m^2) females	87	[71, 101]	102	[82, 119]	115	[94, 139]	<**0.001**	<**0.001**
LV mass index, (g/m^2) males	107	[92, 136]	121	[89, 145]	120	[102, 144]	**0.009**	**0.002**
LVH, *n* %	43	31%	35	57%	179	51%	<**0.001**	<**0.001**
LV ejection fraction, (%)	55	[53, 60]	45	[43, 46]	30	[25, 35]	<**0.001**	<**0.001**
RV e-d diameter, (mm)	36	[32, 40]	38	[36, 41]	38	[34, 42]	<**0.001**	<**0.001**
TAPSE, (mm)	20	[17, 25]	20	[16, 24]	17	[13, 20]	<**0.001**	<**0.001**
LA e-s area, (cm^2)	24	[21, 28]	23	[20, 26]	26	[22, 30]	**0.002**	**0.006**
LA volume index, (mL/m^2)	40	[31, 48]	38	[30, 44]	43	[34, 54]	**0.001**	**0.008**
LA volume index > 34 (mL/m^2), *n* %	78	57%	37	61%	214	61%	**0.011**	**0.040**
E/A ratio	1.33	[0.85, 1.80]	0.91	[0.71, 1.46]	1.20	[0.81, 2.23]	0.058	0.969
E/é ratio	12.0	[9.5, 15.0]	10.5	[8.3, 13.7]	13.0	[10.1, 17.2]	<**0.001**	**0.034**
E/é ≥ 13, *n* %	49	36%	13	21%	128	37%	0.005	**0.023**
E/é > 14, *n* %	36	26%	11	18%	111	32%	0.003	0.017
cMRI (*n* = 50)								
Patients (*n*; % of HF phenotype cohort)	14	10%	6	10%	30	9%	0.839	0.599
Myocardial infarction (*n*; %)	5	36%	4	67%	8	27%	0.166	0.540
Remote T1 (ms)	984	[956, 1011]	984	[956, 1010]	994	[974, 1031]	0.428	0.288
Remote ECV (%)	26	[24, 27]	28	[24, 30]	26	[25, 28]	0.605	0.375

A, mitral inflow Doppler velocity at atrial contraction; cMRI, cardiac magnetic resonance imaging; é, early diastolic mitral annular tissue Doppler velocity; E, mitral inflow Doppler E-wave velocity; E/A ratio, a ratio of mitral E to A velocity; ECV, extracellular volume; E/é ratio, a ratio of mitral E to mean value of septal and lateral tissue é velocity; e-d, end-diastolic; e-s, end-systolic; LA, left atrial; LV, left ventricular; LVH, left ventricular hypertrophy; RV, right ventricular, TAPSE, tricuspid annular plane systolic excursion; T1, longitudinal recovery time. Continuous variables are presented as median and interquartile range [IQR] and categorical variables as numbers (*n*) and percentages (%).

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Quality of life

The median MLHFQ score (0–105) was 38 (Q1; Q3; 17; 52) in HFpEF, 23 (8; 47) in HFmrEF, and 32 (17; 53) in HFrEF (P = 0.023). Subscores differed between HF phenotypes, displaying for physical function 18 (7; 26) in HFpEF, 11 (3; 20) in HFmrEF, and 15 (7; 25; P = 0.015) in HFrEF and for emotional function in HFpEF 8 (2; 12), in HFmrEF 4 (1; 10), and in HFrEF 7 (3; 13; P = 0.051), respectively. Women compared with men irrespective of HF type had overall a higher MLHFQ total score (39 vs. 30; P = 0.009,) and subscores for physical function (19 vs. 13; $P < 0.001$) and emotional score (8 vs. 6; $P < 0.001$), respectively, indicating worse QoL. For EQ-5D, a relatively large proportion had restrictions (*Figure S2*). There was no difference in visual analogue scale overall health status in HFpEF vs. HFmrEF and HFrEF, 65 vs. 70 vs. 70 (P = 0.051). But whereas men reported similar health status in HFpEF 75, HFmrEF 70, and HFrEF 70 (P = 0.331), women with HFpEF had worse QoL compared with HFmrEF and HFrEF (50, 68 vs. 70; P = 0.030), respectively.

Comparison with SwedeHF new onset HF cohort and with other HF cohorts and HFpEF RCTs

To assess if our patient cohort resembled new onset HF reported in SwedeHF, we compared patient characteristics of HFpEF (defined as LVEF $>$ 50%) and HFrEF (LVEF $<$ 50%). The patients in PREFERS and SwedeHF were largely similar (*Table S4*). PREFERS patients were slightly younger with somewhat fewer comorbidities. A previous MI was more prevalent in SwedeHF (in PREFERS 10% in both HFpEF and HFrEF) vs. 26% and 33% in HFpEF and HFrEF, respectively, in SwedeHF. Likewise established ischaemic HF aetiology was higher in SwedeHF (4% and 11% in PREFERS in HFpEF and HFrEF) vs. 26% and 40% in HFpEF and HFrEF, respectively, in SwedeHF. In PREFERS, median eGFR was higher, NT-proBNP and NYHA class lower indicating better renal function and less severe HF state compared with SwedeHF.

Discussion

We report clinical characteristics and cardiac imaging results in *new onset* HF patients, whereof 137 (25%) were HFpEF, 61 (11%) HFmrEF, and 349 (64%) HFrEF (*Figure 1*) using the most recent definition the *Universal definition and classification of heart failure*.[1] Overall, HFpEF patients, were older, more often women, and had greater comorbidity burden. Our patients were carefully characterized with detailed imaging and biological data, recruited in a broad clinical setting, and treated according to current HF guideline following confirmation of HF diagnosis. They are thus well suited for further exploration of molecular and structural components in HF pathophysiology over the full range of LVEF in a representative HF population. Our study will contribute to the emerging understanding of HF, in specific in HFpEF, and will add valuable knowledge to future HF studies (*Figure 2*).

New onset heart failure

We included only *new onset* HF and unlike in many previous studies excluded patients with severe valvular disease, hypertrophic cardiomyopathy, or infiltrative myocardial disease. PREFERS patients with HFpEF were 9 years older than those with HFrEF, more commonly women, and with more hypertension, AF, higher body mass index, and more comorbidities (*Figure S1*). Our HFpEF patients resemble those in recent HFpEF randomized controlled trials[10,11] although our patients were not all in stable state at inclusion.

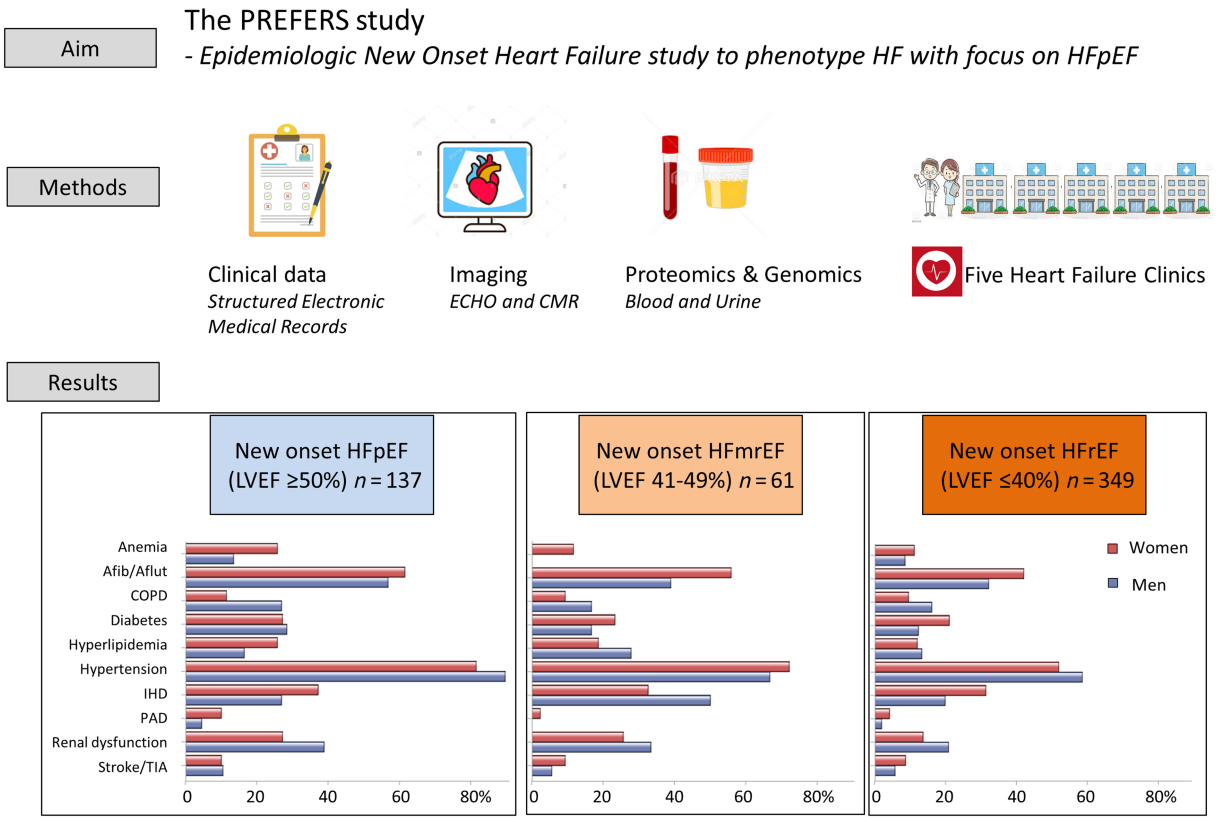
We chose to present our result with respect to the Universal HF definition HFpEF.[1] In our original study design, HFpEF was defined as LVEF $\geq$ 45%. Lately, higher[12] LVEF threshold for HFpEF has been proposed reflecting the evolving knowledge of HFpEF pathophysiology. Characteristics of the HFmrEF group (*Tables 1–3* and *S1–S3*) support the growing understanding that this group may be divided and partly share pathophysiology with HFrEF thus suitable for guidelines indicated HFrEF treatment.[12–16] Further, comparing the HFmrEF groups according to the ESC HF guidelines, many patients (n = 41) were reclassified to HFmrEF, thus embraced by in existing guidelines on HF treatment and suggesting considerable uncertainties for LVEF measurements measured in clinical practice commonly ending with either 0% (or 5%).

Given the still enigmatic HFpEF group, mostly lacking evidence-based treatment, we specifically aimed to enrol such patients with the full spectra of even mild diastolic dysfunction. Nonetheless, more than 70% of our enrolled HFpEF patients fulfilled ESC guidelines 2016 criteria for HFpEF, which included functional or structural impairment.[2] In addition, NT-proBNP levels in our HFpEF patients reflected inclusion within 2–4 weeks following an acute HF admission.

Our patients were recruited in a broad clinical setting.[7] We were not able to capture all *new onset* HF patients within our catchment area in the recruiting hospitals during the study period. Still, when our study patients were compared with *new onset* HF patients entered in SwedeHF Registry during the same time-period (*Table S4*), our patients were largely similar but with less severe HF. In summary, we believe we have included patients with *new onset* HF representative for the Swedish population provided they were in good enough condition to accept participation in the study. Therefore, it is not surprising that our study patients were healthier than those in SwedeHF and in other clinical cohorts.

None of our study patients had an established HF diagnosis at the time of study inclusion reflecting that HF aetiology was

Figure 2 Percentage of patients with the most common comorbidities divided by HF type displayed by sex (female patients *n* = 192, male patients *n* = 355). Men are represented in blue and women in red. HF, heart failure; HFmrEF, heart failure with mildly reduced left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; LVEF, left ventricular ejection fraction.



not fully assessed when included. Although an established ischaemic HF aetiology was lower in PREFERS than in the SwedeHF (*Table S4*), overall presence of ischaemic heart disease was 28–32% comparable with other incident HF cohorts. Interestingly, although only performed in a small subset, presence of previous MI by cMRI was not different between the groups. We could not confirm the results of previous studies suggesting that patients with HFrEF and HFmrEF much more commonly have ischemic heart disease than patients with HFpEF.[17,18] Our limited cMRI findings thus support the notion of undetected ischaemia as only a minority of our new onset HF patients had a previous diagnosis of MI. In SwedeHF, which allowed new onset HF patients' entry up to 6 months from diagnosis around one-fourth had undefined HF diagnosis suggesting that these patients might remain without established aetiology (*Table S4*). Our results thus indicate that the importance of establishment of HF aetiology in connection with medical care for *new onset* HF.

The PREFERS HFpEF patients are overall representative and comparable with other HFpEF cohorts enabling us to achieve one of the aims of the PREFERS, to investigate novel treatment targets in patients with HFpEF. A short HF duration is associated with better survival than chronic HF.[19,20] We will address outcomes in PREFERS using the Swedish Death Registry and the Swedish National Health Care Registry for total and cardiovascular mortality and for HF readmissions, with a minimum follow-up of 2 years and a maximal of 6 years.[6]

Quality of life

Interestingly, our patients with new onset HF overall had worse quality of life than previously reported from HF patients recruited at discharge from hospital (within 1 month) or following an outpatient visit.[21] In addition, both total and physical scores were significantly worse in HFpEF compared with HFmrEF and HFrEF. Like in the KaRen study, PREFERS women had worse quality of life than men and with a greater difference in HFpEF.[22] Overall, women with HF have

long been known to have worse quality of life than men.[23,24] The reason for this remains to be determined.

Echocardiography and cardiac magnetic resonance imaging

As expected, HFpEF patients had smaller LV size and a higher relative LV wall thickness and less concentric LV hypertrophy or remodelling, while HFrEF had more eccentric LV hypertrophy or remodelling. In contrast to HFrEF, HFpEF patients had normal RV function and size, and seldom secondary mitral regurgitation. Both HFpEF and HFrEF patients had high filling pressures and structural parameters indicative of diastolic dysfunction. The severity of systolic dysfunction parameters was thus incremental from HFpEF to HFrEF including HFmrEF irrespective of definition.

Overall, our HFrEF patients were in more advanced disease state than our HFpEF patients. These findings underline the importance of HF awareness and a structured diagnostic and therapeutic approach.[7] Our previous results indicate that HF medication prescription increase and need for HF hospitalizations decline when such a process is implemented in a larger population.[7,25]

Although we only could perform cMRI in 50 patients, we found no signs of diffuse fibrosis or in remote native T1 or ECV between the HF groups regardless of the cut-off values for LVEF. However, this absence does not preclude that fibrosis was present. This will be further explored in an ongoing biopsy study within CABG PREFERS[6] and in the PREFERS-Hypertension study NCT04190420 focusing on the transition from hypertension to HF.[26] Moreover, in our previous exploratory translational study of elective CABG patients undergoing perioperative myocardial biopsies, we reported differences in gene expression for cardiac muscle contraction, oxidative phosphorylation, endocytosis/cell remodelling, matrix organization, and fibrosis in patients with HFpEF compared with HFrEF characteristics.[27]

Biomarkers in blood and urine

Heart failure with preserved left ventricular ejection fraction patients had significantly lower haemoglobin values, and more commonly had anaemia than the HFrEF group suggesting inflammation and/or iron deficiency. Detection and treatment of iron deficiency is established in HFrEF but has not been extensively studied in HFpEF,[28] especially in new onset HF. Previous studies from HFrEF suggest that chronic inflammation and iron deficiency contribute to anaemia. Anaemia may be important in the evolution of HFpEF given the importance of iron for mitochondrial function, oxidative injuries, and collagen synthesis.[29] The high proportion in PREFERS and the even higher in SwedeHF highlights the importance of further studies on iron deficiency in HFpEF patients.

In HFpEF, eGFR was lower indicative of renal dysfunction, which may reflect the decompensated HF stage rather than underlying drivers of HF type. In a recent Dutch study, only natriuretic peptides and UACR were associated with HFpEF contrasting to HFrEF.[30] Further, differences in renal dysfunction reflected by eGFR and UACR have been suggested to play different roles in cardiac structure/function in HFpEF.[31] This lends support to different distinct disease mechanisms between HF types and highlights the need for more extensive phenotyping including biomarkers.[30,31] Recent phenotyping models indeed reveal novel phenotypes with distinct proteomic signatures within the HFpEF group,[32] perhaps indicative of new HFpEF endotypes. We previously reported HFpEF to be associated with a distinct profile of circulating metabolites indicative of increased collagen synthesis and down-regulated NO-signalling as compared with HFrEF[33] in a subset of PREFERS patients and intend to further explore the underlying HFpEF pathophysiology.

Limitations

The enrolment of PREFERS patients was performed at the HF clinics as a part of clinical care, which is linked to challenges. Still, it is also a strength that our patients were included in routine clinical practice and that it is built on a common HF organization in Stockholm[7] enabling uniformed data collection from patients' charts, echocardiography, and central biobanking. Even though we cannot exclude that many of our patients had insidious symptoms of longer duration before being diagnosed, they did not have a previous HF diagnosis. We cannot exclude that some patients presented with tachycardia-induced cardiomyopathy in view of the high presence of AF. Patient charts provided scarce data on the aetiology reflecting study design. Although the subgroup of patients who underwent cMRI was small, the proportions were well distributed for the different HF phenotypes in the total cohort.

Conclusions

In this detailed characterization of new onset HF, 25% had HFpEF (EF $\geq$ 50%), 11% had HFmrEF, and 64% had HFrEF (LVEF $\leq$ 40%). Our data of *new onset* HF patients recruited in a broad clinical setting showed that HFpEF patients were older, more often women, and had greater comorbidity burden than HFrEF. PREFERS is well suited to further explore biomarker and imaging underlying components of new onset HF pathophysiology over the full range of LVEF, with a specific focus on HFpEF, in a representative HF population. Our study

will add and deepen the knowledge on the HF syndrome and contribute to future HF study design.

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Conflict of interest

CL reports consulting fees from AstraZeneca, Roche diagnostics and Bayer and speaker honoraria from Novartis, Astra, Bayer, Medtronic, Impulse Dynamics, and Vifor. CH reports consulting fees from Novartis, AnaCardio, and Roche Diagnostics and speaker and honoraria from MSD, supported by the Swedish Research Council (grant 20180899). HP reports speaker honoraria from Vifor and Novartis. LHL reports personal fees from Merck, grants and personal fees from Vifor-Fresenius, grants and personal fees from AstraZeneca, personal fees from Bayer, grants from Boston Scientific, personal fees from Pharmacosmos, personal fees from Abbott, personal fees from Medscape, personal fees from Myokardia, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Novartis, personal fees from Sanofi, personal fees from Lexicon, and personal fees from Radcliffe cardiology, outside the submitted work. ME reports postdoc grants from Novartis foundation for medical and biological research. PL reports consulting fees from Novartis. No potential conflict of interest was reported by the other authors.

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Supporting information

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

Figure S1. Number of co-morbidities presented per HF type in all patients (n = 547) (COPD, atrial fibrillation/flutter, ischemic heart disease, diabetes, hypertension, renal disease). Darker colour indicates increasing number of comorbidities.
Figure S2. Percent of patients in the three grades (no restriction, some restriction, severe restriction) of the five EQ 5D dimensions presented per HF type.
Table S1. Clinical characteristics HF PREFERS patients categorized according to the ESC HF guidelines. Continuous variables are presented as median and interquartile range [IQR] and categorical variables as numbers (n) and percentages (%).
Table S2. Laboratory and ECG variables in HF PREFERS patients categorized according to the ESC HF guidelines. Continuous variables are presented as median and lower and upper quartiles (Q1;Q3) and categorical variables as numbers (n) and percentages (%).
Table S3. Imaging measures in HF PREFERS patients categorized according to the ESC HF guidelines. Continuous variables are presented as median and lower and upper quartiles (Q1;Q3) and categorical variables as numbers (n) and percentages (%)
Table S4. Patient characteristics of PREFERS patients and HF patients enrolled in Swede HF January 1^{st,} 2015 – December 31^{st,} 2018. Patients selected having the diagnosis of HF $<$ 6 months according to the Swede HF registry. Continuous variables are presented as median and interquartile range [IQR] and categorical variables as numbers (n) and percentages (%).

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