Characteristics of patients with heart failure with preserved ejection fraction in primary care: a 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 heart failure (HF) subtype. Improvements in management of HFpEF is dependent on improved identification and characterisation of patients in primary care.

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

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

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

Results: In total, 93 (61%) of 152 patients were confirmed HFpEF. The mean age of patients with HFpEF was 79 years, 46% were female, 80% had hypertension, and 37% took ≥10 medications. Patients with HFpEF were more likely to be obese, pre-frail or 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.

Conclusion: 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 wellbeing through comorbidity management, medication rationalisation, rehabilitation, and supported self-management.

How this fits in

HFpEF is common (about half of all patients with HF) but the condition is often unrecognised and poorly managed. To the authors’ knowledge, no previous studies have provided a detailed...
characterisation of patients with HFrEF within primary care HF registers. This study confirmed diagnosis and phenotyped a cohort of patients recruited from primary care with possible HFrEF, comparing patients in whom HFrEF was confirmed with patients in whom HFrEF was refuted. Patients with HFrEF were differentiated from patients not meeting HFrEF 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 HF were extremely limited in patients with HFrEF. Management of comorbidities in HFrEF is essential but complex. It 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 HFrEF and heart failure with reduced ejection fraction (HFrEF).

Introduction
HFrEF accounts for half of all HF and 70% of those with HF aged >65 years.\(^1\) Current evidence suggests HFrEF 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, HFrEF remains poorly diagnosed, managed, and researched.\(^3-6\) Under-recognition of HFrEF relates to lack of awareness and uncertainty regarding its pathophysiology, treatment, and diagnostic criteria. Pathways to HF diagnosis are variable, and limited knowledge of HFrEF and a lack of relevant echocardiographic information leads to under-identification in primary care.\(^3-5,7\)

Most patients with HF are managed in primary care, especially those with HFrEF 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 HFrEF 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 HFrEF 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 HFrEF) 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, the baseline characteristics of those patients in the cohort who were confirmed as having HFrEF are described, and they are compared to patients in whom HFrEF was not confirmed.

Method

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) score from high deprivation to more affluent areas (IMD 2–9). Owing 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 HFrEF 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 GPs 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.
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 elsewhere.15

Variables
Variables included: physical characteristics; past medical history and comorbidities; heart function (12-lead electrocardiogram and transthoracic echocardiogram [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 (6-minute walk distance, 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).
[EHFScB] Scale); 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 HfPfEF to give a sample of 200 patients. It was anticipated that 40% of patients on HF registers would be identifiable as possible HfPfEF.

**Statistical analysis**
Patient characteristics and assessments were described using frequencies, measures of central tendency, and proportions as appropriate. Normality for continuous data were assessed using the Shapiro-Wilk test and Q-Q plots. 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 per cent. Descriptive statistics are presented for the cohort, and comparisons according to confirmed HfPfEF versus non-HfPfEF using χ² 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 3.6.3) and IBM SPSS Statistics (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 were eligible (Figure 1). Ninety-three (61%) were clinically adjudicated to have HfPfEF. Participants with HfPfEF (Table 1) had a mean age of 79 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 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 per cent reported occasional incontinence, and 4% were incontinent or had indwelling catheters.

Although the initial aim was to characterise and follow-up patients with HfPfEF, the authors took the opportunity in this baseline analysis to compare patients confirmed as HfPfEF with those not considered to have HfPfEF. The non-HfPfEF group primarily had a mixture of other HF diagnoses (for example, valvular heart disease, hypertrophic cardiomyopathy, and recovered EF), although the investigations were only intended to diagnose patients without HfPfEF. When delineating by confirmation of HfPfEF, patients with HfPfEF were more likely to be pre-frail or frail, and have greater functional impairment based on 6MWD and gait speed. Patients with HfPfEF were less physically active and spent more time in very low levels of activity compared with those not confirmed HfPfEF. Patients with HfPfEF walked 65 m less than the non-HfPfEF group, and took >2 seconds longer to walk 10 m. Sarcopaenia was more prevalent in the HfPfEF versus non-HfPfEF group (40% versus 29%, P = 0.176) (Table 1).

Laboratory tests were available for 131 (86%) participants (Table 2). Values were not significantly different between groups, although an estimated glomerular filtration rate (eGFR) <30 ml/min was more frequent in those with HfPfEF compared with those without. Natriuretic peptides (NT-proBNP) levels were a median of 301 pg/ml (interquartile range [IQR] 73–1029) in the HfPfEF group, and 332 pg/ml (IQR 147–1112) in those without HfPfEF. A small number of patients (six with HfPfEF) presented with NT-proBNP levels >2000 pg/ml. Twice as many patients with HfPfEF had HbA1c levels >48 mmol/l than those without HfPfEF (26% versus 13%, P = 0.085), and mean HbA1c in 39 patients known to have diabetes was 56.4±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 HfPfEF). 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 medications. Most patients were prescribed diuretics, and about half were on beta-blockers. In contrast to pharmacological treatment, cardiac rehabilitation was infrequent.
Table 1 Characteristics of sample and by HFpEF diagnosis

| Characteristic                              | n   | Total sample, n = 152, %a | Confirmed HFpEF, n = 93, %a | Non-HFpEF, n = 59, %a | P value for comparisonb |
|---------------------------------------------|-----|---------------------------|-----------------------------|-----------------------|-------------------------|
| Age, years, mean (SD)                       | 152 | 78 (8.6)                  | 79 (7.1)                    | 77 (10.5)             | 0.156                   |
| Sex, female                                 | 152 | 40                        | 46                          | 29                    | 0.039                   |
| LVEF, mean (SD)                             | 148 | 56.9 (9.2)                | 58.1 (7.1)                  | 54.4 (10.8)           | 0.023                   |
| History of smoking                          | 152 | 67                        | 60                          | 79                    | 0.015                   |
| CCI, mean (SD)                              | 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                        | 32                          | 26                    | 0.498                   |
| Chronic lung disease                        | 150 | 29                        | 32                          | 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 | 9                         | 7                           | 12                    | 0.226                   |
| Previous stroke or TIA                      | 150 | 14                        | 14                          | 16                    | 0.781                   |
| Cancer                                      | 150 | 16                        | 14                          | 19                    | 0.404                   |
| BMI, mean (SD)                              | 151 | 30.4 (6.6)                | 30.9 (6.2)                  | 29.4 (7.1)            | 0.179                   |
| Overweight                                  | 151 | 26                        | 25                          | 28                    | 0.053                   |
| Obese                                       | 151 | 50                        | 57                          | 39                    |                         |
| Combined overweight or obese               | 151 | 76                        | 82                          | 67                    | 0.036                   |
| NYHA class I                                | 152 | 22                        | 17                          | 31                    | 0.118                   |
| NYHA class II                               | 152 | 57                        | 62                          | 48                    |                         |
| NYHA class III                              | 152 | 20                        | 20                          | 21                    |                         |
| Leg oedema                                  | 152 | 45                        | 46                          | 43                    | 0.707                   |
| Sinus rhythm                                | 152 | 45                        | 50                          | 39                    | 0.435                   |
| Atrial fibrillation                         | 152 | 34                        | 32                          | 39                    |                         |
| Other                                       | 152 | 21                        | 19                          | 23                    |                         |
| Heart rate, mean (SD)                       | 145 | 68 (14)                   | 68 (13)                     | 69 (15)               | 0.556                   |
| SBP, mean (SD)                              | 150 | 136 (23)                  | 138 (23)                    | 134 (22)              | 0.346                   |
| SBP >150, mean %                            | 150 | 31                        | 33                          | 28                    | 0.535                   |
| DBP, mean (SD)                              | 150 | 77 (12)                   | 77 (12)                     | 78 (11)               | 0.577                   |
| DBP >90, mean %                             | 150 | 16                        | 15                          | 18                    | 0.643                   |
| Pulse pressure, mean (SD)                   | 150 | 59 (19)                   | 61 (17)                     | 56 (20)               | 0.142                   |
| MoCA score, mean (SD)                       | 146 | 25.4 (3.3)                | 24.9 (4.3)                  | 24.8 (5.7)            | 0.951                   |
| Mild cognitive impairment                   | 146 | 58                        | 63                          | 48                    | 0.194                   |
| Pre-frail                                   | 148 | 32                        | 36                          | 27                    | 0.101                   |
| Frail                                       | 148 | 22                        | 26                          | 18                    |                         |
| Combined pre-frail and frail                | 148 | 54                        | 63                          | 45                    | 0.033                   |
| 6-minute walk distance, mean (SD)           | 117 | 296 (127)                 | 273 (123)                   | 338 (125)             | 0.007                   |
| Time to walk 10 m, sec, mean (SD)           | 117 | 10.8 (6.4)                | 11.7 (7.4)                  | 9.1 (3.6)             | 0.014                   |
| Gait speed, m/s, mean (SD)                  | 117 | 1.13 (0.47)               | 1.05 (0.39)                 | 1.3 (0.55)            | 0.010                   |

continued on next page
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 females, advanced age, and multimorbidity. Significant differences by group were found, as patients with HFpEF had more obesity, pre-frailty or 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.

Table 1

| Characteristic                                      | n   | Total sample, n = 152, %a | Confirmed HFpEF, n = 93, %a | Non-HFpEF, n = 59, %a | P value for comparisonb |
|-----------------------------------------------------|-----|---------------------------|-----------------------------|------------------------|-------------------------|
| 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                   |
| Sarcopenia                                          | 147 | 35                        | 40                          | 29                     | 0.176                   |
| Occasional incontinence                             | 151 | 17                        | 16                          | 19                     | 0.867                   |
| Incontinent or catheterised                         | 151 | 4                         | 4                           | 4                      |                         |

Patients with known hypertension

| Parameter                | n   | Total sample, n = 152, mean (SD)a | Confirmed HFpEF, n = 93, mean (SD)a | Non-HFpEF, n = 59, mean (SD)a | P value for comparison |
|--------------------------|-----|-----------------------------------|------------------------------------|-------------------------------|-----------------------|
| SBP, mean (SD)           | 122 | 142.3 (22.2)                      | 144.5 (22.8)                       | 138.9 (20.9)                 | 0.203                 |
| DBP, mean (SD)           | 122 | 79.8 (10.9)                       | 79.3 (11.1)                        | 80.6 (10.8)                  | 0.529                 |
| Pulse pressure, mean (SD)| 122 | 62.6 (18.7)                       | 65.2 (18.6)                        | 58.3 (18.4)                  | 0.059                 |

*Unless otherwise stated. **Bold indicates statistically significant value. BMI = body mass index. CCI = Charlson Comorbidity Index. DBP = diastolic blood pressure. HFpEF = heart failure with preserved ejection fraction. IQR = interquartile range. LVEF = left ventricular ejection fraction. MoCA = Montreal Cognitive Assessment. NYHA = New York Heart Association. SBP = systolic blood pressure. SD = standard deviation. TIA = transient ischaemic attack.

Table 2

| Parameter            | n   | Total sample, n = 152, mean (SD)a | Confirmed HFpEF, n = 93, mean (SD)a | Non-HFpEF, n = 59, mean (SD)a | P value for comparison |
|----------------------|-----|-----------------------------------|------------------------------------|-------------------------------|-----------------------|
| NT-proBNP, pg/ml, median (IQR) | 111 | 314 (124–1055)                    | 301 (73–1029)                      | 332 (147–1112)               | 0.841                 |
| eGFR                 | 129 | 66 (21)                           | 65 (21)                            | 70 (20)                      | 0.190                 |
| eGFR <30, %          | 129 | 5                                 | 8                                  | 0                             | 0.042                 |
| Random glucose, mmol/l | 120 | 6.8 (4)                           | 6.9 (3)                            | 6.7 (4)                      | 0.797                 |
| Sodium, mmol/l       | 129 | 139 (3)                           | 139 (3)                            | 139 (3)                      | 0.286                 |
| Potassium, mmol/l    | 128 | 4.2 (0.5)                         | 4.2 (0.4)                          | 4.2 (0.5)                    | 0.401                 |
| Creatinine, μmol/l   | 130 | 93 (39)                           | 95 (43)                            | 90 (31)                      | 0.570                 |
| Urea, mmol/l         | 122 | 8.6 (5)                           | 8.9 (6)                            | 8.1 (3)                      | 0.378                 |
| Haemoglobin, g/l     | 131 | 131 (17)                          | 130 (15.5)                         | 135 (19)                     | 0.130                 |
| Haematocrit, %       | 129 | 0.4 (0.04)                        | 0.39 (0.05)                        | 0.41 (0.06)                  | 0.141                 |
| Platelets            | 130 | 229 (77)                          | 232 (77)                           | 227 (76)                     | 0.677                 |
| HbA1c                | 129 | 45 (13)                           | 46 (12)                            | 43 (14)                      | 0.250                 |
| HbA1c >48, %         | 129 | 22                                | 26                                 | 13                           | 0.085                 |
| HbA1c known diabetes | 39  | 56.4 (16.7)                       | 56.5 (14.2)                        | 56.2 (22.6)                  | 0.955                 |

*Unless otherwise stated. eGFR = estimated glomerular filtration rate. HbA1c = glycosylated haemoglobin A1c. HFpEF = heart failure with preserved ejection fraction. NT-proBNP = N-terminal pro B-type natriuretic peptide. SD = standard deviation.

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 females, advanced age, and multimorbidity. Significant differences by group were found, as patients with HFpEF had more obesity, pre-frailty or 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.
### Table 3 Patient reported measures by HFpEF diagnosis

| Patient reported outcome measures                              | HFpEF, n = 93, %a | Non-HFpEF, n = 59, %a | P value for comparison |
|-----------------------------------------------------------------|--------------------|------------------------|------------------------|
| **Kansas City Cardiomyopathy Questionnaire**                    |                    |                        |                        |
| Physical limitations, mean (SD)                                 | 67 (28)            | 73 (28)                | 0.205                  |
| Quality of life, mean (SD)                                      | 69 (29)            | 73 (25)                | 0.410                  |
| Symptom total, mean (SD)                                        | 72 (25)            | 78 (26)                | 0.171                  |
| Clinical summary, mean (SD)                                     | 70 (24)            | 77 (25)                | 0.118                  |
| Summary, mean (SD)                                              | 71 (25)            | 74 (25)                | 0.374                  |
| **Hospital Anxiety and Depression Scale**                       |                    |                        |                        |
| Depression mean (SD)                                           | 7.6 (2.3)          | 7.2 (2.5)              | 0.236                  |
| Moderate-to-severe depressive symptoms                          | 8.9                | 6.9                    | 0.810                  |
| Anxiety mean (SD)                                               | 5.2 (4.4)          | 4.7 (3.9)              | 0.455                  |
| Moderate-to-severe anxiety symptoms                             | 11.2               | 12.1                   | 0.904                  |
| **EQ-SD-5L**                                                    |                    |                        |                        |
| Quality of life visual analogue scale, mean (SD)                | 70 (19)            | 73 (19)                | 0.387                  |
| No problems with mobility                                       | 29                 | 36                     | 0.815                  |
| No problems with self-care                                      | 73                 | 66                     | 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 or lack of energy                                       | 81                 | 61                     | 0.012                  |
| Chest pain                                                      | 82                 | 83                     | 0.978                  |
| Difficulty sleeping                                             | 47                 | 46                     | 0.901                  |
| Dizziness or loss of balance                                    | 48                 | 35                     | 0.130                  |
| Total score, mean (SD)                                          | 24.4 (18.4)        | 22.3 (20.5)            | 0.503                  |
| **EHFScB**                                                      |                    |                        |                        |
| Total score, mean (SD)                                          | 46.5 (21.2)        | 43.5 (22.2)            | 0.426                  |
| **Responded ‘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 or legs become more swollen than usual I contact my doctor or nurse | 41 | 46 | 0.930 |
| If I gain 2 kg in 1 week I contact my doctor or nurse           | 72                 | 70                     | 0.937                  |

*Unless otherwise stated. EHFSCB = European Heart Failure Self-care Behaviours. EQ-SD-5L = EuroQoL - 5 dimensions - 5 levels. HFpEF = heart failure with preserved ejection fraction. SD = standard deviation.
As might be expected in an older multimorbid sample, patients were taking multiple medications. Sixty-five per cent 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 healthcare provider for signs and symptoms of worsening HF. Patients did not

| Table 4 Pharmacological treatment by HFpEF diagnosis |
|-----------------------------------------------|
| Pharmacological agent                  | HFpEF, n = 93, %a | Non-HFpEF, n = 59, %a | P value for comparison |
|-------------------------------------------|-------------------|-----------------------|------------------------|
| Prescribed medications, mean (SD)        | 8.3 (4.0)         | 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                | 18                    | 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 antiplatelet                       | 7                 | 5                     | 0.729                  |
| Anticoagulation                          | 51                | 65                    | 0.100                  |
| Anticoagulation if AFb                    | 96                | 91                    | 0.409                  |
| Antidepressants                          | 16                | 9                     | 0.232                  |
| Anti-anaemia drugs                       | 14                | 5                     | 0.111                  |
| Uric acid-related drugs                  | 19                | 18                    | 0.813                  |
| NSAIDs                                   | 2                 | 2                     | 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                 | 0                     | 0.168                  |

*Unless otherwise stated. a n = 48. 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. SD = standard deviation. SGLT2 = sodium glucose co-transporter-2.
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.

**Strengths and limitations**

This study presents a well-phenotyped cohort of patients with HFrEF recruited mainly from primary care practices in two 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. Over half of the eligible sample did not respond to the study invitation, and 58% of those responding declined participation. Information about non-responders or 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 the sample; however, it is notable that the sample was older, multimorbid, 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 HFrEF. Confirmation of HFrEF was clinically adjudicated using symptoms, signs, NT-proBNP, and echocardiogram data, following European Society of Cardiology (ESC) guidelines criteria. Future studies may include additional testing to determine diagnosis.

**Comparison with existing literature**

The prevalence of comorbidities has been reported to be higher in HFrEF than HFrEF, consistent with the idea that comorbid conditions drive the inflammatory response leading to HFrEF. The older patients with HFrEF with multiple comorbid conditions, such as obesity, hypertension, diabetes, and kidney disease, has been described as ‘garden variety’ HFrEF, indicating that this is a frequent phenotype encountered in clinical practice. However, this common phenotype contrasts with HF clinical trials where limited reporting of comorbid conditions and low prevalence of obesity and multimorbidity is usual in recruited patients with HFrEF. 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. 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. This analysis fills a gap in the literature by detailing the characteristics of the prevalent patient who is older and multimorbid with HFrEF in primary care, revealing areas of need in their management.

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

Exercise intolerance in HFrEF is owing to both cardiac and peripheral factors, with pro-inflammatory factors, fatty infiltration, and impaired oxidative metabolism leading to decreased muscle strength. The average 6MWD difference between groups was 65 m. A recent meta-analysis found each 50 m 6MWD reduction was significantly associated with increased risk of all-cause mortality, readmission rates, and combined death or readmission. Although all patients had low activity levels, the average vector magnitude was lower in those with HFrEF compared with patients without HFrEF, and less than in a UK Biobank sample of patients with HF and in another study of HFrEF. Somewhat surprisingly, despite symptoms and limited functional status, quality-of-life scores were moderately high. The developers of the KCCQ define scores from 50 to 74 as fair to good health status, and ≥75 as good to excellent. The overall score on the EHFSbc Scale was low compared with a sample of 1192 patients with either HFrEF or HFrEF (mean score 58.3, mean age 72 years, mean EF 45%), indicating fewer self-care behaviours among the cohort in the present study.
Implications for practice

The study demonstrates that multimorbidity, polypharmacy, obesity, pre-frailty and 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 owing to commissioning restrictions, and primary care therefore takes the lead in managing patients.\textsuperscript{8,30} Current recommendations to manage comorbid conditions and to use diuretics\textsuperscript{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,\textsuperscript{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 (for example, angiotensin-converting enzyme inhibitor for blood pressure control), as they do not exert the same protective effect in HFpEF.\textsuperscript{2} 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 almost 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.\textsuperscript{6} 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, such as 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.\textsuperscript{27,31} Home-based targeted rehabilitation, such as in the REACH-HFpEF pilot study,\textsuperscript{27} may improve patient and carer outcomes and be key to ensuring patient participation. The Rehab-HF trial demonstrated that patients who were recently hospitalised and very frail with HF benefit from rehabilitation.\textsuperscript{32}

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 co-transporter-2 (SGLT2) inhibitors, spironolactone, and sacubitril with valsartan may be effective, even if in specific subgroups.\textsuperscript{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.\textsuperscript{33}

Patients recruited from primary care with confirmed HFpEF demonstrate marked impairment across a range of domains including multimorbidity, functional impairment, and frailty. 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 wellbeing through comorbidity management, medication rationalisation, rehabilitation, and self-management.

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