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Characteristics of Patients with Heart Failure with Preserved Ejection Fraction in Primary Care: Cross-sectional analysis

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Abstract

Background: Many patients with heart failure with preserved ejection fraction (HFpEF) are undiagnosed, and UK general practice registers do not typically record HF sub-type. Improvements in management of HFpEF is dependent on improved identification and characterisation of patients in primary care.

Aims: To describe a cohort of patients recruited from primary care with suspected HFpEF and compare patients in whom HFpEF was confirmed and refuted.

Design and Setting: Baseline data from a longitudinal cohort study of patients with suspected HFpEF recruited from primary care in two areas of England.

Methods: A screening algorithm and review were used to find patients on HF registers without a record of reduced ejection fraction. Baseline evaluation included cardiac, mental and physical function, clinical characteristics and patient reported outcomes. Confirmation of HFpEF was clinically adjudicated by a cardiologist.

Results: Ninety-three (61%) of 152 patients were confirmed HFpEF. The mean age of patients with HFpEF was 79.3, 46% were female, 80% had hypertension, and 37% took 10 or more medications. Patients with HFpEF were more likely to be obese, pre-frail/frail, report more dyspnoea and fatigue, were more functionally impaired, and less active than patients in whom HFpEF was refuted. Few had attended cardiac rehabilitation.

Conclusions: Patients with confirmed HFpEF had frequent multimorbidity, functional impairment, frailty and polypharmacy. Although comorbid conditions were similar between people with and without HFpEF, the former had more obesity, symptoms and worse physical function. These findings highlight the potential to optimise well-being through comorbidity management, medication rationalisation, rehabilitation, and supported self-management.

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How this fits in

Heart failure with preserved ejection fraction (HFpEF) is common (about half of all patients with heart failure) but the condition is often unrecognised and poorly managed. No previous studies have provided a detailed characterisation of patients with HFpEF within primary care heart failure registers. In this study we confirmed diagnosis and phenotyped a cohort of patients recruited from primary care with possible HFpEF, comparing patients in whom HFpEF was confirmed with patients in whom HFpEF was refuted. Patients with HFpEF were differentiated from patients not meeting HFpEF diagnostic criteria by higher levels of obesity, frailty and symptoms, and worse physical functioning. Self-management and self-monitoring of worsening signs and symptoms of heart failure were extremely limited in patients with HFpEF . Management of comorbidities in HFpEF is essential but complex and needs to incorporate medication reviews and increased use of non-pharmacological interventions such as self-management support and exercise training or cardiac rehabilitation. Polypharmacy could be decreased by better differentiation between patients with HFpEF and HFrEF.

Characteristics of Patients with Heart Failure with Preserved Ejection Fraction in Primary Care: Baseline analysis of the OPTIMISE HFpEF cohort

Introduction

Heart Failure with Preserved Ejection Fraction (HFpEF) accounts for half of all heart failure (HF) and 70% of those with HF over the age of 65 [1]. Current evidence suggests HFpEF is driven by comorbid conditions especially obesity, hypertension, diabetes and kidney disease, leading to systemic inflammation and endothelial microvascular dysfunction [1,2]. Despite its prevalence, HFpEF remains poorly diagnosed, managed and researched [3-6]. Under-recognition of HFpEF relates to lack of awareness and uncertainty regarding its pathophysiology, treatment, and diagnostic criteria. Pathways to HF diagnosis are variable, and limited knowledge of HFpEF and a lack of relevant echocardiographic information lead to under-identification in primary care [3-5, 7].

Most patients with HF are managed in primary care, especially those with HFpEF who may not be referred to specialists, or if referred not provided with a treatment plan [3,8]. Evidence for effective pharmacological treatment specific to HFpEF is sparse, current recommendations are to control comorbid conditions and use diuretics to manage volume overload [9]. Lack of pharmacological treatment is thought to relate to patient heterogeneity, leading to interest in defining phenotypes that might respond to specific therapy. Phenotyping has been based on populations recruited into clinical trials with limited comorbidity or admitted for acute HF, and thus not representative of most patients in the community [10-13]. Characterising patients with HFpEF in primary care is an essential step towards improving diagnosis and management, as well as recruiting into trials.

This analysis presents baseline data from a longitudinal observational study that is a component of the Optimising Management of Patients with Heart Failure with Preserved Ejection Fraction in Primary Care (Optimise HFpEF) study [14]. Patients were recruited based on a search of primary care HF registers for patients with no record of reduced ejection fraction. In this report we describe the baseline characteristics of those patients in the cohort who were confirmed as having HFpEF, and compare them to patients in whom HFpEF was not confirmed.

Methods

Study design and setting

Study participants were recruited from 30 general practices in two regions of England: East of England and Oxfordshire/Thames Valley. Practices were included from cities, towns and semi-rural areas

varying by Index of Multiple Deprivation (IMD) from high deprivation to more affluent areas (IMD 2 – 9). Due to slow accrual, patients were also recruited from an older persons' clinic in London and a HF service in Cambridgeshire receiving primary care referrals. The study is supported by an active Patient Advisory Group, and patients were involved in development and analysis.

Participants

Patients with possible HFpEF were identified via an electronic medical record screening algorithm of HF registers in general practices and physical record screening in the outpatient clinics. The algorithm was designed to screen out patients with codes for left ventricular systolic dysfunction (LVSD) and cardiomyopathy. Patients identified in the electronic search were screened by General Practitioners against study criteria. Exclusion criteria included an EF <50%, moderate to severe systolic dysfunction, significant cognitive impairment or end of life care. Patients deemed eligible were invited to participate by letter from the practice. Those interested attended a baseline assessment where informed consent was obtained. Ethical approval was granted by the London–Surrey Research Ethics Committee (REC reference: 17/LO/2136).

HFpEF diagnosis was clinically adjudicated by a cardiologist based on a global evaluation of the available history of any heart failure symptoms, signs of HF, consideration of natriuretic peptide levels and evidence of relevant structural heart disease and/or diastolic dysfunction on transthoracic echocardiogram (TTE) as per European Society of Cardiology (ESC) guidelines criteria at start of recruitment (Box 1). A more detailed discussion of the diagnostic process for the study is available [15].

Variables

Variables included: physical characteristics; past medical history and comorbidities; heart function (12 lead electrocardiogram and TTE); oedema assessment, breathlessness and fatigue (modified Borg), frailty assessment by Clinical Frailty Scale (CFS), Survey of Health, Ageing and Retirement in Europe Frailty Instrument (SHARE-FI); cognition assessment (Montreal Cognitive Assessment [MOCA]); physical functioning (six minute walk test, gait speed) and physical activity levels (7 day accelerometer wear); laboratory testing (biochemistry, haematology, biomarkers); anxiety and depression (Hospital Anxiety and Depression Score [HADS]); HF quality of life (Kansas City Cardiomyopathy Questionnaire[KCCQ]), HF self-care (European Heart Failure Self-Care Behaviour Questionnaire [EHSCB]); HF symptoms (Symptom Status Questionnaire – Heart Failure), and health related quality of life (EQ-5D-5L). Validated assessments, standardised equipment and a detailed Manual of Operations and Procedures promoted consistency across sites.

Sample size

The target sample size was 270 recruited with an estimated 25% not being confirmed as HFpEF [16] to give a sample of 200 patients. We anticipated that 40% of patients on HF registers would be identifiable as possible HFpEF [5].

Statistical analysis

Patient characteristics and assessments were described using frequencies, measures of central tendency and proportions as appropriate. Normality for continuous data was assessed using the Shapiro-Wilk test and Qplots. Normally distributed data are presented as mean ± standard deviation, non-parametric as median and interquartile range (25-75%) and categorical data as absolute number and percent. Descriptive statistics are presented for the cohort, and comparisons according to confirmed HFpEF versus non-HFpEF using Chi Square for categorical variables and t-tests for normally distributed continuous data. Where data are missing, values are reported as such. Statistical analyses were performed using R, version 3.63 and SPSS, version 27.

Results

In primary care 52% of patients on HF registers were considered eligible. Between July 2018 and November 2019 152 patients were recruited, 16% of those eligible (Figure 1). Ninety-three (61%) were clinically adjudicated to have HFpEF. Participants with HFpEF (Table 1) had mean age 79.3 years (± 7.1), 46% were female and 60% had a history of smoking. Mean Charlson Comorbidity Index (CCI) was 4.8, and the majority were overweight or obese. Functional impairment was evident by six-minute walk distance (6MWD) and gait speed, and 63% had mild cognitive impairment. Over half were considered pre-frail or frail, and 40% were considered sarcopaenic by grip strength and gait speed. Sixteen percent reported occasional incontinence, and 4% were incontinent or had indwelling catheters.

Although our initial aim was to characterise and follow-up patients with HFpEF, we took the opportunity in this baseline analysis to compare patients confirmed as HFpEF with those not considered to have HFpEF. The non-HFpEF group primarily had a mixture of other HF diagnoses (e.g. valvular heart disease, hypertrophic cardiomyopathy, recovered EF), although the investigations were only intended to diagnose non-HFpEF patients. When delineating by confirmation of HFpEF, HFpEF patients were more likely to be pre-frail or frail, and have greater functional impairment based on 6MWD and gait speed. Patients with HFpEF were less physically active and spent more time in very low levels of activity compared to those not confirmed HFpEF [17]. Patients with HFpEF walked 65

metres less than the non-HFpEF group, and took more than two seconds longer to walk 10 metres. Sarcopaenia was more prevalent in the HFpEF versus non-HFpEF group (40% vs 29%, p = 0.176).

Laboratory tests were available for 131 (86%) participants (Table 2). Values were not significantly different between groups, although an estimated glomerular filtration rate (eGFR) less than 30ml/min was more frequent in those with HFpEF compared to those without. Natriuretic peptides (NT-proBNP) levels were a median of 301 pg/ml (IQR 73 - 1029) in the HFpEF group, and 332pg/ml (IQR 147 – 1112) in those without HFpEF. A small number of patients (6 with HFpEF) presented with NT-proBNP levels $\geq$ 2000pg/ml. Twice as many patients with HFpEF had HbA1c levels greater than 48 mmol/L than those without HFpEF (26.5% vs 13%, p = 0.085), and mean HbA1c in 39 patients known to have diabetes was 56.4 $\pm$ 16.7 mmol/L.

Patient reported outcome measures (Table 3) showed no statistically significant differences in scores except for daytime dyspnoea and fatigue (worse in people with HFpEF). Pharmacological treatment (Table 4) did not differ significantly between groups, with both prescribed an average of eight medications. Approximately one third of patients were on 10 or more medications. Most patients were prescribed diuretics, and about half were on beta-blockers. In contrast to pharmacological treatment, cardiac rehabilitation was infrequent.

Discussion

Summary

In this cohort of patients recruited mainly from HF registers in primary care (86%), the predominant characteristics of patients with HFpEF were a greater proportion of women, advanced age and multi-morbidity. Significant differences by group were found, as patients with HFpEF had more obesity, pre-frailty/frailty, functional impairment by 6MWD and gait speed, demonstrated lower levels of activity, and had greater likelihood of reporting symptoms such as dyspnoea and fatigue than those not confirmed HFpEF.

As might be expected in an older multi-morbid sample, patients were taking multiple medications. Sixty-five percent of patients with HFpEF were taking diuretics, but many presented with signs and symptoms of volume overload such as peripheral oedema. Although few abnormalities were found in laboratory values, HbA1c levels in patients with diabetes indicated that glycaemic control was less than optimal. Findings on the EHFSCB indicated that few patients with HFpEF agreed with statements that they regularly performed actions recommended for self-management such as monitoring weight gain or notifying a health care provider for signs and symptoms of worsening HF. Patients did not

report high levels of depression or anxiety symptoms, and quality of life scores were moderately high on both the KCCQ and EQ-5D-5L visual analogue scale.

Comparison with Other Studies

The prevalence of comorbidities has been reported to be higher in HFpEF than HFrEF, consistent with the idea that comorbid conditions drive the inflammatory response leading to HFpEF [16]. The elderly HFpEF patient with multiple comorbid conditions such as obesity, hypertension, diabetes and kidney disease, has been described as 'garden variety' HFpEF, indicating that this is a frequent phenotype encountered in clinical practice [1]. However, this common phenotype contrasts with HF clinical trials where limited reporting of comorbid conditions and low prevalence of obesity and multi-morbidity is usual in recruited patients with HFpEF [13]. Studies have attempted to delineate patients into distinct phenotypes based on clinical and diagnostic characteristics using patient samples from secondary care centres and clinical trials [10-12]. Currently there is no agreement on distinct phenogroups, and others have called for simpler designations using single characteristics such as sex, obesity and atrial fibrillation [18-19]. This analysis fills a gap in the literature by detailing the characteristics of the prevalent older, multi-morbid patient with HFpEF in primary care, revealing areas of need in their management.

Multiple studies have shown a greater prevalence of women among populations with HFpEF, although unclear if this is related to higher survival rates of women at older ages, or factors such as the stronger relationship between obesity and incident HFpEF among women compared to men [20]. Overweight and obesity is highly prevalent in patients with HFpEF (up to 80%) as is frailty [19, 21, 22]. A recent analysis of 4605 older patients (mean age 80.3) with HFpEF hospitalisation found that 41% had frailty, and that frailty was the most important predictor of re-hospitalisation, and second (after age) for mortality [22].

Exercise intolerance in HFpEF is due to both cardiac and peripheral factors, with pro-inflammatory factors, fatty infiltration and impaired oxidative metabolism leading to decreased muscle strength [23]. The average 6MWD difference between groups was 65 metres. A recent meta-analysis found each 50 metre 6MWD reduction was significantly associated with increased risk of all-cause mortality, readmission rates and combined death or readmission [24]. Although all patients had low activity levels, the average vector magnitude was lower in those with HFpEF compared to non-HFpEF patients, and less than in a UK Biobank sample of patients with HF and in another study of HFpEF [17, 25, 26].

Somewhat surprisingly, despite symptoms and limited functional status, quality of life scores were moderately high. The developers of the KCCQ define scores from 50 – 74 as fair to good health status,

and 75 and over as good to excellent [27]. The overall score on the EHFSCB scale was low compared to a sample of 1192 patients with either HFpEF or HFrEF (mean score 58.3, mean age 72 years, mean EF 45%) indicating fewer self-care behaviours among our cohort [28].

Implications for Practice

Our study demonstrates that multimorbidity, polypharmacy , obesity, pre-frailty/frailty, poor physical function, low activity levels and symptoms are prevalent in patients with HFpEF and present key management challenges. Patients with HFpEF often sit outside of specialist HF services in the UK due to commissioning restrictions, and primary care therefore takes the lead in managing patients [8, 29]. Current recommendations to manage comorbid conditions and to use diuretics [9] are not trivial given the number of co-existing conditions, detrimental effects of polypharmacy, and challenges of fluid balance in older adults with renal and functional impairment.

Implications for primary care practice begin with the identification of patients with HFpEF, which likely needs specialist support [15] but is important in ensuring appropriate treatment. For example, a decrease in polypharmacy in HFpEF could be enhanced by differentiation of HFpEF from HFrEF. Medications indicated for HFrEF should not be prescribed unless there is another indication (e.g. ACE inhibitor for blood pressure control), as they do not exert the same protective effect in HFpEF [1]. Medication reviews in primary care provide the opportunity to consider the necessity for specific medications.

Over half of the patients in both groups were prescribed diuretics, which often limit their ability and willingness to leave the house. The challenge of managing diuresis is further complicated if patients have incontinence as reported by 20% of patients in the sample. Managing fluid balance also requires consideration of patient behaviours and support to enable patients to monitor signs and symptoms, limit fluid and excessive salt intake if appropriate, and know when to contact a healthcare provider [9]. Scores on the EHFSCB indicated that many patients did not practice behaviours related to self-management. Teaching and supporting self-management should be a component of HF reviews, and all providers need to facilitate this partnership with patients.

Interventions to improve general health status like physical activity, dietary enhancement and management of breathlessness should be introduced. Exercise training or bespoke cardiac rehabilitation could be developed and commissioned given the evidence of benefit [26,30]. Home-based targeted rehabilitation such in the REACH-HFpEF pilot study [26] may improve patient and carer outcomes and be key to ensuring patient participation. The Rehab-HF trial demonstrated that recently hospitalised and very frail patients with HF benefit from rehabilitation [31].

New therapies to treat HFpEF may be added to current medication regimens in the future. Indications from recent studies are that medications such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, spironolactone, and sacubitril/valsartan may be effective, even if in specific sub-groups [1]. The American Heart Association and American College of Cardiology have made a limited recommendation for the use of spironolactone in some patients with HFpEF [32].

Strengths and Limitations

This study presents a well-phenotyped cohort of patients with HFpEF recruited mainly from primary care practices in 2 regions in England, indicating the challenges and problems faced. Recruitment was slow, and likely limited by focusing on patients on practice HF registers, so patients not yet diagnosed with HF or with HF not added to the register were excluded. Future studies may find more patients by searching the practice adult population for those on diuretics or combinations of medications used for HF [33]. Over half of the eligible sample did not respond to the study invitation, and 58% of those responding declined participation. Information about non-respondents/those declining was not collected, but it is plausible that some may have had poorer health or not thought the study was relevant to them. Limited recruitment may have introduced bias in our sample however, it is notable that our sample was older, multimorbid and functionally impaired, and came from both low and high areas of deprivation. The sample was limited by a high proportion of patients not confirmed as HFpEF. Confirmation of HFpEF was clinically adjudicated using symptoms, signs, NT-proBNP and echocardiogram data following ESC guidelines criteria [9]. Future studies may include additional testing to determine diagnosis.

Conclusions

Patients recruited from primary care with confirmed HFpEF demonstrate marked impairment across a range of domains including multi-morbidity, functional impairment and frailty. Patients with HFpEF had more obesity, reported more symptoms and had worse physical function than patients not confirmed as HFpEF. These findings highlight the need to recognise and record HFpEF as a diagnosis, which would enable clinicians to identify patients and work together to optimise well-being through comorbidity management, medication rationalisation, rehabilitation, and self-management.

Ethical approval was granted by the London–Surrey Research Ethics Committee (REC reference: 17/LO/2136).

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CONFLICT OF INTEREST

CJT reports personal fees from Vifor and Novartis, and non-financial support from Roche outside the submitted work. The authors declare that there is no conflict of interest.

AUTHOR'S CONTRIBUTIONS

All authors have approved the manuscript and agree to be accountable for all aspects of work. CD is the senior and corresponding author.

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Box 1

ESC Criteria for Diagnosis of HFpEF [9]

• Signs and symptoms of heart failure
• Ejection fraction ≥ 50%
• Elevated natriuretic peptides:
  ○ NT-proBNP ≥ 125 pg/ml
  ○ BNP ≥ 35 pg/ml
• Evidence of relevant structural heart disease and/or diastolic dysfunction:
  ○ Left ventricular hypertrophy (LVH): left ventricular mass index ≥ 115 g/m^2 for males and ≥ 95 g/m^2 for females
  ○ Increased left atrial volume index (LAVI): > 34 mL/m^2
  ○ Early diastolic tissue velocity (e'mean septal-lateral < 9cm/s)
  ○ Ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e' ≥ 13)
  ○ E/A ratio < 1 or > 2
  ○ Deceleration time (DecT) of mitral valve early diastolic inflow (MV-E) m/s (normal is < 240 m/s
  ○ Isovolumetric relaxation time (IVRT)

BNP = brain natriuretic peptide; cm/sec = centimetres per second; DecT = deceleration time; E= early mitral diastolic inflow; e' = early diastolic tissue velocity; E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity; g/ m^2 = grams per metre squared; LAVI = left atrial volume index; LVH = left ventricular hypertrophy; m/s = metres per second; mL/ m^2 = millilitres per metre squared; MV = mitral valve; pg/mL = picograms per millilitre; RV = right ventricle; TRV = peak tricuspid regurgitation velocity

Table 1 Characteristics of Sample and by HFpEF Diagnosis

	N	Total Sample n=152	Confirmed HFpEF n=93	Non-HFpEF n=59	p value for comparison
Mean Age	152	78.5 (8.6)	79.3 (7.1)	77 (10.5) years	0.156
Female Sex	152	40%	46%	29%	**0.039**
Mean LVEF	148	56.9 (9.2)	58.1 (7.1)	54.4 (10.8)	**0.023**
History of smoking	152	67%	60%	79%	**0.015**
Mean CCI	150	4.6 (2.6)	4.8 (2.8)	4.2 (2.2)	0.157
Hypertension	150	80%	80%	77%	0.636
Diabetes	150	29%	31.5%	26%	0.498
Chronic lung disease	150	29%	31.5%	23%	0.251
Moderate to severe kidney disease	150	33%	34%	32%	0.789
Previous myocardial infarction	149	13%	12%	14%	0.730
Peripheral vascular disease	150	8.5%	6.5%	12%	0.226
Previous stroke or TIA	150	14%	14%	16%	0.781
Cancer	150	16%	14%	19%	0.404
BMI mean	151	30.4 (6.6)	30.9 (6.2)	29.4 (7.1)	0.179
Overweight Obese	151	26% 50%	25% 57%	28% 39%	0.053
Combined overweight/obese	151	76%	82%	67%	**0.036**
NYHA Class I NYHA Class II NYHA Class III	152	22% 57% 20%	17% 62% 20%	31% 48% 21%	0.118
Leg oedema	152	45%	46%	43%	0.707
Sinus rhythm Atrial fibrillation Other	152	45% 34% 21%	49.5% 32% 19%	39% 39% 23%	0.435
Mean Heart rate	145	68.5 (14)	68 (13.5)	69.5 (14.6)	0.556
Mean Systolic blood pressure Mean SBP $\geq$ 150	150	136.4 (23) 31%	137.8 (23) 33%	134 (22) 28%	0.346 0.535
Mean Diastolic blood pressure Mean DBP $\geq$ 90	150	77.3 (12) 16%	77 (12) 15%	78 (11) 18%	0.577 0.643
Patients with known hypertension SBP DBP Pulse pressure	122	 142.3 (22.2) 79.8 (10.9) 62.6 (18.7)	 144.5 (22.8) 79.3 (11.1) 65.2 (18.6)	 138.9 (20.9) 80.6 (10.8) 58.3 (18.4)	 0.203 0.529 0.059
Pulse pressure	150	59 (19)	61 (17)	56 (20)	0.142
Mean MOCA score Mild cognitive impairment	146	25.4 (3.3) 57.5%	24.9 (4.3) 63%	24.8 (5.7) 48%	0.951 0.194
Pre-frail Frail	148	32% 22%	36% 26%	27% 18%	0.101
Combined Pre-frail/Frail	148	54%	63%	45%	**0.033**
Mean 6 minute walk distance	117	296.5 (127)	273 (123)	338 (125)	**0.007**
Mean Time (sec) to walk 10 m	117	10.8 (6.4)	11.7 (7.4)	9.1 (3.6)	**0.014**
Mean Gait speed (m/s)	117	1.13 (.47)	1.05 (0.39)	1.3 (0.55)	**0.010**
Activity Levels by median daily vector magnitude (IQR)	124	16.2 (12.2 – 20.2)	15.4 (12.0 – 18.3)	18.2 (12.9-21.5)	**0.018**
Sarcopaenia	147	35%	40%	29%	0.176
Occasional incontinence Incontinent or catheterised	151	17% 4%	16% 4%	19% 3.5%	0.867

BMI = body mass index; CCI = Charlson Comorbidity Index; DBP = diastolic blood pressure; m = metres; m/s = metres per second; MOCA = Montreal Cognitive Assessment; NYHA = New York Heart Association; SBP = systolic blood pressure; sec = seconds; TIA = transient ischaemic attack.

Table 2 Laboratory values by HFpEF diagnosis

Parameter	n	Total Sample n=152	Confirmed HFpEF n=93	Non-HFpEF n=59	p value for comparison
Median (IQR) NT-proBNP (pg/ml)	111	314 (124 – 1055)	301 (73 – 1029)	332 (147 – 1112)	0.841
eGFR	129	66 (21)	64.6 (20.7)	69.6 (19.7)	0.190
eGFR <30	129	5.5%	8.5%	0%	0.042
Random glucose (mmol/L)	120	6.8 (3.6)	6.9 (3.3)	6.7 (4)	0.797
Sodium (mmol/L)	129	139 (3.3)	139 (3)	138.6 (3.2)	0.286
Potassium (mmol/L)	128	4.2 (0.5)	4.2 (0.43)	4.2 (0.48)	0.401
Creatinine	130	93 (39)	94.6 (43)	90.5 (31)	0.570
Urea	122	8.6 (5.2)	8.9 (6)	8.1 (3)	0.378
Haemoglobin (g/L)	131	131 (17)	129.6 (15.5)	134.6 (19)	0.130
Haematocrit (%)	129	0.4 (0.04)	0.39 (.05)	0.41 (0.6)	0.141
Platelets	130	229.5 (77)	232.5 (77)	227 (76)	0.677
HbA1c	129	44.9 (12.7)	45.8 (12)	43 (13.9)	0.250
HbA1c >48	129	22.5%	26.5%	13%	0.085
HbA1c known diabetes	39	56.4 (16.7)	56.5 (14.2)	56.2 (22.6)	0.955

eGFR = estimated glomerular filtration rate; g/L = grams per litre; HbA1c = glycosylated haemoglobin A1c; IQR = interquartile range; mmol/L = millimoles per litre; pg/ml = picograms per millilitre.

Table 3. Patient Reported Measures by HFpEF Diagnosis

PROMs	HFpEF n=93	Non-HFpEF n=59	p value for comparison
KCCQ			
KCCQ Physical Limitations	67 (28)	73 (28)	0.205
KCCQ Quality of life	69.4 (29)	73 (25.5)	0.410
KCCQ Symptom Total	72 (25)	78 (26)	0.171
KCCQ Clinical Summary	70 (24)	76.6 (25)	0.118
KCCQ Summary	71 (25)	74 (25)	0.374
HADS			
HADS Depression	7.6 (2.3)	7.2 (2.5)	0.236
Moderate to severe depressive symptoms	8.9%	6.9%	0.810
HADS Anxiety	5.2 (4.4)	4.7 (3.9)	0.455
Moderate to severe anxiety symptoms	11.2%	12.1%	0.904
EQ-5D-5L			
EQ-5D-5L QoL VAS	70 (19.4)	72.9 (18.9)	0.387
No problems with mobility	29%	36%	0.815
No problems with self-care	73%	65.5%	0.524
No problems with usual activities	40%	50%	0.519
No pain or discomfort	47%	55%	0.698
No anxiety or depression	58%	71%	0.121
Symptom Status Questionnaire (reported symptoms)			
Daytime dyspnoea	63%	46%	**0.035**
Orthopnoea	22%	25%	0.743
Fatigue/lack of energy	81%	61%	**0.012**
Chest pain	82%	82.5%	0.978
Difficulty sleeping	47%	46%	0.901
Dizziness or loss of balance	48%	35%	0.130
Mean Total Score	24.4 (18.4)	22.3 (20.5)	0.503
European Heart Failure Self-Care Behaviour Scale			
Mean Total Score	46.5 (21.2)	43.5 (22.2)	0.426
Percent responding '*do not agree at all*' on some individual items on EHFSCB scale			
I weigh myself every day	61%	68%	0.475
If my shortness of breath increases, I contact my doctor or nurse	48%	39%	0.418
If my feet/legs become more swollen than usual I contact my doctor or nurse	41%	46%	0.930
If I gain 2kg in one week I contact my doctor or nurse	72%	70%	0.937

EHFSCB = European Heart Failure Self-care Behaviours; EQ-5D-5L = ; HADS = Hospitals Anxiety and Depression Scale; HFpEF = heart failure with preserved ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; kg = kilograms; QoL = Quality of life; VAS = visual analogue scale.

Table 4. Pharmacological Treatment by HFpEF Diagnosis

Pharmacological agent	HFpEF n=93	Non-HFpEF n=59	p value for comparison
Number of prescription medications	8.3 ± 4	7.8 ± 3.9	0.454
≥ 10 medications	37%	30%	0.398
ACEI	34%	37%	0.698
ARB	30%	32%	0.840
ARNI	1%	2%	0.743
MRA	12%	17.5%	0.355
Beta blockers	48%	54%	0.475
Calcium channel blockers	32%	40%	0.315
Loop diuretics	57%	51%	0.456
Any diuretic	65%	61%	0.673
Digoxin	16%	22%	0.334
Statins	58%	63%	0.552
Aspirin	21%	28%	0.316
Other anti-platelet	7%	5%	0.729
Anticoagulation	51%	65%	0.100
Anti-coagulation if AF (n = 48)	96%	90.5%	0.409
Antidepressants	16%	9%	0.232
Anti-Anaemia drugs	13.5%	5.3%	0.111
Uric acid related drugs	19%	17.5%	0.813
NSAIDs	2.2%	1.8%	0.845
Patients with Diabetes (n = 44)			
Insulin	25%	40%	0.307
Biguanides	48%	47%	0.927
Sulfonylureas	15%	20%	0.666
SGLT2 inhibitors	7%	0%	0.535
DPP4 inhibitors	17%	20%	0.822
Non-Pharmacologic Management			
Attended CR in past	13%	16%	0.640
Currently attending CR	3.3%	0%	0.168

ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CR = cardiac rehabilitation; DPP4 = dipeptidyl peptidase-4; HFpEF = heart failure with preserved ejection fraction; MRA = mineralocorticoid receptor antagonist; NSAIDs = non-steroidal anti-inflammatory drugs; SGLT2 = sodium glucose cotransporter-2;

Figure 1. Patient Flow Chart