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) ≥ 50%] was compared with HF with mildly reduced LVEF (HFmrEF; LVEF 41–49%) and with HF with reduced LVEF (HFrEF; LVEF ≤ 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 ≥ 14 was present in 26% of HFpEF vs. 32% of HFrEF (P = 0.017) and left atrial volume index > 34 mL/m² 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.

Clinical trial registration: Clinicaltrials.gov identifier: NCT03671122.

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%; HfEF), mildly reduced (HFmrEF; 41–49%2 or 40–49%),2 and reduced (HFrEF; ≤40%1 or <40%). The relative proportion of HfEF is increasing, lacks evidence-based therapy2 but carries similar high risks for HF readmissions and all-cause mortality as HFrEF. It has been suggested that the pathophysiology for HfEF 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, HfEF 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 HfEF need to be identified to design effective therapies in HfEF.4

We have previously characterized HfEF 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 pathophysiological mechanisms of new onset HF over the full range of LVEF and to contribute to the identification of novel drug targets for HfEF.

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 m²), 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 design6 used LVEF < 45% defined HFrEF and ≥45% HfEF. Left ventricular hypertrophy (LVH) was defined as left ventricular mass index > 95 g/m² in women and >115 g/m² in men. E/e ratio was calculated using the average between septal and lateral é as ≥ 13² 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.
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 enrolls 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. In brief, we hypothesized that HFrEF is characterized by collagen synthesis reflected by procollagen type 1 (PICP) and HFrEF by collagen degradation reflected by carboxyterminal telopeptide collagen type I (CITP). To detect a 20% difference between phenotypes (at the time of study design defined as HFrEF ≥ 45%, HFR < 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 HFrEF (LVEF > 50%) (30%) and HFR (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 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 χ² 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 χ² 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 HFrEF, n = 61 (11%), HFrEF (LVEF 41–49%), and 349 (64%) HFrEF (LVEF ≤ 40%) (Figure 1) Most

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 HFrEF (31% with more than or equal to four comorbidities) compared with 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 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 HFrEF patients had a history of atrial fibrillation, diabetes, pulmonary disease, peripheral artery disease, and hypertension. In contrast, few with HFrEF had a history of coronary revascularization. HFrEF and HFrEF were associated with higher systolic blood pressure and more peripheral oedema and HFrEF with higher heart rate. The majority with HFrEF and HFrEF were treated with renin angiotensin inhibitors, angiotensin II receptor inhibitors, or angiotensin receptor-neprilysin inhibitor (92% and 93%, respectively) compared with 70% of HFrEF patients. Thiazides, calcium antagonists, and oral anticoagulants were more commonly prescribed in HFrEF.

Patients with HFrEF had lower eGFR (Table 2) haemoglobin and more commonly had anaemia than HFrEF patients. High-sensitive CRP was higher in HFrEF. ECG revealed (Table 2) significantly more AF in 43% in HFrEF and 34% in HFrEF compared with 29% in HFrEF. QRS width and QTc was significantly longer in HFrEF 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 HFrEF. With this definition, HFrEF (n = 102) vs. HFrEF patients (n = 137) 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 ≤ 40%; n = 308). Compared with HFrEF, HFrEF had slightly higher proportion of CAD and LDL. HFrEF patients had the lowest NT-proBNP compared with both HFrEF and HFrEF (730 vs. 896 and 1210 ng/L; P < 0.001) (Tables S1–S2).

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

|                              | HFpEF (LVEF ≥ 50%) n = 137 | HFrEF (LVEF 41–49%) n = 61 | HFrEF (LVEF ≤ 40%) n = 349 | P value overall | P value HFpEF vs. HFrEF |
|------------------------------|------------------------------|-----------------------------|-----------------------------|----------------|------------------------|
| **Demographics**             |                              |                             |                             | 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)                     | <0.001         | <0.001                 |
| Paroxysmal                   | 14 (10)                     | 5 (8)                       | 20 (6)                      | <0.001         | <0.001                 |
| 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)                     | 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)                     | 0.073          | 0.022                  |
| Dilated cardiomyopathy       | 1 (1)                       | 3 (5)                       | 45 (13)                     | <0.001         | <0.001                 |
| Hypertrophic cardiomyopathy  | 2 (1)                       | 0 (0)                       | 4 (1)                       |                |                        |
| **Clinical findings**        |                              |                             |                             |                |                        |
| NYHA class                   | 7 (5)                       | 14 (23)                     | 22 (36)                     | <0.001         | 0.388                  |
| I                            | 59 (43)                     | 29 (48)                     | 173 (50)                    | 0.260          | 0.087                  |
| II                           | 36 (26)                     | 12 (20)                     | 82 (23)                     | 0.073          | 0.022                  |
| III                          | 0 IV                        | 0 (0)                       | 3 (1)                       | <0.001         | <0.001                 |
| 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                  |
| Demographics          | HFpEF (LVEF ≥ 50%) n = 137 | HFrEF (LVEF 41–49%) n = 61 | HFrEF (LVEF ≤ 40%) n = 349 | P value overall | P value HFpEF vs. HFrEF |
|-----------------------|----------------------------|----------------------------|-----------------------------|-----------------|-------------------------|
| 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                   |
| Treatmenta            |                            |                            |                             |                 |                         |
| ARB                   | 52 (38)                    | 18 (30)                    | 80 (23)                     | 0.004           | <0.001                  |
| ACE inhibitor         | 43 (32)                    | 37 (61)                    | 233 (67)                    | <0.001          | <0.001                  |
| Angiotensin receptor  | 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                   |
| Nitrate long-standing | 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 (%).

*Treatment may have been instituted at incident heart failure hospitalization estimated to be within previous 4–6 weeks.
| Laboratory variable          | HFrEF (LVEF ≤ 40%) | HFrEF (LVEF 41–49%) | HFrEF (LVEF ≥ 50%) | n value | P value overall | P value HFrEF vs. HFrEF |
|-----------------------------|--------------------|---------------------|--------------------|---------|----------------|------------------------|
| Creatinine (μmol/L)         | 87 [77, 100]       | 74 [65, 85]         | 89 [77, 108]       | 137     | 0.437          | 0.288                  |
| eGFR (ml/min/1.73 m²)       | 74 [59, 86]        | 71 [58, 82]         | 68 [54, 78]        | 61      | <0.001         | <0.001                 |
| (MDRD), n (%)               | 349                | 61                  | 137                |         | <0.001         | <0.001                 |
| ≥90                         | 15 11%             | 7 11%               | 63 18%             |         | <0.001         | <0.001                 |
| 60–89                       | 68 52%             | 33 54%              | 215 62%            |         | <0.001         | <0.001                 |
| 30–59                       | 44 33%             | 15 25%              | 55 16%             |         | <0.001         | <0.001                 |
| <30                         | 1 0.7%             | 2 3%                | 0 0%               |         | <0.001         | <0.001                 |
| Urine albumin/creatinine ratio | 2.3 [0.8, 5.5] | 2.2 [0.9, 3.9]  | 1.9 [0.7, 5.1]  | 896 | 0.310          | 0.669                  |
| NT-proBNP (mg/L)            | 1160 [563, 2370]   | 746 [252, 1420]     | 896 [462, 1645]    | 137     | <0.001         | 0.005                  |
| hsTroponin T (nanog/L)      | 141 52%            | 33 54%              | 63 18%             |         | <0.001         | <0.001                 |
| Potassium (mmol/L)          | 4.2 [4.0, 4.4]     | 4.2 [4.0, 4.4]      | 4.2 [4.0, 4.4]     |         | <0.001         | <0.001                 |
| Sodium (mmol/L)             | 141 [139, 142]     | 141 [139, 142]      | 141 [139, 142]     |         | <0.001         | <0.001                 |
| 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)          | 138 [132, 148]     | 138 [132, 148]      | 133 [125, 142]     |         | <0.001         | <0.001                 |
| White blood cells (10E9/L)  | 6.1 [5.0, 7.2]     | 6.75 [5.7, 8.3]     | 6.5 [5.0, 7.9]     |         | 0.047          | 0.153                  |
| Platelets (10E9/L)          | 221 [165, 257]     | 233 [197, 274]      | 229 [187, 276]     |         | 0.222          | 0.578                  |
| AST (μkat/L)                | 0.42 [0.35, 0.54]  | 0.42 [0.35, 0.54]   | 0.39 [0.29, 0.49]  |         | 0.590          | 0.699                  |
| ALT (μkat/L)                | 0.37 [0.29, 0.47]  | 0.42 [0.32, 0.61]   | 0.39 [0.29, 0.49]  |         | 0.030          | 0.022                  |
| HbA1c (mmol/mol)            | 42 [37, 45]        | 41 [38, 46]         | 42 [38, 47]        |         | 0.359          | 0.523                  |
| Glucose (mmol/L)            | 6.0 [5.5, 6.8]     | 6.0 [5.5, 6.8]      | 6.1 [5.4, 7.0]     |         | 0.938          | 0.773                  |
| TSH (mE/L)                  | 2.3 [1.4, 2.8]     | 2.0 [1.3, 4.0]      | 2.3 [1.4, 3.2]     |         | 0.978          | 0.870                  |
| Uric acid (μmol/L)          | 396 [328, 473]     | 404 [338, 482]      | 396 [327, 483]     |         | 0.835          | 0.957                  |
| Total cholesterol (mmol/L)  | 4.6 [3.5, 5.6]     | 4.6 [3.5, 5.6]      | 4.3 [3.8, 5.2]     |         | 0.098          | 0.075                  |
| LDL (mmol/L)                | 2.7 [2.0, 3.5]     | 2.7 [2.0, 3.5]      | 2.3 [1.8, 3.1]     |         | 0.001          | 0.011                  |
| Triglycerides (mmol/L)      | 1.20 [0.94, 1.60]  | 1.20 [0.94, 1.60]   | 1.10 [0.85, 1.60]  |         | 0.118          | 0.196                  |

ALT, alaninaminotransferase; AST, aspartataminotransferase; 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 PREFERENCES patients categorized according to the proposed universal classification of HF

| Echocardiography                        | HFpEF (LVEF ≥ 50%) | HFmrEF (LVEF 41–49%) | HFrEF (LVEF ≤ 40%) | P value overall | P value HFpEF vs. HFrEF |
|----------------------------------------|--------------------|----------------------|---------------------|-----------------|------------------------|
| LV e-d diameter, (mm)                  | Median 48 [43, 52] | Median 55 [48, 61]   | Median 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/m²)                   | 96 [79, 116]       | 115 [88, 139]        | 119 [99, 143]      | <0.001          | <0.001                 |
| LV mass index, (g/m²) females          | 87 [71, 101]       | 102 [82, 119]        | 115 [94, 139]      | <0.001          | <0.001                 |
| LV mass index, (g/m²) males            | 107 [92, 136]      | 121 [89, 145]        | 120 [102, 144]     | 0.009           | 0.002                  |
| LVH, n %                               | 43 [53, 60]        | 45 [43, 46]          | 30 [25, 35]        | <0.001          | <0.001                 |
| LV ejection fraction, (%)              | 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, (cm²)                     | 24 [21, 28]        | 23 [20, 26]          | 26 [22, 30]        | 0.002           | 0.006                  |
| LA volume index, (mL/m²)               | 40 [31, 48]        | 38 [30, 44]          | 43 [34, 54]        | 0.001           | 0.008                  |
| LA volume index > 34 (mL/m²), 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/e ratio                              | 12.0 [9.5, 15.0]   | 10.5 [8.3, 13.7]     | 13.0 [10.1, 17.2]  | <0.001          | 0.034                  |
| E/e ≥ 13, n %                          | 49 [36%]           | 13 [21%]             | 128 [37%]          | 0.005           | 0.023                  |
| E/e > 14, n %                          | 36 [26%]           | 11 [18%]             | 111 [32%]          | 0.003           | 0.017                  |
| cMRI (n = 50)                           | 14 [10%]           | 6 [10%]              | 30 [9%]            | 0.839           | 0.599                  |
| Patients (n; % of HF phenotype cohort) | 5 [36%]            | 4 [67%]              | 8 [27%]            | 0.166           | 0.540                  |
| Myocardial infarction (n; %)           | 984 [956, 1011]    | 984 [956, 1010]      | 994 [974, 1031]    | 0.428           | 0.288                  |
| Remote T1 (ms)                         | 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; e, 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/e ratio, a ratio of mitral E to mean value of septal and lateral tissue e 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 (%).
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. 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 S2). Our HFpEF patients resemble those in recent HFrEF randomized controlled trials 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. In our original study design, HFpEF was defined as LVEF ≥ 45%. Lately, higher 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. 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. 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. 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
not fully assessed when included. Although an established ischaemic HF aetiology was lower in PREFERES 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.\textsuperscript{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 PREFERES HFpEF patients are overall representative and comparable with other HFpEF cohorts enabling us to achieve one of the aims of the PREFERES, to investigate novel treatment targets in patients with HFpEF. A short HF duration is associated with better survival than chronic HF.\textsuperscript{19,20} We will address outcomes in PREFERES 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.\textsuperscript{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.\textsuperscript{21} In addition, both total and physical scores were significantly worse in HFpEF compared with HFmrEF and HFrEF. Like in the KaRen study, PREFERES women had worse quality of life than men and with a greater difference in HFpEF.\textsuperscript{22} Overall, women with HF have
long been known to have worse quality of life than men.\textsuperscript{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 HfMR EF 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.\textsuperscript{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.\textsuperscript{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 PREFERENCE\textsuperscript{5} and in the PREFERENCE-Hypertension study NCT04190420 focusing on the transition from hypertension to HF.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{29} The high proportion in PREFERENCE 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.\textsuperscript{30} Further, differences in renal dysfunction reflected by eGFR and UACR have been suggested to play different roles in cardiac structure/function in HfPEF.\textsuperscript{31} This lends support to different distinct disease mechanisms between HF types and highlights the need for more extensive phenotyping including biomarkers.\textsuperscript{30,31} Recent phenotyping models indeed reveal novel phenotypes with distinct proteomic signatures within the HfPEF group,\textsuperscript{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\textsuperscript{33} in a subset of PREFERENCE patients and intend to further explore the underlying HfPEF pathophysiology.

**Limitations**

The enrolment of PREFERENCE 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\textsuperscript{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 HfMR EF, 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. PREFERENCE 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 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. 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 1st, 2015 – December 31st, 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 (%).

References

1. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Bohn M, Butler J, Drazner MH, Michael Felker G, Filipatos G, Fiuzat M, Fonarow GC, Gomez-Mesa J, Heidenreich P, Imamura T, Jankowska EA, Januzzi J, Khazanie P, Kimugawa K, Lam CSP, Matsue Y, Metra M, Ohtani T, Francesco Piepoli M, Ponikowski P, Rosano GMC, Sakata Y, Seferovic P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J, Zieroth S. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail. 2021; 23: 352–380.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk

ESC Heart Failure 2022; 9: 2125–2138
DOI: 10.1002/ehf2.13922
V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieck B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur J Heart Fail*. 2016; 18: 981–975.

3. Paulus WJ, Zile MR. From systemic inflammation to myocardial fibrosis: the heart failure with preserved ejection fraction paradigm revisited. *Circ Res*. 2021; 128: 1451–1467.

4. Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB, Shah S, Ahmed A, Bonow RO, Cleland JG, Cody J, Corbascio M, Lundeberg J, Maret E, Ugander M, Persson B, Corbascio M, Lundeberg J, Daubert JC. Rationale and design of the PREFERS study of dyssynchrony in heart failure with preserved ejection fraction: current status and future directions. *JACC Heart Fail* [Review]. 2014; 2: 97–112.

5. Donal E, Lund LH, Linde C, Edner M, Lafitte S, Persson H, Bauer F, Ohrvik J, Ennezet PV, Hage C, Lofman I, Juilillere Y, Logeart D, Derumeaux G, Gueret P, Daubert JC. Rationale and design of the Karolinska-Rennes (KaRen) prospective study of dysynchrony in heart failure with preserved ejection fraction. *Eur J Heart Fail* [Research Support, Non-U.S Gov]. 2009; 11: 198–204.

6. Linde C, Eriksson MJ, Hage C, Wallen H, Persson B, Corbacho M, Lunderberg J, Maret E, Ugander M, Persson H. Rationale and design of the PREFERS (preserved and reduced ejection fraction epidemiological regional study) Stockholm heart failure study: an epidemiological regional study in Stockholm county of 2.1 million inhabitants. *Eur J Heart Fail*. 2015; 18: 1297–1307.

7. Matan D, Löfström U, Corovic Cabrera C, Linde C, Eriksson MJ, Lundeberg J, Hage C, Wallen H, Reorganization of heart failure management and improved outcome—the 4D HF project. *Scand Cardiovasc J*. 2020; 55: 1–8.

8. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996; 37: 53–72.

9. Rector R, Kubo S, Cohn J. Patients self-assessment of their congestive heart failure II. Content reliability and validity of a new measure: the Minnesota living with heart failure questionnaire. *Heart Failure*. 1987; 3: 198–209.

10. Solomon SD, Rizkala AR, Lefkowitz MP, Shi VC, Gong J, Anavekar N, Anker SD, Arango JL, Aronov J, Atar D, Ben-Gal T, Boytsov SA, Chen CH, Chopra VK, Cleland J, Comin-Colet J, Duengen HD, Echewerra Correa LE, Filippatos G, Flammer AJ, Galinier M, Godoy A, Goncalvesova E, Janssens S, Katova T, Kober L, Lelonek M, Lissen G, Lund LH, O'Meara E, Merkely B, Milicic D, Oh BH, Perrone SV, Ranjith N, Saito Y, Saraiva JF, Shah S, Seferovic PM, Senni M, Sibulo AS Jr, Sim D, Sweitzer NK, Taurio J, Vinereanu D, Vrtovsek B, Widimsky J Jr, Zibert J, Zweiker R, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieck B, Pitt B, Rosano G, Sabbah HN, Senni M, Solomon SD, Stockbridge N, Teerlink JR, Georgiopoulou VV, Gheorghiade M. Developing therapies for heart failure with preserved ejection fraction: current status and future directions. *JACC Heart Fail* [Review]. 2014; 2: 97–112.

11. Anker SD, Butler J, Filippatos G, Khan MS, Ferreira JP, Bocchi E, Böhm M, Rocca HBP, Choi DJ, Chopra V, Chugani E, Giannetti A, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Seronde MF, Sim D, Spinar J, Squire I, Taddei S, Tsutsu H, Verma S, Vinereanu D, Zhang J, Jamal W, Schmauzer K, Schmieder RE, Bruckmann M, Pocock SJ, Zannad F, Packer M. Baseline characteristics of patients with heart failure with preserved ejection fraction in the PARAGON-HF trial. *Circ Heart Fail*. 2018; 11: e004962.

12. Solomon SD, Vaduganathan M, Claggett B, Packer M, Zile M, Swedberg K, Rouleau J, A, Pfeffer M, Desai A, H. Lund L, Kober L, Anand I, Sweitzer N, Lissen G, Merkely B, Luis Arango J, Vinereanu D, Chen CH, Senni M, Sibulo A, Boytsov S, Shi V, Rizkala A, Lefkowitz M, McMurray J. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation*. 2020; 141: 352–361.

13. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, O'Meara E, Shah SJ, McKinlay S, Fleg JL, Sogpho G, Pitt B, Pfeffer MA. Influence of ejection fraction on the effect of sacubitril/valsartan. *Circ Heart Fail*. 2017; 10: 1574–1585.

14. Greene SJ, Hernandez AF, Dunning A, Ambrosy AP, Armstrong BW, Butler J, Cerbin LP, Coles A, Ezekowitz JA, Metra M, Starling RC, Teerlink JR, Voors AA, O'Connor CM, Mentz RJ. Hospitalization for recently diagnosed versus worsening chronic heart failure: insights from the ASCEND-HF trial. *J Am Coll Cardiol*. 2017; 69: 3029–3039.

15. Butt JH, Foxhol EL, Gerds TA, Andersson C, McMurray J, Petrie M, Gustafsson F, Madelaire C, Kristensen SL, Gislason GH, Torp-Pedersen C, Kober L, Schou M. Readmission and death in patients admitted with new-onset versus worsening of chronic heart failure: insights from a nationwide cohort. *Eur J Heart Fail*. 2020; 22: 1777–1785.

16. Berg J, Lindgren P, Mehnert M, Edner M, Dahlstrom U, Kahan T. Determinants of utility based EuroQoL five-dimensional questionnaire in patients with chronic heart failure and their change over time: results from the Swedish heart failure registry. *Value Health*. 2015; 18: 439–448.

17. Faxon UL, Hage C, Donal E, Daubert JC, Linde C, Lund LH. Patient reported outcome in HFpEF: sex-specific differences in quality of life and association with outcome. *Int J Cardiol*. 2018; 267: 128–132.

18. Dewan P, Rorth R, Jhund PS, Shen L, Raperelli V, Petrie MC, Abraham WT, Desai AS, Dickstein K, Kober L, Mogensen UM, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, McMurray J. Differential impact of heart failure with reduced ejection fraction on men and women. *J Am Coll Cardiol*. 2019; 73: 29–40.

19. Chandra A, Vaduganathan M, Lewis EF, Claggett BL, Rizkala AR, Wang W, Lefkowitz MP, Shi VC, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F
25. Thorvaldsen T, Benson I, Dahlström U, Edner M, Lund LH. Use of evidence-based therapy and survival in heart failure in Sweden 2003-2012. *Eur J Heart Fail*. 2016; 18: 503–511.

26. Ekstrom M, Hellman A, Hasselstrom J, Hage C, Kahan T, Ugander M, Wallen H, Persson H, Linde C. The transition from hypertension to hypertensive heart disease and heart failure: the PREFERENCES hypertension study. *ESC Heart Fail*. 2020; 7: 737–746.

27. Das S, Frisk C, Eriksson MJ, Valentinsson A, Corbascio M, Hage C, Kumar C, Asp M, Lundeberg J, Maret E, Persson H, Linde C, Persson B. Transcriptomics of cardiac biopsies reveals differences in patients with or without diagnostic parameters for heart failure with preserved ejection fraction. *Sci Rep*. 2019; 9: 3179.

28. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J*. 2015; 36: 657–668.

29. Dong FZ, Zhang X, Culver B, Chew HG Jr, Kelley RO, Ren J. Dietary iron deficiency induces ventricular dilation, mitochondrial ultrastructural aberrations and cytochrome c release: involvement of nitric oxide synthase and protein tyrosine nitration. *Clin Sci (Lond)*. 2005; 109: 277–286.

30. de Boer RA, Nayor M, deFilippi CR, Enserro D, Bhamhomi V, Kizer JR, Blaha MJ, Brouwers FP, Cushman M, Lima JAC, Bahrami H, van der Harst P, Wang TJ, Gansevoort RT, Fox CS, Gaggin HK, Kop WJ, Liu K, Vasan RS, Psaty BM, Lee DS, Hillege HL, Bartz TM, Benjamin EJ, Chan C, Allison M, Gardin JM, Januzzi JL Jr, Shah SJ, Levy D, Herrington DM, Larson MG, van Gilst WH, Gottlieb JC, Bertoni AG, Ho JE. Association of cardiovascular biomarkers with incident heart failure with preserved and reduced ejection fraction. *JAMA Cardiol*. 2018; 3: 215–224.

31. Gori M, Senni M, Gupta DK, Charytan DM, Kraigher-Kraner E, Pieske B, Claggett B, Shah AM, Santos AB, Zile MR, Voors AA, McMurray JJ, Packer M, Bransford T, Lefkowitz M, Solomon SD. Association between renal function and cardiovascular structure and function in heart failure with preserved ejection fraction. *Eur Heart J* [Research Support, Non-US Gov't]. 2014; 35: 3442–3451.

32. Woolley RJ, Ceelen D, Owerkerk W, Tromp J, Figarska SM, Anker SD, Dickstein K, Filippatos G, Zannad F, Marco M, Ng I, Samani N, van Veldhuisen D, Lang C, Lam CS, Voors A. Machine learning based on biomarker profiles identifies distinct subgroups of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2021; 23: 983–991.

33. Hage C, Löfgren L, Michopoulos F, Nilsson R, Davidson P, Kumar C, Ekström M, Eriksson MJ, Lyngå P, Persson B, Wallén H, Gan LM, Persson H, Linde C. Metabolomic profile in HFpEF vs HFrEF patients. *J Card Fail*. 2020; 26: 1050–1059.