ESC European Society of Cardiology

European Journal of Heart Failure (2023)
doi:10.1002/ejhf.2962

RESEARCH ARTICLE

Impact of comorbidities on health status measured using the Kansas City Cardiomyopathy Questionnaire in patients with heart failure with reduced and preserved ejection fraction

Mingming Yang[1,2], Toru Kondo[1,3], Carly Adamson[1], Jawad H. Butt[1,4], William T. Abraham[5], Akshay S. Desai[6], Karola S. Jering[6], Lars Køber[4], Mikhail N. Kosiborod[7], Milton Packer[8], Jean L. Rouleau[9], Scott D. Solomon[6], Muthiah Vaduganathan[6], Michael R. Zile[10], Pardeep S. Jhund[1], and John J.V. McMurray[1]*

[1]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [2]Department of Cardiology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, China; [3]Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [4]Department of Cardiology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; [5]Division of Cardiovascular Medicine, The Ohio State University, Columbus, OH, USA; [6]Cardiovascular Division, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA; [7]Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City, Kansas City, MS, USA; [8]Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, TX, USA; [9]Institut de Cardiologie de Montréal, Université de Montréal, Montréal, QC, Canada; and [10]RHJ Department of Veterans Affairs Medical Center, Medical University of South Carolina, Charleston, SC, USA

Received 15 May 2023; revised 18 June 2023; accepted 28 June 2023

Aim

Patients with heart failure (HF) often suffer from a range of comorbidities, which may affect their health status. The aim of this study was to assess the impact of different comorbidities on health status in patients with HF and reduced (HFrEF) and preserved ejection fraction (HFpEF).

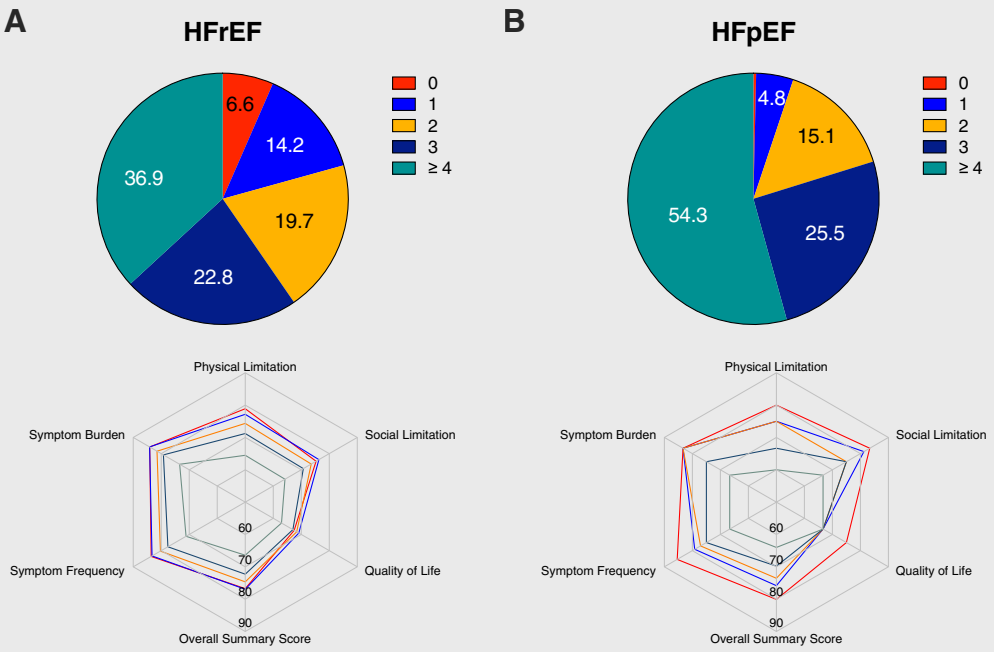
Methods and results

Using individual patient data from HFrEF (ATMOSPHERE, PARADIGM-HF, DAPA-HF) and HFpEF (TOPCAT, PARAGON-HF) trials, we examined the Kansas City Cardiomyopathy Questionnaire (KCCQ) domain scores and overall summary score (KCCQ-OSS) across a range of cardiorespiratory (angina, atrial fibrillation [AF], stroke, chronic obstructive pulmonary disease [COPD]) and other comorbidities (obesity, diabetes, chronic kidney disease [CKD], anaemia). Of patients with HFrEF ($n = 20\,159$), 36.2% had AF, 33.9% CKD, 33.9% diabetes, 31.4% obesity, 25.5% angina, 12.2% COPD, 8.4% stroke, and 4.4% anaemia; the corresponding proportions in HFpEF ($n = 6563$) were: 54.0% AF, 48.7% CKD, 43.4% diabetes, 53.3% obesity, 28.6% angina, 14.7% COPD, 10.2% stroke, and 6.5% anaemia. HFpEF patients had lower KCCQ domain scores and KCCQ-OSS (67.8 vs. 71.3) than HFrEF patients. Physical limitations, social limitations and quality of life domains were reduced more than symptom frequency and symptom burden domains. In both HFrEF and HFpEF, COPD, angina, anaemia, and obesity were associated with the lowest scores. An increasing number of comorbidities was associated with decreasing scores (e.g. KCCQ-OSS 0 vs. ≥4 comorbidities: HFrEF 76.8 vs. 66.4; HFpEF 73.7 vs. 65.2).

*Corresponding author. British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow, G12 8TA, UK. Tel: +44 141 3303479, Fax: +44 141 3306955, Email: john.mcmurray@glasgow.ac.uk

Conclusions Cardiac and non-cardiac comorbidities are common in both HFrEF and HFpEF patients and most are associated with reductions in health status although the impact varied among comorbidities, by the number of comorbidities, and by HF phenotype. Treating/correcting comorbidity is a therapeutic approach that may improve the health status of patients with HF.

Graphical Abstract



Kansas City Cardiomyopathy Questionnaire (KCCQ) domain and overall summary scores (KCCQ-OSS) according to cumulative comorbidity burden in patients with heart failure with reduced (HFrEF, *A*) and preserved ejection fraction (HFpEF, *B*). Comorbidities used to calculate the burden are the following: angina, atrial fibrillation, stroke, chronic obstructive pulmonary disease; obesity; diabetes; chronic kidney disease; anaemia; hypertension; myocardial infarction. Comorbidity burden is presented as number of comorbidities: 0, 1, 2, 3, ≥4. Mean KCCQ scores for each domain and the KCCQ-OSS (each score out of 100) are shown. The centre of the plot represents a score of 50 and the outer limit represents a score of 90. The greater the reduction in the coloured rings from the outer ring of the web, the greater the reduction in each domain score or KCCQ-OSS. The coloured lines show the reduction in health status with increasing number of comorbidities.

Keywords Heart failure • Comorbidity • Quality of life • Symptoms • Natriuretic peptides • Kansas City Cardiomyopathy Questionnaire

Introduction

Both cardiac and non-cardiac comorbidities are increasingly prevalent in patients with heart failure (HF). Many comorbidities have been consistently associated with higher rates of all-cause mortality and HF admissions and readmissions in acute and chronic HF, both in clinical trials and in registries.[1–3] While it is also clear that individual comorbidities are associated with worse health-related quality of life (HRQoL) in patients with HF, the relative impact of different comorbidities on HRQoL has not been studied systematically. Similarly, the cumulative impact of multiple comorbidities on HRQoL has not been investigated. Additionally, how comorbidities affect HRQoL in patients with HF and reduced ejection fraction (HFrEF) compared to those with HF and preserved ejection fraction (HFpEF) has not been reported.[4,5] As comorbidities themselves may be treatment targets in HF, a better understanding of their impact on HRQoL may help in achieving the important therapeutic goal of improving patient symptoms and well-being in HF. Therefore, we conducted a comprehensive analysis of the association between a wide spectrum of comorbidities and HRQoL in two large HFrEF and HFpEF populations created by pooling patient-level data from five randomized controlled trials.[6–10] In all

patients, HRQoL was assessed using the validated 23-item Kansas City Cardiomyopathy Questionnaire (KCCQ).

Methods

Trials and patients

In the present study, we pooled individual patient-level data from three HFrEF trials (ATMOSPHERE, NCT00853658; PARADIGM-HF, NCT01035255; and DAPA-HF, NCT03036124) and two HFpEF trials (TOPCAT, NCT00094302; and PARAGON-HF, NCT01920711) that collected KCCQ data. The designs and results of these trials are published[6–10] and are summarized in online supplementary *Table S1*. Patients randomized in Russia and Georgia were excluded from the analysis of TOPCAT due to concerns about trial conduct in those countries.[11] All the trials were approved by the ethics committee at participating centres and written informed consent was provided by all the patients.

Identification and definition of the comorbidities

We initially examined 10 comorbidities: investigator-reported history of angina, atrial fibrillation (AF), stroke, chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), hypertension, and myocardial infarction. We also investigated obesity (defined as a body mass index $\geq$30 kg/m^2), chronic kidney disease (CKD) defined by an estimated glomerular filtration rate <60 ml/min/1.73 m^2, and moderate to severe anaemia defined as a haemoglobin level <110 g/L. We have focused on eight of these (four cardiorespiratory and four other comorbidities) in the manuscript because two (history of hypertension and myocardial infarction) were not associated with any meaningful difference in KCCQ scores (however, these are included in the online supplementary material).

Kansas City Cardiomyopathy Questionnaire scores

As recently reviewed by Spertus *et al.*,[12] the 23-item KCCQ includes 23 items that map to seven domains: symptom frequency; symptom burden; symptom stability (which measures recent changes in symptoms, comparing the frequency of symptoms at the time of completing the KCCQ with their frequency 2 weeks earlier); physical limitations (quantifying the limitations patients experience, the extent to which HF symptoms restrict routine activities); social limitations (quantifying the extent to which HF symptoms limit engagement in social activities); quality of life; and self-efficacy (patient understanding of how to manage their HF). The symptom frequency and symptom burden domains combined create the total symptom score, and this can be combined with the physical limitations domain to create the clinical summary score (this is believed to most closely correspond to the New York Heart Association [NYHA] classification). The symptom, physical limitations, social limitations, and quality of life domains can also be combined to create the overall summary score (OSS). The symptom stability and self-efficacy scales are not included in any summary score. All domains/scores are represented on a 0 to 100-point scale, and lower scores indicate more severe symptoms and/or limitations. Using this scale, health status can be quantified as follows: 0 to <25: very poor to poor; 25 to <50: poor to fair; 50 to <75: fair to good; and 75 to 100: good to excellent. Further details of the specific questions and regulatory evaluation are provided elsewhere.[12,13] For this analysis, we examined the specific domains contributing to the OSS (and calculated the OSS) at baseline in patients with and without each comorbidity of interest.

Statistical analysis

Data are shown as means (standard deviations), medians with interquartile ranges (IQR), or frequencies with percentages as appropriate. Spider plots were used to compare the differences in KCCQ domains and KCCQ-OSS between patients with and without each comorbidity. These plots presented depict the mean KCCQ scores for each domain, as well as the KCCQ-OSS, with each score ranging from 0 to 100. In these web-like figures with a spider's web structure, the centre of the plot represents a score of 50, while the outer limit represents a score of 90. The extent of reduction in the coloured rings from the outer ring indicates the magnitude of reduction in each domain score or the KCCQ-OSS. The differences between the two rings demonstrate the disparity in health status between patients with and without the specific comorbidity being studied. A larger difference between these rings indicates a more substantial difference in health status associated with the presence of each comorbidity. Ordinal logistic regression model was applied to evaluate the relationship between each KCCQ score and the comorbidities, with all the models adjusted for age and sex.

In sensitivity analyses, propensity score matching was conducted to evaluate the difference in KCCQ scores between the presence or absence of the comorbidity of interest after adjusting age, sex and the comorbidity other than the comorbidity of interest. We carried out this 1:1 nearest neighbour-matching with exact matching constraints according to the propensity score estimated by a logistic algorithm. KCCQ-OSS between patients with and without each comorbidity within each HF phenotype were compared before and after propensity score matching using Student's *t*-test. Differences in KCCQ-OSS between patients with and without each comorbidity were also compared using Student's *t*-test in the HFrEF and HFpEF groups.

The statistical analyses were performed using Stata/SE version 17.0 (Stata Corp, College Station, TX, USA), and $p < 0.05$ was considered statistically significant.

Results

A total of 20 159 patients with HFrEF and 6563 with HFpEF were included in the present analysis. The proportion of patients who completed the instruments according to each comorbidity and HF phenotype are presented in online supplementary *Tables S2* and *S3*.

Prevalence of different comorbidities

The majority of patients had a least one comorbidity, and a detailed distribution of the comorbidities of interest and their combinations are shown in online supplementary *Figures S1* and *S2*. Of patients with HFrEF, 36.2% had AF, 33.9% CKD, 33.9% diabetes, 31.4% obesity, 25.5% angina, 12.2% COPD, 8.4% stroke, 4.4% anaemia, 68.4% hypertension, and 42.5% myocardial infarction (*Table 1*). Each comorbidity (except myocardial infarction) was

more prevalent in HFpEF; the corresponding proportions were: 54.0% AF, 48.7% CKD, 43.4% diabetes, 53.3% obesity, 28.6% angina, 14.7% COPD, 10.2% stroke, 6.5% anaemia, 94.1% hypertension, and 22.0% myocardial infarction (*Table 2*). The comorbidity burden in patients with HFpEF was much higher than that in those with HFrEF, that is, 79.8% of patients with HFpEF had three or more comorbidities, compared to 59.7% of patients with HFrEF (*Graphical Abstract*).

Baseline characteristics of patients according to comorbidities

The baseline characteristics of patients overall, and according to the presence of the comorbidities of interest, are shown in *Table 1* (HFrEF) and *Table 2* (HFpEF).

Demographics, social habits, and physiological measures

Among participants with HFrEF, those with CKD were older and patients with obesity were younger. A relatively higher proportion of patients with CKD, obesity and anaemia were women, and COPD was common in men. A relatively larger proportion of patients with obesity, AF, angina, and COPD were White and the opposite was true for anaemia. Patients with COPD had higher rates of smoking. Blood pressure and heart rate did not differ meaningfully across the range of comorbidities of interest. These same patterns were observed in patients with HFpEF.

Heart failure history and characteristics

Among participants with HFrEF, those with the comorbidities of interest had longer-standing HF, more often had prior hospitalization (except for patients with anaemia) and were more likely to be in NYHA functional class III or IV, than the population overall. Generally, patients with these selected comorbidities had more symptoms (including fatigue) and signs of HF, and higher N-terminal pro-B-type natriuretic peptide levels (except for obesity) but mean left ventricular ejection fraction did not differ meaningfully across the comorbidities. Again, these patterns were broadly similar in patients with HFpEF.

Kansas City Cardiomyopathy Questionnaire domain scores and overall summary scores

The KCCQ domain scores and OSS for HFrEF and HFpEF are shown in online supplementary *Figure S3*. Among patients with HFrEF, all domain scores and the OSS were reduced from a potential score of 100. The symptom frequency and symptom burden domains were reduced less than the physical and social limitations domains and quality of life, which was the domain with the lowest score. As a result, the OSS in patients with HFrEF was reduced to 71.3.

In HFpEF, the symptom frequency and symptom burden domains, as well as the physical limitations domain, were reduced more than in HFrEF. The social limitations domains and quality of life were reduced to the same extent in HFrEF. As a result, the OSS in patients with HFpEF was reduced to 67.8.

The KCCQ domain scores and OSS in patients with and without the selected comorbidities of interest are shown in *Figures 1* and *2* and online supplementary *Tables S4* and *S5*. The changes in the scores related to each comorbidity are also shown in online supplementary *Tables S6* and *S7*. In addition, the relationship between NYHA class and the components of the OSS in patients with HFrEF and HFpEF are shown in online supplementary *Figure S4*.

Mean domain scores and Kansas City Cardiomyopathy Questionnaire overall summary score according to individual cardiorespiratory comorbidities

In patients with HFrEF, all four cardiorespiratory comorbidities shown in *Figure 1* were associated with lower domain scores and OSS (contrasting with hypertension and prior myocardial infarction, which were not, as shown in online supplementary *Figure S5*). The pattern was similar in HFpEF except for one comorbidity, AF, which was not associated with lower scores (the picture was similar if AF on the baseline electrocardiogram was used instead) (online supplementary *Figure S6*).

In both HFrEF and HFpEF, COPD and angina were associated with the greatest reductions in scores (and history of stroke with the smallest difference).

These patterns were essentially the same in the propensity score-matched sensitivity analysis (online supplementary *Figures S7-S9*).

Mean domain scores and Kansas City Cardiomyopathy Questionnaire overall summary score according to other individual comorbidities

In patients with HFrEF, the other four comorbidities shown in *Figure 2* were associated with lower domain scores and OSS. Among these comorbidities, obesity was associated with the greatest reduction in scores and the impact of obesity was greater in HFpEF than in HFrEF. In contrast to obesity, diabetes was associated with a substantially smaller reduction in scores in both HF phenotypes. Anaemia was also associated with moderate reductions in scores in HFrEF but the reduction scores related to anaemia were much larger in HFpEF (*Figure 2*). CKD was associated with smaller reductions in domain scores and OSS in both HF phenotypes.

These patterns were essentially the same in the propensity score-matched sensitivity analysis (online supplementary *Figure S7-S9*). A comparison of the decrement in KCCQ-OSS according to each comorbidity of interest in the propensity score-matched analysis is shown in online supplementary *Figure S10* and online supplementary *Tables S8* and *S9*.

Mean domain scores and Kansas City Cardiomyopathy Questionnaire overall summary score associated with multiple comorbidities (multimorbidity)

As shown in *Graphical Abstract*, cumulative comorbidity was associated with stepwise reductions in domain scores and OSS in patients with HFrEF. The relationship was less graded in patients with HFpEF

Table 1 **Clinical characteristics according to comorbidities in heart failure with reduced ejection fraction**

	All patients	Angina	AF	Stroke	COPD	Obesity	DM	CKD	Anaemia	HTN	MI
n (%)	20 159 (100)	5135 (25.5)	7299 (36.2)	1683 (8.4)	2452 (12.2)	6316 (31.4)	6834 (33.9)	6836 (33.9)	873 (4.4)	13 795 (68.4)	8573 (42.5)
Demographic characteristics											
Age, years	64.2 ± 11.5	66.9 ± 9.6	67.6 ± 10.1	66.8 ± 10.0	67.7 ± 9.5	63.0 ± 10.8	65.2 ± 10.0	69.1 ± 9.7	65.8 ± 12.5	66.0 ± 10.5	66.0 ± 10.0
Age >70 years	6406 (31.8)	1971 (38.4)	3114 (42.7)	638 (37.9)	991 (40.4)	1633 (25.9)	2164 (31.7)	3320 (48.6)	360 (41.2)	4944 (36.2)	3010 (35.1)
Female sex	4466 (22.2)	1108 (21.6)	1472 (20.2)	342 (20.3)	392 (16.0)	1549 (24.5)	1482 (21.7)	1801 (26.3)	349 (40.0)	3214 (23.3)	1403 (16.4)
Race											
White	13 469 (66.8)	4142 (80.7)	5918 (81.1)	1225 (72.8)	2016 (82.2)	5237 (82.9)	4686 (68.6)	5016 (73.4)	405 (46.4)	10 077 (73.0)	6391 (74.5)
Black	763 (3.8)	90 (1.8)	178 (2.4)	73 (4.3)	80 (3.3)	305 (4.8)	256 (3.7)	203 (3.0)	52 (6.0)	590 (4.3)	148 (1.7)
Asian	4389 (21.8)	696 (13.6)	828 (11.3)	273 (16.2)	256 (10.4)	368 (5.8)	1477 (21.6)	1162 (17.0)	366 (41.9)	2114 (15.3)	1458 (17.0)
Other	1538 (7.6)	207 (4.0)	375 (5.1)	112 (6.7)	100 (4.1)	406 (6.4)	415 (6.1)	455 (6.7)	50 (5.7)	1014 (7.4)	576 (6.7)
Physiological measurements											
SBP, mmHg	122.3 ± 16.6	124.7 ± 16.0	122.9 ± 16.4	123.1 ± 16.6	123.8 ± 16.4	125.3 ± 16.8	124.2 ± 16.8	121.6 ± 16.3	120.5 ± 16.8	125.5 ± 16.5	122.0 ± 16.0
BMI, kg/m^2	27.1 (24.0–31.0)	27.9 (24.9–31.6)	28.0 (25.0–32.0)	27.1 (24.2–31.0)	27.7 (24.2–32.0)	33.0 (31.2–36.0)	28.7 (25.1–32.7)	27.4 (24.3–31.0)	25.0 (21.9–28.7)	28.0 (25.0–32.0)	27.4 (24.4–31.0)
Medical history											
AF	7299 (36.2)	1962 (38.2)	N/A	798 (47.4)	1062 (43.3)	2760 (43.7)	2437 (35.7)	2976 (43.5)	268 (30.7)	5541 (40.2)	2622 (30.6)
HTN	13 795 (68.4)	4224 (82.3)	5541 (75.9)	1347 (80.0)	1900 (77.5)	5127 (81.2)	5421 (79.3)	5159 (75.5)	567 (64.9)	N/A	6324 (73.8)
CHD[a]	12 746 (63.2)	N/A	4371 (59.9)	1239 (73.6)	1713 (69.9)	4047 (64.1)	4918 (72.0)	4776 (69.9)	555 (63.6)	9394 (68.1)	N/A
Stroke	1683 (8.3)	527 (10.3)	798 (10.9)	N/A	227 (9.3)	532 (8.4)	661 (9.7)	724 (10.6)	72 (8.2)	1347 (9.8)	856 (10.0)
COPD	2452 (12.2)	789 (15.4)	1062 (14.5)	227 (13.5)	N/A	885 (14.0)	933 (13.7)	962 (14.1)	91 (10.4)	1900 (13.8)	1151 (13.4)
DM	6834 (33.9)	1982 (38.6)	2437 (33.4)	661 (39.3)	933 (38.1)	2827 (44.8)	N/A	2664 (39.0)	362 (41.5)	5421 (39.3)	3357 (39.2)
CKD	6836 (33.9)	1941 (37.8)	2976 (40.8)	724 (43.0)	962 (39.2)	2246 (35.6)	2664 (39.0)	N/A	422 (48.3)	5159 (37.4)	3269 (38.1)
Anaemia[b]	873 (4.4)	167 (3.3)	268 (3.7)	72 (4.4)	91 (3.8)	164 (2.6)	362 (5.4)	422 (6.3)	N/A	567 (4.2)	342 (4.1)
HF characteristics and investigations											
Time since HF diagnosis											
≤1 year	5982 (29.7)	1064 (20.7)	1681 (23.0)	335 (19.9)	584 (23.8)	1561 (24.7)	1765 (25.8)	1536 (22.5)	312 (35.7)	3725 (27.0)	1923 (22.4)
>1–5 years	7616 (37.8)	2041 (39.7)	2762 (37.8)	638 (37.9)	961 (39.2)	2424 (38.4)	2591 (37.9)	2585 (37.8)	311 (35.6)	5363 (38.9)	3314 (38.7)
>5 years	6557 (32.5)	2030 (39.5)	2856 (39.1)	710 (42.2)	907 (37.0)	2331 (36.9)	2477 (36.3)	2713 (39.7)	250 (28.6)	4707 (34.1)	3334 (38.9)
Previous hospitalization for HF	11 713 (58.1)	3192 (62.2)	4511 (61.8)	993 (59.0)	1583 (64.6)	3787 (60.0)	4123 (60.3)	4004 (58.6)	501 (57.4)	8177 (59.3)	4909 (57.3)
NYHA class III/IV	6197 (30.8)	2063 (40.2)	2727 (37.4)	623 (37.0)	1020 (41.6)	2241 (35.5)	2246 (32.9)	2236 (32.7)	321 (36.8)	4629 (33.6)	2735 (31.9)
Symptoms/signs											
Dyspnoea at rest	612 (4.0)	245 (6.1)	286 (5.2)	54 (4.4)	114 (6.1)	242 (5.2)	230 (4.7)	218 (4.4)	19 (3.2)	482 (4.7)	247 (3.8)
Orthopnoea	971 (6.3)	264 (6.6)	353 (6.4)	65 (5.3)	163 (8.7)	365 (7.9)	376 (7.8)	329 (6.7)	45 (7.6)	691 (6.7)	395 (6.1)
PND	756 (4.9)	263 (6.6)	304 (5.6)	57 (4.7)	123 (6.6)	280 (6.0)	266 (5.5)	260 (5.3)	37 (6.3)	558 (5.4)	308 (4.8)
Fatigue	7691 (50.0)	2507 (62.5)	3104 (56.7)	693 (57.0)	1072 (57.5)	2515 (54.2)	2440 (50.4)	2549 (52.0)	312 (52.8)	5411 (52.7)	3382 (52.3)
Oedema	3192 (20.7)	1161 (28.9)	1496 (27.3)	287 (23.6)	513 (27.5)	1398 (30.1)	1189 (24.5)	1155 (23.6)	144 (24.4)	2473 (24.1)	1425 (22.0)
JVD	1477 (9.6)	417 (10.4)	638 (11.7)	126 (10.4)	194 (10.4)	433 (9.3)	468 (9.7)	479 (9.8)	78 (13.2)	1062 (10.4)	574 (8.9)
Rales	1365 (8.9)	491 (12.2)	624 (11.4)	111 (9.1)	242 (13.0)	466 (10.1)	480 (9.9)	456 (9.3)	57 (9.6)	1021 (10.0)	576 (8.9)
ECG findings and NT-proBNP											
AF/atrial flutter	4888 (24.4)	1202 (23.6)	4779 (65.9)	511 (30.5)	671 (27.5)	1898 (30.2)	1601 (23.6)	1856 (27.4)	154 (17.8)	3765 (27.5)	1434 (16.8)
NT-proBNP, pg/ml	1423 (792–2747)	1355 (752–2531)	1734 (1021–3094)	1572 (922–3118)	1560 (827–3008)	1219 (713–2149)	1422 (805–2796)	1811 (1004–3496)	2313 (1095–4768)	1445 (808–2761)	1334 (763–2536)
AF/atrial flutter[c]	1860 (1134–3237)	1840 (1091–3393)	1846 (1131–3233)	1995 (1162–3440)	1949 (1185–3513)	1577 (997–2647)	1835 (1152–3346)	2267 (1363–4039)	2869 (1739–4754)	1827 (1133–3222)	2010 (1248–3587)
No AF/atrial flutter[c]	1272 (720–2519)	1205 (676–2262)	1486 (808–2799)	1429 (814–2879)	1420 (743–2800)	1055 (641–1915)	1300 (732–2585)	1618 (894–3258)	2197 (994–4816)	1280 (722–2518)	1202 (710–2311)

Table 1 (Continued)

	All patients	Angina	AF	Stroke	COPD	Obesity	DM	CKD	Anaemia	HTN	MI
LVEF and other laboratory investigations											
LVEF, %	29.5 ± 6.3	30.7 ± 5.9	30.4 ± 6.1	29.8 ± 6.3	29.9 ± 6.3	30.3 ± 6.2	29.9 ± 6.2	29.7 ± 6.3	29.7 ± 6.2	30.2 ± 6.1	29.9 ± 6.0
Haemoglobin, g/L	138.0	139.0	140.0	140.0	140.0	141.0	137.0	135.0	104.0	139.0	138.0
	(127.0–149.0)	(128.0–149.0)	(129.0–151.0)	(128.0–150.0)	(128.0–150.0)	(130.0–151.0)	(126.0–147.0)	(124.0–146.0)	(99.0–107.0)	(128.0–149.0)	(128.0–149.0)
eGFR, ml/min/1.73 m^2	68.0 (55.0–82.0)	66.0 (53.0–78.0)	64.0 (52.0–77.0)	63.0 (50.0–76.0)	65.0 (52.0–79.0)	67.0 (54.0–80.0)	65.0 (52.0–80.0)	50.0 (43.0–55.0)	60.0 (46.0–76.0)	66.0 (53.0–79.0)	65.0 (53.0–78.0)
Medication and other interventions											
Diuretics	16 769 (83.2)	4223 (82.2)	6322 (86.6)	1400 (83.2)	2122 (86.5)	5551 (87.9)	5974 (87.4)	6003 (87.8)	751 (86.0)	11 629 (84.3)	6935 (80.9)
Digitalis	5668 (28.1)	1076 (21.0)	2955 (40.5)	452 (26.9)	658 (26.8)	1550 (24.5)	1873 (27.4)	1737 (25.4)	259 (29.7)	3509 (25.4)	1662 (19.4)
Beta-blocker	18 801 (93.3)	4804 (93.6)	6783 (92.9)	1568 (93.2)	2147 (87.6)	6012 (95.2)	6398 (93.6)	6357 (93.0)	771 (88.3)	12 931 (93.7)	8049 (93.9)
MRA	10 643 (52.8)	2568 (50.0)	3861 (52.9)	896 (53.2)	1252 (51.1)	3512 (55.6)	3659 (53.5)	3623 (53.0)	412 (47.2)	7249 (52.5)	4403 (51.4)
ACEI/ARB/ARNI	19 857 (98.5)	5059 (98.5)	7163 (98.1)	1644 (97.7)	2400 (97.9)	6240 (98.8)	6695 (98.0)	6665 (97.5)	846 (96.9)	13 608 (98.6)	8433 (98.4)
ICD[d]	3533 (17.5)	903 (17.6)	1396 (19.1)	324 (19.3)	533 (21.7)	1353 (21.4)	1352 (19.8)	1549 (22.7)	119 (13.6)	2353 (17.1)	1989 (23.2)
CRT-P or CRT-D	1321 (6.6)	336 (6.5)	575 (7.9)	145 (8.6)	190 (7.7)	453 (7.2)	504 (7.4)	649 (9.5)	43 (4.9)	842 (6.1)	612 (7.1)

Data are presented as mean ± standard deviation, median (interquartile range) for continuous measures, and *n* (%) for categorical measures.
ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with a defibrillator; CRT-P, cardiac resynchronization therapy with a pacemaker; DM, diabetes mellitus; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; HTN, hypertension; ICD, implantable cardioverter defibrillator; JVD, jugular venous distension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; N/A, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PND, paroxysmal nocturnal dyspnoea; SBP, systolic blood pressure.
[a]CHD: angina, MI, percutaneous coronary intervention, coronary artery bypass grafting, ischaemic aetiology.
[b]Haemoglobin <110 g/L.
[c]Based on ECG.
[d]Including CRT-D.

where the decrement in scores with two comorbidities was not very different than with one comorbidity (*Graphical Abstract*). However, there were clear additional reductions in domain scores and OSS with 3 and ≥4 comorbidities. In both HF phenotypes, the physical and social limitations domains, and quality of life were reduced more with multiple comorbidities than the symptom frequency and symptom burden domains.

The severity of reductions in Kansas City Cardiomyopathy Questionnaire overall summary score according to combined comorbidities

In both HFrEF and HFpEF, there was a stepwise increase in the proportion of patients with moderate, severe, and very severe reductions in the OSS with an increasing number of comorbidities (*Figure 3*).

Discussion

To the best of our knowledge, this is the first large-scale comparison, using patient-level data, of different comorbidities and their associations with KCCQ domains in both HFrEF and HFpEF.[1,4,5,14–18] Most, but not all, the comorbidities examined were associated with reductions in domain scores and, as a result, the KCCQ-OSS. Of interest, some comorbidities were associated with lower scores than others (e.g. obesity compared with CKD) and the reductions in scores were generally greater in patients with HFpEF compared to those with HFrEF (e.g. obesity and anaemia). There was a stepwise reduction in domain scores and OSS with an increasing number of comorbidities.

We initially examined the 10 most commonly collected comorbidities in HF trials but focused on only eight of these because a history of hypertension and a history of myocardial infarction were not associated with a reduction in health status; the latter was notable because angina was very clearly associated with reduced scores.[1,4,5,14–18] The other comorbidity associated with substantial reductions in scores was obesity, especially in patients with HFpEF, and this too was notably different from diabetes which had much less impact on health status, despite the overlap between these two conditions.[15,19–24]

Chronic obstructive pulmonary disease was also associated with more prominent reductions in domain scores than other comorbidities.[18,25–29] None of these conclusions was changed in any meaningful way by our propensity score-matching sensitivity analyses undertaken to account for overlap between the comorbidities of interest. In addition to the more striking impact of obesity on health status in HFpEF, compared to HFrEF, a similar difference was seen for anaemia which was also associated with much lower scores in patients with HFpEF, compared to HFrEF.[30–32] Curiously, the opposite was seen for AF, which appeared to be associated with little if any impact on health status, even in a propensity score-matching sensitivity analysis.

Another notable finding was that, generally, the largest reductions in domain scores were for quality of life, social limitations, and physical limitations rather than symptom burden or symptom frequency. This is clinically important because physician-based

Table 2 Clinical characteristics according to comorbidities in heart failure with preserved ejection fraction

	All patients	Angina	AF	Stroke	COPD	Obesity	DM	CKD	Anaemia	HTN	MI
n (%)	6563 (100)	1874 (28.6)	3305 (54.0)	666 (10.2)	961 (14.7)	3492 (53.3)	2850 (43.4)	3195 (48.7)	428 (6.5)	6172 (94.1)	1442 (22.0)
Demographic characteristics											
Age, years	72.4 ± 8.8	71.8 ± 8.8	74.1 ± 8.0	72.8 ± 8.4	72.7 ± 8.5	70.7 ± 8.5	71.2 ± 8.6	74.6 ± 8.1	72.4 ± 9.4	72.4 ± 8.8	71.4 ± 8.8
Age >70 years	3986 (60.7)	1090 (58.2)	2274 (68.8)	411 (61.7)	597 (62.1)	1839 (52.7)	1558 (54.7)	2265 (70.9)	250 (58.4)	3744 (60.7)	803 (55.7)
Female sex	3361 (51.2)	867 (46.3)	1642 (49.7)	337 (50.6)	411 (42.8)	1851 (53.0)	1355 (47.5)	1776 (55.6)	269 (62.9)	3199 (51.8)	515 (35.7)
Race											
White	5291 (80.6)	1609 (85.9)	2839 (85.9)	525 (78.8)	821 (85.4)	2965 (84.9)	2252 (79.0)	2616 (81.9)	279 (65.2)	4988 (80.8)	1190 (82.5)
Black	404 (6.2)	79 (4.2)	101 (3.1)	47 (7.1)	76 (7.9)	294 (8.4)	216 (7.6)	177 (5.5)	78 (18.2)	393 (6.4)	58 (4.0)
Asian	626 (9.5)	148 (7.9)	285 (8.6)	83 (12.5)	45 (4.7)	100 (2.9)	269 (9.4)	284 (8.9)	48 (11.2)	559 (9.1)	159 (11.0)
Other	242 (3.7)	38 (2.0)	80 (2.4)	11 (1.7)	19 (2.0)	133 (3.8)	113 (4.0)	118 (3.7)	23 (5.4)	232 (3.8)	35 (2.4)
Physiological measurements											
SBP, mmHg	129.7 ± 15.6	130.2 ± 15.4	127.9 ± 15.4	130.4 ± 16.0	129.6 ± 16.3	130.6 ± 15.7	131.1 ± 15.7	128.9 ± 15.9	129.1 ± 16.5	130.4 ± 15.5	129.5 ± 15.5
BMI, kg/m^2	30.5 (26.8–34.9)	30.7 (27.3–34.9)	30.4 (26.8–34.8)	30.5 (26.7–35.0)	31.6 (27.2–35.6)	34.6 (32.2–38.0)	32.2 (28.3–36.5)	30.5 (27.0–34.9)	30.1 (26.0–34.9)	30.7 (27.0–35.1)	30.1 (26.7–34.2)
Medical history											
AF	3305 (50.4)	821 (43.8)	N/A	384 (57.7)	496 (51.6)	1739 (49.8)	1289 (45.2)	1774 (55.6)	162 (37.9)	3101 (50.3)	542 (37.6)
Hypertension	6172 (94.1)	1788 (95.4)	3101 (93.8)	646 (97.0)	906 (94.3)	3348 (95.9)	2753 (96.6)	3024 (94.6)	410 (95.8)	N/A	1343 (93.1)
CHD[a]	3257 (49.6)	N/A	1459 (44.1)	380 (57.1)	520 (54.1)	1693 (48.5)	1651 (57.9)	1614 (50.5)	228 (53.3)	3055 (49.5)	N/A
Stroke	666 (10.2)	216 (11.6)	384 (11.6)	N/A	118 (12.3)	357 (10.2)	321 (11.3)	377 (11.8)	53 (12.4)	646 (10.5)	187 (13.0)
COPD	961 (14.7)	295 (15.8)	496 (15.0)	118 (17.7)	N/A	575 (16.5)	440 (15.4)	490 (15.4)	67 (15.7)	906 (14.7)	236 (16.4)
DM	2850 (43.4)	962 (51.3)	1289 (39.0)	321 (48.2)	440 (45.8)	1808 (51.8)	N/A	1487 (46.5)	248 (57.9)	2753 (44.6)	760 (52.7)
CKD	3195 (48.7)	897 (47.9)	1774 (53.7)	377 (56.6)	490 (51.0)	1727 (49.5)	1487 (52.2)	N/A	279 (65.2)	3024 (49.0)	727 (50.4)
Anaemia[b]	428 (6.5)	119 (6.4)	162 (4.9)	53 (8.0)	67 (7.0)	217 (6.2)	248 (8.7)	279 (8.7)	N/A	410 (6.7)	106 (7.4)
HF characteristics and investigations											
Time since HF diagnosis											
≤1 year	1975 (41.3)	487 (35.2)	996 (39.0)	189 (37.4)	241 (36.1)	894 (38.0)	779 (37.9)	925 (39.6)	87 (40.7)	1867 (40.8)	371 (34.3)
>1–5 years	1672 (34.9)	519 (37.5)	901 (35.2)	186 (36.8)	246 (36.8)	867 (36.9)	749 (36.4)	840 (36.0)	81 (37.9)	1601 (35.0)	401 (37.1)
>5 years	1137 (23.8)	378 (27.3)	660 (25.8)	131 (25.9)	181 (27.1)	591 (25.1)	528 (25.7)	570 (24.4)	46 (21.5)	1105 (24.2)	309 (28.6)
Previous hospitalization for HF	3346 (51.0)	996 (53.1)	1760 (53.3)	358 (53.8)	546 (56.8)	1896 (54.3)	1626 (57.1)	1685 (52.7)	260 (60.7)	3150 (51.0)	753 (52.2)
NYHA class III/IV	1571 (24.0)	553 (29.5)	821 (24.9)	187 (28.1)	289 (30.1)	976 (28.0)	772 (27.1)	815 (25.5)	162 (38.0)	1480 (24.0)	358 (24.8)
Symptoms/signs											
Dyspnoea at rest	394 (6.0)	146 (7.8)	160 (4.9)	40 (6.0)	93 (9.7)	257 (7.4)	192 (6.8)	182 (5.7)	36 (8.5)	366 (6.0)	91 (6.3)
Orthopnoea	1435 (22.0)	468 (25.1)	669 (20.3)	153 (23.0)	286 (29.8)	919 (26.5)	729 (25.7)	743 (23.3)	141 (33.0)	1355 (22.0)	306 (21.3)
PND	191 (4.0)	78 (5.6)	101 (3.9)	26 (5.1)	39 (5.8)	110 (4.7)	92 (4.5)	102 (4.4)	8 (3.7)	186 (4.1)	50 (4.6)
Fatigue	2437 (50.9)	861 (62.0)	1307 (51.1)	308 (60.6)	352 (52.6)	1225 (52.0)	1070 (52.0)	1173 (50.2)	110 (51.4)	2350 (51.3)	555 (51.3)
Oedema	3091 (47.2)	915 (48.8)	1531 (46.4)	341 (51.2)	488 (50.8)	1955 (56.0)	1454 (51.1)	1517 (47.5)	280 (65.4)	2900 (47.0)	676 (46.9)
JVD	959 (15.0)	291 (15.9)	513 (15.9)	96 (14.8)	181 (19.3)	548 (16.1)	417 (15.0)	500 (16.0)	92 (22.3)	899 (14.9)	194 (13.8)
Rales	637 (9.8)	206 (11.1)	275 (8.4)	80 (12.0)	122 (12.8)	352 (10.2)	275 (9.7)	282 (8.9)	66 (15.6)	585 (9.5)	150 (10.5)
ECG findings and NT-proBNP											
AF/atrial flutter	1996 (30.6)	430 (23.1)	1976 (60.1)	244 (36.6)	289 (30.3)	1016 (29.3)	766 (27.0)	1031 (32.5)	85 (20.1)	1871 (30.5)	263 (18.4)
NT-proBNP, pg/ml	913 (472–1638)	778 (426–1530)	1281 (729–1963)	1114 (583–1908)	896 (475–1658)	795 (437–1447)	887 (454–1602)	1042 (548–1858)	1147 (573–2199)	906 (468–1628)	794 (470–1531)
AF/atrial flutter[c]	1578 (1147–2282)	1668 (1178–2259)	1578 (1146–2275)	1722 (1166–2416)	1559 (1142–2352)	1465 (1056–2029)	1571 (1148–2204)	1733 (1260–2535)	2309 (1471–3746)	1580 (1146–2261)	1822 (1201–2448)
No AF/atrial flutter[c]	610 (385–1082)	604 (374–1062)	655 (418–1183)	704 (421–1371)	624 (397–1115)	547 (363–928)	608 (384–1098)	691 (439–1222)	814 (483–1637)	608 (383–1070)	653 (420–1110)

Table 2 (Continued)

	All patients	Angina	AF	Stroke	COPD	Obesity	DM	CKD	Anaemia	HTN	MI
LVEF and other laboratory investigations											
LVEF, %	57.7 ± 7.9	57.0 ± 7.8	57.5 ± 7.5	57.7 ± 7.7	57.3 ± 7.7	57.9 ± 7.8	57.5 ± 7.8	58.0 ± 7.7	58.5 ± 7.6	57.8 ± 7.8	55.5 ± 7.6
Haemoglobin, g/L	133.0 (123.0–144.0)	133.0 (123.0–143.0)	135.0 (124.0–145.0)	132.0 (121.0–143.0)	133.0 (122.0–144.0)	133.0 (123.0–144.0)	130.0 (120.0–141.0)	130.0 (120.0–141.0)	104.5 (100.0–107.0)	133.0 (123.0–144.0)	133.0 (123.0–144.0)
eGFR, ml/min/1.73 m^2	60.6 (48.5–74.8)	60.9 (48.6–75.4)	58.4 (47.2–71.5)	57.2 (45.5–71.2)	59.4 (48.3–75.0)	60.1 (48.1–74.8)	58.8 (46.3–74.5)	48.2 (41.0–54.2)	52.4 (41.5–66.9)	60.4 (48.4–74.7)	59.8 (48.1–75.0)
Medication and other interventions											
Diuretics	6158 (93.9)	1778 (94.9)	3159 (95.6)	633 (95.0)	918 (95.5)	3333 (95.5)	2718 (95.4)	3042 (95.2)	401 (93.7)	5820 (94.3)	1346 (93.3)
Digitalis	652 (9.9)	142 (7.6)	595 (18.0)	75 (11.3)	103 (10.7)	299 (8.6)	254 (8.9)	306 (9.6)	31 (7.2)	597 (9.7)	96 (6.7)
Beta-blocker	5208 (79.4)	1592 (85.0)	2669 (80.8)	540 (81.1)	717 (74.6)	2849 (81.6)	2351 (82.5)	2525 (79.0)	331 (77.3)	4934 (80.0)	1250 (86.7)
MRA[d]	1239 (25.8)	378 (27.2)	703 (27.4)	138 (27.2)	162 (24.2)	608 (25.8)	519 (25.2)	602 (25.7)	56 (26.2)	1163 (25.4)	289 (26.7)
ACEI/ARB/ARNI	6191 (94.4)	1787 (95.4)	3143 (95.1)	632 (94.9)	897 (93.3)	3293 (94.3)	2736 (96.0)	3011 (94.2)	384 (89.7)	5876 (95.2)	1379 (95.6)
ICD[e]	60 (0.9)	23 (1.2)	35 (1.1)	8 (1.2)	7 (0.7)	38 (1.1)	29 (1.0)	35 (1.1)	5 (1.2)	55 (0.9)	25 (1.7)

Data are presented as mean ± standard deviation, median (interquartile range) for continuous measures, and *n* (%) for categorical measures.

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with a defibrillator; CRT-P, cardiac resynchronization therapy with a pacemaker; DM, diabetes mellitus; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; HTN, hypertension; ICD, implantable cardioverter defibrillator; JVD, jugular venous distension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; N/A, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PND, paroxysmal nocturnal dyspnoea; SBP, systolic blood pressure.

[a]CHD: angina, MI, percutaneous coronary intervention, coronary artery bypass grafting, ischaemic aetiology.

[b]Haemoglobin <110 g/L.

[c]Based on ECG.

[d]TOPCAT-Americas excluded.

[e]Including CRT-D.

assessments focus on symptoms and functional limitations and may, therefore, underestimate the impact of HF on patient well-being.[33,34]

The majority of the patients had at least one comorbidity of interest and patients with HFpEF had more comorbidities than those with HFrEF, possibly due to their older age and the greater comorbidity burden experienced by women who make up a higher proportion of patients with HFpEF.[35,36] It was, therefore, also notable that patients with HFpEF, in general, had worse health status than those with HFrEF. Unsurprisingly, a higher number of comorbidities was associated with correspondingly poorer health status.

Our findings have several clinical implications. As mentioned above, they highlight the impact of comorbidities beyond symptoms and functional limitations which are the focus of physician assessment. They also demonstrate the potential of treating comorbidity to improve health status in patients with HF. In particular, the effectiveness of intravenous iron as a treatment for iron deficiency and associated anaemia and the emergence of effective new weight loss therapies may be especially relevant given the large impact of these comorbidities on health status.[21–23,37,38] The impact of angina was perhaps unexpected and this is another comorbidity where effective interventions are available. COPD was also associated with substantial impairment of health status and here too inhaled medications (beta-2 agonists, antimuscarinic agents and corticosteroids), other pharmacologic therapies (theophyllines and roflumilast), along with pulmonary rehabilitation and home oxygen therapy, may be helpful.[18,25–27,29] It is possible that cardiologists may attribute breathlessness mainly to HF in their patients and may not seek expert respiratory input in the management of these patients. Conversely, the large benefits of sodium–glucose cotransporter 2 inhibitors on KCCQ scores may reflect their effect on a range of measures related to key comorbidities including glucose reduction, weight loss, attenuation of rate of decline in estimated glomerular filtration rate over time and increase in haemoglobin/attenuation of reduction in haemoglobin.

Limitations

Our analyses were performed in clinical trial datasets and patients enrolled in trials do not fully represent all patients with HF because of their inclusion and, especially, exclusion criteria for example, patients with severe CKD were excluded.[39] In PARAGON-HF, patients with a body mass index >40 kg/m^2 were excluded.[9] In addition, we used the original trial definitions of HFrEF and HFpEF, the latter including patients with a left ventricular ejection fraction ≥45%, a minority of which would currently be described as having HF with mildly reduced ejection fraction (41–49%). Patients enrolled in the included trials were also well treated compared to what is reported in community-based studies.[9,40] We did not have information on other common comorbidities which would have been interesting to study, including anxiety, depression, sleep apnoea, and thyroid dysfunction. Finally, for most comorbidities, we had only binary information (i.e. present or absent) and did not have more detail on the severity of the comorbidity, and we did

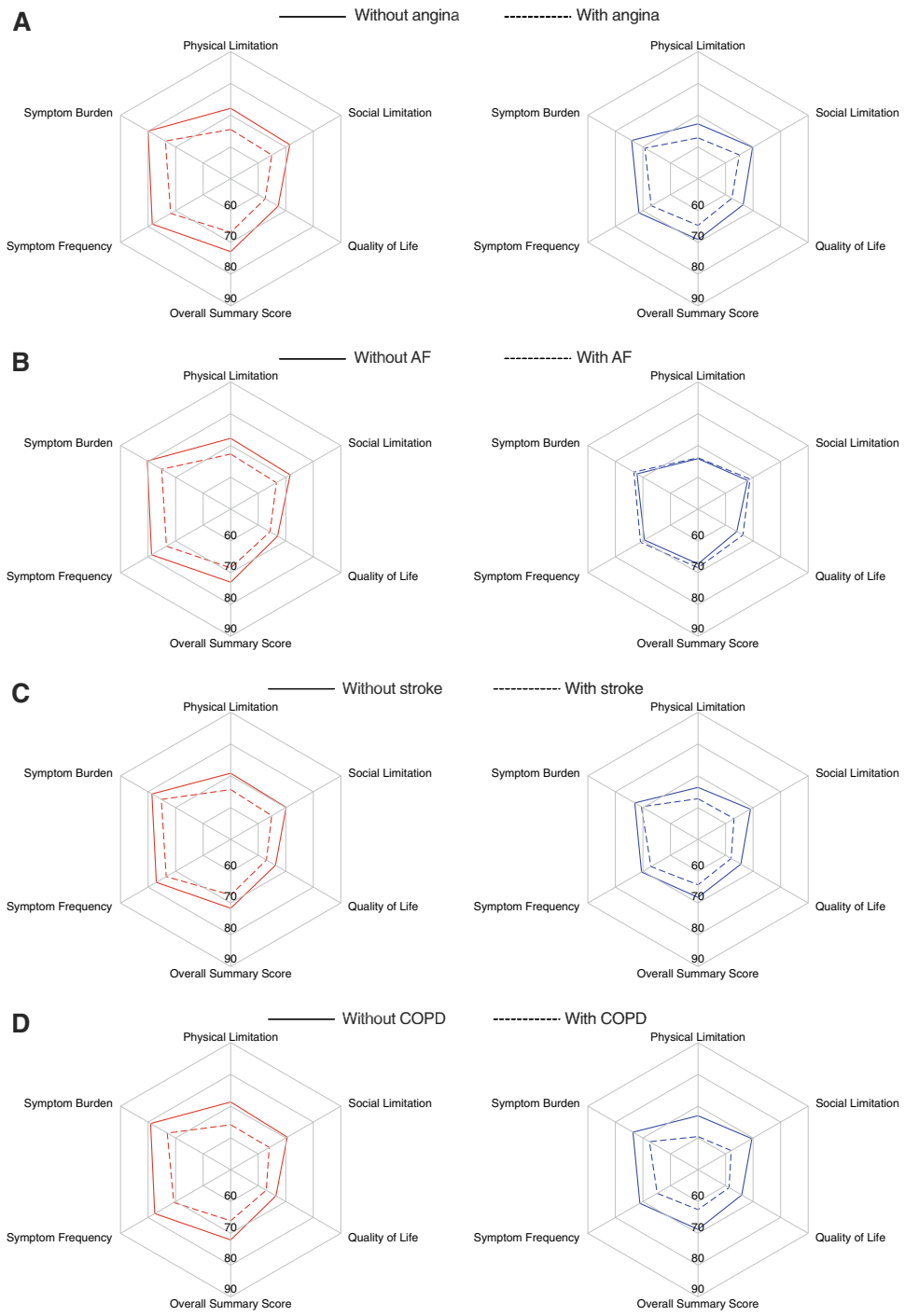


Figure 1 Kansas City Cardiomyopathy Questionnaire (KCCQ) domain and overall summary scores (KCCQ-OSS) in patients with heart failure with reduced and preserved ejection fraction according to individual cardiorespiratory comorbidities: (*A*) angina, (*B*) atrial fibrillation (AF), (*C*) stroke, and (*D*) chronic obstructive pulmonary disease (COPD). This figure shows unadjusted analyses, and the corresponding mean ± standard deviation value for each domain is shown in online supplementary *Table S4*. The figures show the mean KCCQ scores for each domain and the KCCQ-OSS (each score out of 100). The centre of the plot represents a score of 50 and the outer limit represents a score of 90. The solid line shows the score in patients without the comorbidity of interest and the dashed line the patients with the comorbidity. Patients with heart failure and reduced ejection fraction are shown in red and those with preserved ejection fraction in blue. The greater the reduction in the coloured rings from the outer ring of the web, the greater the reduction in each domain score or KCCQ-OSS. The greater the difference between the two rings (solid line vs. dashed line), the greater the associated difference in health status between patients with and without each comorbidity.

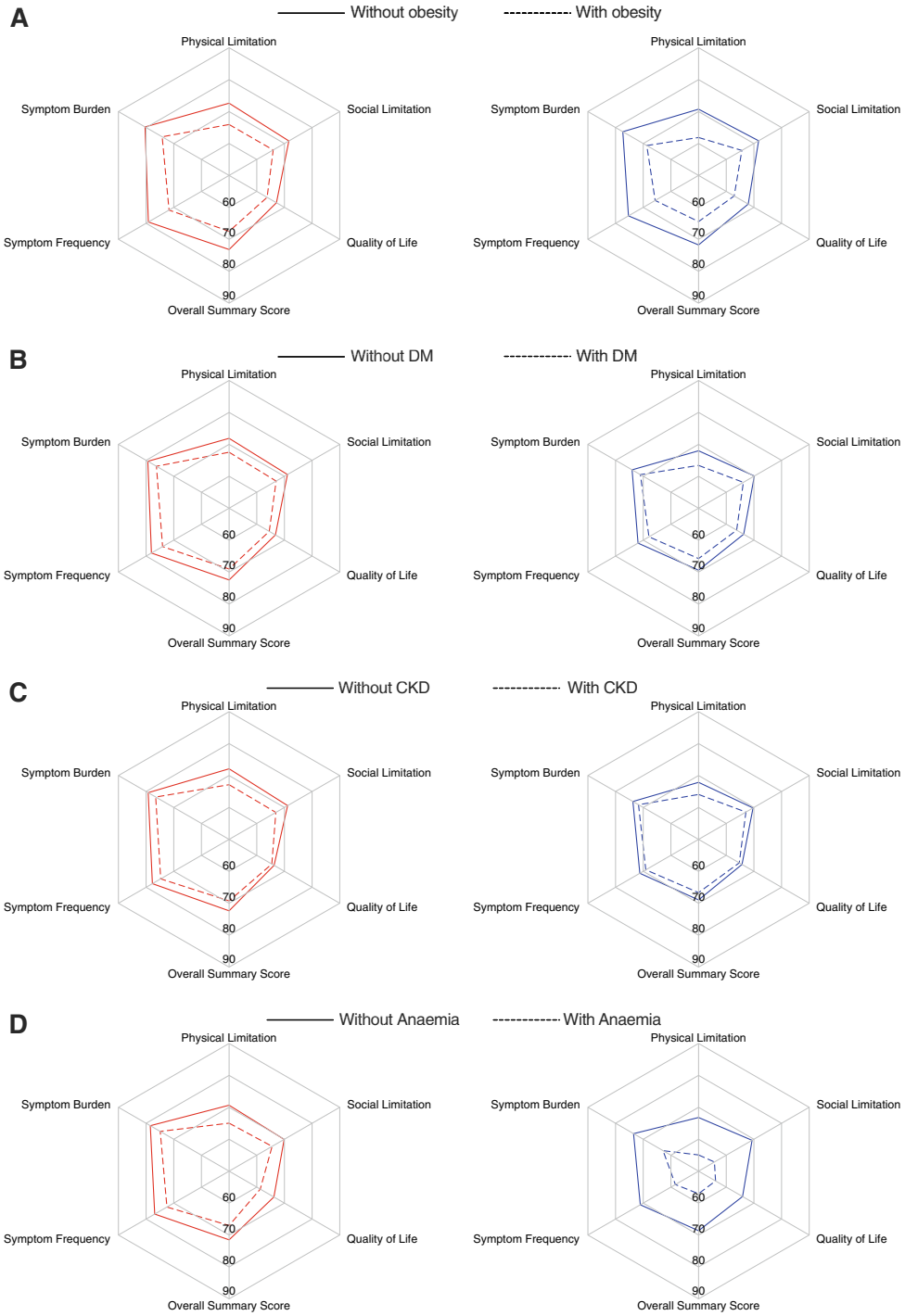


Figure 2 Kansas City Cardiomyopathy Questionnaire (KCCQ) domain and overall summary scores (KCCQ-OSS) in patients with heart failure with reduced and preserved ejection fraction according to other comorbidities: (*A*) obesity, (*B*) diabetes mellitus (DM), (*C*) chronic kidney disease (CKD), and (*D*) anaemia. This figure shows unadjusted analyses, and the corresponding mean ± standard deviation value for each domain is shown in online supplementary *Table S5*. The figures show the mean KCCQ scores for each domain and the KCCQ-OSS (each score out of 100). The centre of the plot represents a score of 50 and the outer limit represents a score of 90. The solid line shows the score in patients without the comorbidity of interest and the dashed line shows patients with the comorbidity. Patients with heart failure and reduced ejection fraction are shown in red and those with preserved ejection fraction in blue. The greater the reduction in the coloured rings from the outer ring of the web, the greater the reduction in each domain score or KCCQ-OSS. The greater the difference between the two rings (solid line vs. dashed line), the greater the associated difference in health status between patients with and without each comorbidity.

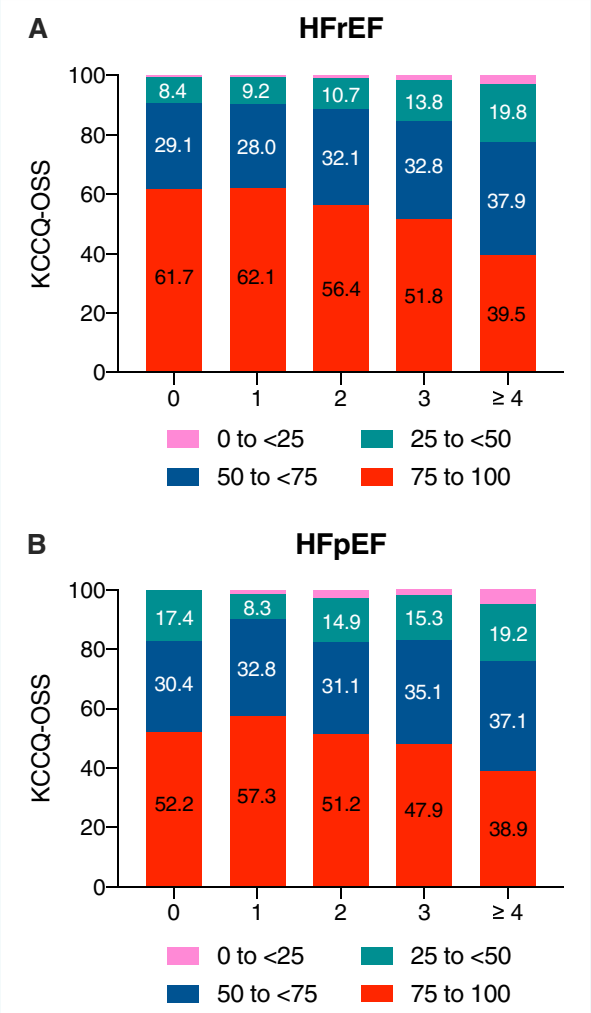


Figure 3 Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OSS) categories according to the number of comorbidities for patients with heart failure and reduced ejection fraction (HFrEF) (*A*) and with heart failure and preserved ejection fraction (HFpEF) (*B*). The figures show the percentage of patients with different health status quantified as follows: 0 to <25: very poor to poor; 25 to <50: poor to fair; 50 to <75: fair to good; and 75 to 100: good to excellent. Comorbidities used to calculate the burden are the following: angina, atrial fibrillation, stroke, chronic obstructive pulmonary disease; obesity; diabetes; chronic kidney disease; anaemia; hypertension; myocardial infarction. Comorbidity burden is presented as number of comorbidities: 0–3, ≥4. The baseline characteristics of patients according to comorbidity burden are shown in online supplementary *Table S10* (HFrEF) and *S11* (HFpEF).

not have other measures of the severity of HF itself, for example, invasive haemodynamic measurements.

Conclusions

Both cardiac and non-cardiac comorbidities were common in patients with HFrEF and HFpEF and most were associated with reductions in health status, although the impact varied among comorbidities, by the number of comorbidities, and by HF phenotype. Reducing comorbidity burden and treating/correcting comorbidity are therapeutic approaches that could improve health status in patients with HF.

Supplementary Information

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

Funding Information

John J.V. McMurray and Pardeep S. Jhund are supported by a British Heart Foundation Centre of Research Excellence (Grant RE/18/6/34217) and the Vera Melrose Heart Failure Research Fund. Mingming Yang is funded by the China Scholarship Council.

Conflict of interest: M.Y. reports travel grants from AstraZeneca. T.K. reports speaker fees from Abbott, Ono Pharma, Otsuka Pharma, Novartis, AstraZeneca, Bristol Myers Squibb, and Abiomed. J.H.B. reports advisory board honoraria from Bayer, consultant fees from Novartis, and travel grants from AstraZeneca. W.T.A. reports personal fees from Abbott, consulting fees from Boehringer Ingelheim, Impulse Dynamics, and Respicardia; has received salary support from V-Wave Medical; and has received research support from the NHLBI, all for studies performed within the heart failure arena. A.S.D. has received grants and personal fees from AstraZeneca during the conduct of the study; personal fees from Abbott, Biofourmis, Boston Scientific, Boehringer Ingelheim, Corvidia, DalCor Pharma, Relypsa, Regeneron, and Merck; grants and personal fees from Alnylam and Novartis; and personal fees from Amgen, outside the submitted work. K.S.J. has received support from the National Institutes of Health (Training Grant 5-T32 HL007604). L.K. reports other support from AstraZeneca and personal fees from Novartis and Boehringer as a speaker. M.N.K. has received research grant support from AstraZeneca, and Boehringer Ingelheim; has served as a consultant or on an advisory board for Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Eli Lilly, Esperion Therapeutics, Janssen, Merck (Diabetes and Cardiovascular), Novo Nordisk, Sanofi, and Vifor Pharma; has received other research support from AstraZeneca; and has received honoraria from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. M.P. reports consulting fees from AbbVie, Akcea, Actavis, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Gilead, Johnson & Johnson, Novo Nordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics, and Theravance. J.L.R. reports grants and consulting fees from Novartis and consulting fees from Abbott, AstraZeneca, MyoKardia, and Sanofi. S.D.S. has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lilly, Mesoblast, MyoKardia, National Institutes of Health/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI; and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, and Sarepta. M.V. has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Pharmacosmos, Relypsa, Roche Diagnostics, and Sanofi, speaker engagements with

Novartis and Roche Diagnostics, and participates in clinical endpoint committees for studies sponsored by Galmed and Novartis. M.R.Z. reports research funding from Novartis and has been a consultant for Novartis, Abbott, Boston Scientific, CVRx, EBR, Endotronics, Ironwood, Merck, Medtronic, and Myokardia V Wave. P.S.J. reports other from AstraZeneca, personal fees from Novartis and Cytokinetics, and grants from Boehringer Ingelheim. J.J.V.M. reports payments through Glasgow University from work on clinical trials, consulting and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardurion, Cytokinetics, Dal-Cor, GSK, Ionis, KBP Biosciences, Novartis, Pfizer, Theracos; personal lecture fees: the Corpus, Abbott, Hikma, Sun Pharmaceuticals, Medscape/Heart.Org, Radcliffe Cardiology, Servier Director, Global Clinical Trial Partners (GCTP).

References

1. van Deursen VM, Urso R, Laroche C, Damman K, Dahlström U, Tavazzi L, *et al.* Co-morbidities in patients with heart failure: An analysis of the European Heart Failure Pilot Survey. *Eur J Heart Fail* 2014;**16**:103–111. https://doi.org/10.1002/ejhf.30
2. Bhatt AS, Ambrosy AP, Dunning A, DeVore AD, Butler J, Reed S, *et al.* The burden of non-cardiac comorbidities and association with clinical outcomes in an acute heart failure trial – Insights from ASCEND-HF. *Eur J Heart Fail* 2020;**22**:1022–1031. https://doi.org/10.1002/ejhf.1795
3. Chioncel O, Benson L, Crespo-Leiro MG, Anker SD, Coats AJS, Filippatos G, *et al.* Comprehensive characterization of non-cardiac comorbidities in acute heart failure – An analysis of ESC-HFA EORP Heart Failure Long-Term Registry. *Eur J Prev Cardiol*. https://doi.org/10.1093/eurjpc/zwad151 Published online ahead of print 13/03/23.
4. Rushton CA, Satchithananda DK, Jones PW, Kadam UT. Non-cardiovascular comorbidity, severity and prognosis in non-selected heart failure populations: A systematic review and meta-analysis. *Int J Cardiol* 2015;**196**:98–106. https://doi.org/10.1016/j.ijcard.2015.05.180
5. Benes J, Kotrc M, Jarolim P, Hoskova L, Hegarova M, Dorazilova Z, *et al.* The effect of three major co-morbidities on quality of life and outcome of patients with heart failure with reduced ejection fraction. *ESC Heart Fail* 2021;**8**:1417–1426. https://doi.org/10.1002/ehf2.13227
6. Desai AS, Lewis EF, Li R, Solomon SD, Assmann SF, Boineau R, *et al.* Rationale and design of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial: A randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. *Am Heart J* 2011;**162**:966–972.e10. https://doi.org/10.1016/j.ahj.2011.09.007
7. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, *et al.*; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004. https://doi.org/10.1056/NEJMoa1409077
8. McMurray JJ, Krum H, Abraham WT, Dickstein K, Køber LV, Desai AS, *et al.*; ATMOSPHERE Committees Investigators. Aliskiren, enalapril, or aliskiren and enalapril in heart failure. *N Engl J Med* 2016;**374**:1521–1532. https://doi.org/10.1056/NEJMoa1514859
9. Solomon SD, Rizkala AR, Gong J, Wang W, Anand IS, Ge J, *et al.* Angiotensin receptor neprilysin inhibition in heart failure with preserved ejection fraction: Rationale and design of the PARAGON-HF trial. *JACC Heart Fail* 2017;**5**:471–482. https://doi.org/10.1016/j.jchf.2017.04.013
10. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, *et al.*; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008. https://doi.org/10.1056/NEJMoa1911303
11. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, *et al.* Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 2015;**131**:34–42. https://doi.org/10.1161/CIRCULATIONAHA.114.013255
12. Spertus JA, Jones PG, Sandhu AT, Arnold SV. Interpreting the Kansas City Cardiomyopathy Questionnaire in clinical trials and clinical care: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**76**:2379–2390. https://doi.org/10.1016/j.jacc.2020.09.542
13. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: A new health status measure for heart failure. *J Am Coll Cardiol* 2000;**35**:1245–1255. https://doi.org/10.1016/s0735-1097(00)00531-3
14. Khan MS, Samman Tahhan A, Vaduganathan M, Greene SJ, Alrohaibani A, Anker SD, *et al.* Trends in prevalence of comorbidities in heart failure clinical trials. *Eur J Heart Fail* 2020;**22**:1032–1042. https://doi.org/10.1002/ejhf.1818
15. Screever EM, van der Wal MHL, van Veldhuisen DJ, Jaarsma T, Koops A, van Dijk K, *et al.* Comorbidities complicating heart failure: Changes over the last 15 years. *Clin Res Cardiol* 2022;**112**:123–133. https://doi.org/10.1007/s00392-022-02076-1
16. Zheutlin AR, Chaitoff A, Niforatos JD. Co-morbidity and polypharmacy burden among adults with self-reported heart failure overall, and by gender and race/ethnicity: NHANES 2007-2018. *J Gen Intern Med* 2022;**38**:551–553. https://doi.org/10.1007/s11606-022-07697-w
17. Chow C, Mentz RJ, Greene SJ. Update on the impact of comorbidities on the efficacy and safety of heart failure medications. *Curr Heart Fail Rep* 2021;**18**:132–143. https://doi.org/10.1007/s11897-021-00512-3
18. Dewan P, Docherty KF, Bengtsson O, Boer RA, Desai AS, Drozdz J, *et al.* Effects of dapagliflozin in heart failure with reduced ejection fraction and chronic obstructive pulmonary disease: An analysis of DAPA-HF. *Eur J Heart Fail* 2021;**23**:632–643. https://doi.org/10.1002/ejhf.2083
19. Shang L, Sun H, Tang B, Hou Y. Metabolic disorders as growing risk factors and comorbidities in heart failure. *Int J Cardiol* 2022;**364**:93–94. https://doi.org/10.1016/j.ijcard.2022.06.004
20. Iyngkaran P, Thomas M, Horowitz JD, Komesaroff P, Jelinek M, Hare DL. Common comorbidities that alter heart failure prognosis – Shaping new thinking for practice. *Curr Cardiol Rev* 2021;**17**:e160721187934. https://doi.org/10.2174/1573403x16666201113093548
21. Borlaug BA, Jensen MD, Kitzman DW, Lam CSP, Obokata M, Rider OJ. Obesity and heart failure with preserved ejection fraction: New insights and pathophysiologic targets. *Cardiovasc Res* 2022;**118**:3434–3450. https://doi.org/10.1093/cvr/cvac120
22. Ciardullo S, Cannistraci R, Mazzetti S, Mortara A, Perseghin G. Twenty-year trends in heart failure among U.S. adults, 1999-2018: The growing impact of obesity and diabetes. *Int J Cardiol* 2022;**362**:104–109. https://doi.org/10.1016/j.ijcard.2022.02.037
23. Adamson C, Kondo T, Jhund P, de Boer RA, Cabrera Honorio JW, Claggett B, *et al.* Dapagliflozin for heart failure according to body mass index: The DELIVER trial. *Eur Heart J* 2022;**43**:4406–4417. https://doi.org/10.1093/eurheartj/ehac481
24. Butt JH, Adamson C, Docherty KF, de Boer RA, Petrie MC, Inzucchi SE, *et al.* Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to N-terminal pro-B-type natriuretic peptide: Insights from the DAPA-HF trial. *Circ Heart Fail* 2021;**14**:e008837. https://doi.org/10.1161/CIRCHEARTFAILURE.121.008837
25. Khan SS, Kalhan R. Comorbid chronic obstructive pulmonary disease and heart failure: Shared risk factors and opportunities to improve outcomes. *Ann Am Thorac Soc* 2022;**19**:897–899. https://doi.org/10.1513/AnnalsATS.202202-152ED
26. Pellicori P, Cleland JGF, Clark AL. Chronic obstructive pulmonary disease and heart failure: A breathless conspiracy. *Cardiol Clin* 2022;**40**:171–182. https://doi.org/10.1016/j.ccl.2021.12.005
27. Mooney L, Hawkins NM, Jhund PS, Redfield MM, Vaduganathan M, Desai AS, *et al.* Impact of chronic obstructive pulmonary disease in patients with heart failure with preserved ejection fraction: Insights from PARAGON-HF. *J Am Heart Assoc* 2021;**10**:e021494. https://doi.org/10.1161/JAHA.121.021494
28. Rohde LE, Claggett BL, Wolsk E, Packer M, Zile M, Swedberg K, *et al.* Cardiac and noncardiac disease burden and treatment effect of sacubitril/valsartan: Insights from a combined PARAGON-HF and PARADIGM-HF analysis. *Circ Heart Fail* 2021;**14**:e008052. https://doi.org/10.1161/CIRCHEARTFAILURE.120.008052
29. Ehteshami-Afshar S, Mooney L, Dewan P, Desai AS, Lang NN, Lefkowitz MP, *et al.* Clinical characteristics and outcomes of patients with heart failure with reduced ejection fraction and chronic obstructive pulmonary disease: Insights from PARADIGM-HF. *J Am Heart Assoc* 2021;**10**:e019238. https://doi.org/10.1161/JAHA.120.019238
30. Ferreira JP, Anker SD, Butler J, Filippatos G, Iwata T, Salsali A, *et al.* Impact of anaemia and the effect of empagliflozin in heart failure with reduced ejection fraction: Findings from EMPEROR-Reduced. *Eur J Heart Fail* 2022;**24**:708–715. https://doi.org/10.1002/ejhf.2409
31. Alnuwaysir RIS, Grote Beverborg N, Hoes MF, Markousis-Mavrogenis G, Gomez KA, Wal HH, *et al.* Additional burden of iron deficiency in heart failure patients beyond the cardio-renal anaemia syndrome: Findings from the BIOSTAT-CHF study. *Eur J Heart Fail* 2022;**24**:192–204. https://doi.org/10.1002/ejhf.2393
32. Docherty KF, Welsh P, Verma S, de Boer RA, O'Meara E, Bengtsson O, *et al.*; DAPA-HF Investigators and Committees. Iron deficiency in heart failure and effect of dapagliflozin: Findings from DAPA-HF. *Circulation* 2022;**146**:980–994. https://doi.org/10.1161/CIRCULATIONAHA.122.060511

33. Khan MS, Butler J, Greene SJ. Patient-reported outcomes for heart failure with preserved ejection fraction: Conducting quality studies on quality of life. *Eur J Heart Fail* 2020;**22**:1019–1021. https://doi.org/10.1002/ejhf.1762
34. Heidenreich PA. Patient-reported outcomes: The future of heart failure care. *JACC Heart Fail* 2019;**7**:875–877. https://doi.org/10.1016/j.jchf.2019.06.006
35. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, *et al.* Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J Am Coll Cardiol* 2012;**59**:998–1005. https://doi.org/10.1016/j.jacc.2011.11.040
36. Mentz RJ, Kelly JP, von Lueder TG, Voors AA, Lam CSP, Cowie MR, *et al.* Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol* 2014;**64**:2281–2293. https://doi.org/10.1016/j.jacc.2014.08.036
37. Jankowska EA, Tkaczyszyn M, Suchocki T, Drozd M, von Haehling S, Doehner W, *et al.* Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: A meta-analysis of randomized controlled trials. *Eur J Heart Fail* 2016;**18**:786–795. https://doi.org/10.1002/ejhf.473
38. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, *et al.*; AFFIRM-AHF Investigators. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: A multicentre, double-blind, randomised, controlled trial. *Lancet* 2020;**396**:1895–1904. https://doi.org/10.1016/s0140-6736(20)32339-4
39. Cherubini A, Oristrell J, Pla X, Ruggiero C, Ferretti R, Diestre G, *et al.* The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011;**171**:550–556. https://doi.org/10.1001/archinternmed.2011.31
40. Lewis EF, Claggett BL, McMurray JJV, Packer M, Lefkowitz MP, Rouleau JL, *et al.* Health-related quality of life outcomes in PARADIGM-HF. *Circ Heart Fail* 2017;**10**:e003430. https://doi.org/10.1161/CIRCHEARTFAILURE.116.003430