CHARACTERISTICS OF SYMPTOMS AND SYMPTOM CHANGE ACROSS DIFFERENT HEART FAILURE SUBTYPES: A SEX-STRATIFIED ANALYSIS

Muzeyyen Seckin[1], Bridget Johnston[1, 2], Mark C Petrie[2, 3], Simon Stewart[1,4], Yih-Kai Chan[5*]

[1] School of Medicine, Dentistry & Nursing, University of Glasgow, Glasgow, UK,
[2] NHS Greater Glasgow and Clyde Glasgow, UK,
[3]Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK,
[4] Institute of Health Research, Notre Dame University of Australia, Fremantle, Australia,
[5] Mary MacKillop Institute for Health Research, Australia Catholic University, Melbourne, Australia,

Muzeyyen Seckin, MSc, RN
PhD student, School of Medicine, Dentistry & Nursing, University of Glasgow, Glasgow, UK
Email: m.seckin.1@research.gla.ac.uk
Bridget Johnston, PhD, RN
Professor, School of Medicine, Dentistry & Nursing, University of Glasgow, Glasgow, UK
Email: Bridget.Johnston@glasgow.ac.uk
Mark C Petrie, PhD, MD
Professor, Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK
Email: mark.petrie@glasgow.ac.uk
Simon Stewart, PhD, RN
Professor, NHMRC of Australia Senior Principal Research Fellow, University of Notre Dame Australia, Fremantle, Australia
Email: simon.stewart@torrens.edu.au
Yih-Kai Chan, PhD
Research Fellow, Mary MacKillop Institute for Health Research, Australia Catholic University, Melbourne, Australia
Email: YihKai.Chan@acu.edu.au

***CORRESPONDING AUTHOR**

Dr Yih-Kai Chan
Melbourne Campus (St Patrick's),
The Mary MacKillop Institute for Health Research
Australia Catholic University
Melbourne, VIC 3000, Australia
Email: YihKai.Chan@acu.edu.au

Word count
Abstract word count: 250 words
Manuscript: 3,500 (+279) words + 5 Tables, 1 Figures and 32 References (except Supplementary materials-2 Tables)

ABSTRACT

Aim: To examine sex-stratified differences in the association of left ventricular ejection fraction-based heart failure (HF) subtypes and the characteristics and correlates of self-reported changes in HF symptoms.

Methods and Results: We report a secondary data analysis from 528 hospitalised individuals diagnosed with HF characterised by a reduced, mildly reduced, or preserved ejection fraction (HFrEF, HFmrEF, or HFpEF) who completed 12-month follow-up within a multicentre disease management trial. There were 302 men (71.1±11.9 years, 58% with HFrEF) and 226 women (77.1±10.6 years, 49% with HFpEF). The characteristics of self-reported symptoms measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline and 12-month were analysed. At baseline, shortness of breath and fatigue predominated; with key differences according to HF subtypes in bilateral ankle oedema (both sexes), walking problems (women) and depressive symptoms (men). At 12month follow-up, most KCCQ scores had not significantly changed. However, 25% of individuals reported worse symptom. In women, those with HFpEF had worse symptoms than those with HFmrEF/HFrEF (p=0.025). On an adjusted basis, women (OR 1.78, 95%CI 1.00-3.16 versus men), those with coronary artery disease (OR 2.01, 95%CI 1.21-3.31) and baseline acute pulmonary oedema (OR 1.67, 95%CI 1.02-2.75) were most likely to report worsening symptoms. Among men, worsening symptoms correlated with a history of hypertension (OR 2.16, 95%CI 1.07-4.35) and a non-English-speaking background (OR 2.30, 95%CI 1.02-5.20).

Conclusion: We found significant heterogeneity (with potential clinical implications) in the symptomatic characteristics and subsequent symptom trajectory according to the sex and HF subtype of those hospitalised with the syndrome.

Trial Registration: ANZCTR12613000921785

Keywords: Heart failure, symptom, sex, left ventricular ejection fraction, secondary data analysis

IMPLICATIONS FOR PRACTICE

- There are potentially important differences in the initial characteristics and post-hospitalisation trajectory of symptoms according to LVEF-based HF subtypes in men and women.
- HFpEF was associated with worsening symptoms at 12 months in women.
- Women and men appear to have different baseline correlates for worsening HF symptoms associated with an acute hospitalisation.
- Individualised assessment and clinical care are needed to reduce potentially debilitating HF symptoms related to LVEF-based HF subtypes in both sexes.

INTRODUCTION

Heart failure (HF) is one of the most common diagnoses made in clinical practice, with increased prevalence and rising medical costs as a result of an ageing population and advances in medical treatment (1). Consequently, HF is a leading cause of unplanned hospitalisation among older individuals. Unplanned hospitalisations are one of the major components of its burden on the healthcare systems worldwide (2). Clinically, a higher probability of hospital admission and death is linked to worsening symptoms (3-5). People living with HF may experience a broad range of symptoms (1, 6) that are often become severe, prolonged and persistent (7); this combination being a marker of worsening progression of HF (7). Thus, addressing worsening of symptoms represents an important therapeutic goals for targeted therapies in HF (8, 9).

The type and progression of symptoms may differ on an individual basis according to the

underlying pathophysiology of their HF and left ventricular ejection fraction (LVEF). According to the recently updated European Society of Cardiology (ESC) guidelines (1), HF can be categorised into three distinct phenotypes based on the measurement of LVEF. This includes HF with reduced ejection fraction (HFrEF-LVEF ≤40%); HF with mildly reduced ejection fraction (HFmrEF-LVEF 41-49%); and HF with preserved ejection fraction (HFpEF-LVEF ≥50%). Previous studies have found symptom differences across LVEF-based HF subtypes in some symptoms such as palpitation (HFpEF>HFmrEF) (10), peripheral oedema (HFpEF>HFrEF) (11), and pain (HFpEF>HFrEF) (12). Within the broad HF patient population, the sex-specific distribution of HF subtypes and associated symptoms are potentially different in men and women (13-17). For example, in the primary care setting, it has been reported that 52% of women are managed for HFpEF and 41% of men for HFrEF (age group 65-79 years) (18). Although symptom characteristics appear to differ by sex and HF subtypes, sex-stratified differences in symptom characteristics and change according to HF subtypes remain under-investigated and reported – something this study seeks to address.

We have developed a research framework based on Riegel's "The Situation-Specific Theory of Heart Failure Self-care" (19), which includes "Symptom perception" as the core concept of self-care and is influenced by problem, person, and environmental factors. In this recent study, we have formed the related factors associated with symptoms characteristics and changes over one year (as problem factors) according to LVEF-based HF subtypes (as problem factors) in men and women (as person factors).

STUDY AIMS

Given the paucity of data exploring this important issue, the primary aims of this study were 1) to examine differences in baseline characteristics by LVEF-based HF subtypes in men and women separately; 2) to examine differences in baseline symptoms and symptom change

between LVEF-based HF subtypes in men and women separately; and 3) to identify factors associated with worsening symptoms in cohort, men and women separately.

METHODS

This is a retrospective secondary data analysis of a previously published randomised controlled trial comparing two forms of nurse-led management in a real-world cohort of HF patients (the WHICH? II Trial-"the Which Heart failure Intervention is most Cost-effective in reducing Hospital stay") (20). The WHICH? II Trial had been prospectively registered at the Australian New Zealand Clinical Trial Registry (*ANZCTR12613000921785)* (20). Ethics approval of the WHICH? II Trial (20) was obtained from Central Northern Adelaide Health Service (*HREC/13/TQEHLMH/99*), Melbourne Health (*HREC 2013.145*), St Vincent's Hospital Sydney (*HREC/13/SVH/313*) and Prince of Wales Hospital, Sydney (*HREC/13/SVH/313*). For the present secondary analysis, an approval was obtained from the University of Glasgow Medical, Veterinary & Life Sciences College Ethics Committee (Project no:*200200145/13.07.2021).* This investigation conforms with the principles outlined in the Declaration of Helsinki (21). Written informed consent for participation was provided by all participants.

Study setting

The WHICH? II Trial (20), was a multicentre, randomised controlled trial that tested the hypothesis that an intensified HF management programme (INT-HF-MP) would be superior to gold-standard HF management (SM) in reducing healthcare costs for 12 months following an acute hospitalisation. Participants allocated to the INT-HF-MP group received a combination of face-to-face and structured telephone support (STS) based on their location and underwent a Green, Yellow, Red Risk and Need for HF (GARDIAN-HF) assessment (22). As originally reported (20), data were obtained from participants with chronic HF

randomised to the 'INT-HF-MP' versus 'SM' groups from four geographically dispersed hospitals in Australia by trained personnel applying a standardised study protocol of profiling and follow-up.

Study cohort

In the original trial (20), 787 study participants met the following eligibility criteria: (a) aged ≥18 years, (b) chronic HF as confirmed by a cardiologist with NYHA Class II-IV, and c) discharged to home following an acute index hospitalisation. Majority (59%) were men aged 71.7±12.0 years while women were significantly older (77.5±10.7 years) (**Supplementary Table S1**). Overall, HFrEF and HFpEF were most common in men (59%) and women (49%), respectively. For our analyses, we excluded 259 participants (185/23.5% died and 74/9.4% did not return for reprofiling) who did not complete 12-month follow-up according to the study protocol (**Figure 1**). Consequently, comprehensive baseline and 12-month follow-up data were available for 528 participants.

Study data

As part of the WHICH? II Trial protocol (20), baseline data collection included sociodemographic factors, symptoms (shortness of breath, fatigue, bilateral ankle oedema, nocturnal cough, paroxysmal nocturnal dyspnoea, sleeping problems due to orthopnoea, walking problems, and pain), depressive symptoms, and quality of life using standardised case report forms administered by trained personnel. At subsequent 12-month follow-up of surviving participants, the same profiling was repeated. Charlson Comorbidity Index score (23) was also calculated to reflect each participant's underlying comorbid burden of disease.

Outcomes and measures

As originally reported, there was no difference between the two study groups for any of the primary or secondary outcome measures at 12-month (20). This included the pattern of

readmission, mortality, and healthcare costs on an intention-to-treat basis. It also included responses to the Kansas City Cardiomyopathy Questionnaire (KCCQ), which used to measure self-reported HF symptoms and quality of life scores from baseline to 12-month (24). The KCCQ is a 23-item questionnaire and includes the following domains: "physical limitation"; "symptoms" (total; frequency; burden and stability); "self-efficacy and knowledge"; "social limitation"; and "quality of life" (24). Values for all domains range from 0 to 100, with higher scores indicating lower symptom burden and better quality of life. The sensitivity, reproducibility, and validity of the KCCQ to clinical changes have been previously evaluated in subjects with HF (24). A two-item ARROL tool was also used to measure depressive symptoms at baseline and 12-month (25), whilst the EQ-5D-5L questionnaire was used to assess general quality of life of study participants over the same 12-month timeframe (26).

Heart failure subtypes

As originally reported (20), the WHICH? II Trial purposefully sought to recruit a real-world clinical cohort with a range of different HF subtypes and comorbid profiles (consequently increasing the potential to recruit more eligible women into the trial). For this secondary analysis study, we have grouped the study cohort according to the recently updated European Society of Cardiology criteria (1) for categorising HF cases according to their left ventricular ejection fraction (LVEF, assessed and confirmed by echocardiography prior to trial randomisation)-HF with reduced ejection fraction (HFrEF-LVEF ≤40%); HF with mildly reduced ejection fraction (HFmrEF-LVEF 41-49%); and HF with preserved ejection fraction (HFpEF-LVEF ≥50%) (1). In our analyses, these three different HF subtypes are predominately described and compared on a sex-specific basis.

Worsening, stable, and improved symptoms

The KCCQ symptom stability score was used to determine the presence/absence of

worsening symptoms at 12-month follow-up (compared to baseline). A lower symptom stability score indicates worsening symptoms, while a higher score indicates an improvement in self-reported symptoms (24). Using these data, the study cohort's symptomatic status was categorised as follows, based on their baseline to 12-month KCCQ symptom stability score – **a**) Improved (positive score change = 26 to 100), **b**) Stable/persistent (score unchanged = -25 to +25), or **c**) Worsened (negative score change = -26 to -100 including -25 to -49, moderate and ≥-50, severe).

Study endpoints

The primary endpoint was the change in self-reported symptom scores from baseline to 12-month as reflected by the participants' responses to the KCCQ (according to the three pre-specified groups outlined above), according to sex and their underlying three LVEF-based HF subtypes.

Statistical analysis

Summary statistics are presented as means (± standard deviation, SD) for normally distributed or median (interquartile range, IQR) for non-gaussian distributed continuous variables, and number of cases (percentages, %) for categorical variables. Baseline characteristics were compared among three LVEF groups in men and women separately using one-way ANOVA for continuous variables and chi-square (X^2) tests for categorical variables. Chi-square (X^2) test was also used to examine the differences of symptom presences in men and women according to LVEF-based HF subtypes at baseline. Repeated measures ANOVA was used to assess changes in KCCQ symptom scores between baseline and 12-month for men and women separately. Binary logistic regression (entry model) was used to identify the independent correlates of a worsened symptomatic characteristic changes at 12-month (versus those with stable or improved symptoms), with

inclusion of all baseline variables associated with a univariate p-value <0.1 (from **Table 1 and Supplementary Table S1**) when comparing baseline differences across HF subtypes on a sex-specific basis. Three different multivariate models were constructed to derive adjusted odds ratios (OR) and 95% confidence intervals (95%CI) for men and women combined (with the inclusion of sex in the model) and then separately for men and women. Statistical significance was accepted at a two-sided α of 0.05. All statistical analyses were performed using SPSS V25.0 (SPSS Inc, IBM).

Patient and public involvement (PPI)

Patient and public involvement (PPI) were included in this study. To refine these study findings and make the research more relevant to patients, caregivers, and healthcare professionals, two volunteer advisors (one person with heart failure and one informal caregiver) were included. This involvement supported a more comprehensive person-centred care research from their own perspective in this study. The first author (MS) brought together and discussed the study findings to arrive at the final version.

RESULTS

Study cohort

As shown in **Figure 1**, the underlying distribution of HF subtypes was significantly different among men and women. In men, 58% had HFrEF, while, in women, only 31% had HFrEF. In contrast, only 22% of men had HFpEF, while 49% of women had HFpEF.

Table 1 summarises the baseline characteristics of men and women according to the three HF subtypes. Men with HFrEF were typically younger with a lower body mass index (BMI), were more likely to be employed and had less comorbidity including atrial fibrillation (AF), cerebrovascular disease, and a history of malignancy than men with HFmrEF/HFpEF. They also had less severe functional impairment according to their NYHA Class whilst recording a

higher brain natriuretic peptide (BNP) level than those with HFmrEF and HFpEF ($p<0.05$ for all comparisons). Women with HFpEF were significantly older, had a higher BMI, and were more likely to be married, from a non-English speaking environment, and a history of hypertension, AF, and prior hospital episodes than women with HFrEF/HFmrEF. Women with HFpEF were also less likely to have a history of smoking, coronary artery disease, and recorded lower BNP levels than at least one of the other groups ($p<0.05$ for all comparisons).

Symptom differences based on LVEF-based HF subtypes in men and women

We found women reported significant differences in KCCQ symptom (total, burden, frequency, and stability) scores and EQ-5D-5L quality of life scores ($p<0.05$) according to HF subtypes, but no significant differences in men (with minimal symptom differences across HF subtypes) (**Table 1**). At baseline, shortness of breath and fatigue were the most prominent symptoms in both sexes irrespective of HF subgroups (**Table 2**). However, bilateral ankle oedema was proportionally higher in those with HFpEF compared to HFmrEF/HFrEF in both sexes ($p=0.019$ for men and $p<0.0001$ for women). More women with HFpEF than HFrEF/HFmrEF reported walking problems ($p=0.019$). Men with HFrEF experienced more depressive symptoms than those with HFmrEF/HFpEF ($p=0.020$).

Symptom scores change based on LVEF-based HF subtypes in men and women

Overall, KCCQ total symptom, symptom frequency and symptom burden scores did not change significantly during the 12 months of follow-up in both sexes irrespective of their HF subtypes (**Table 3**). Only symptom stability score change was statistically significant in women only across the three HF subgroups ($p=0.03$).

Worsened, stable, and improved symptoms

Within the HFrEF subgroup, 48% of men and 55% of women improved their symptoms, a

further 18% of men and 22% of women reported no change during the 12 months period (**Table 4**). Approximately 47% of men with HFmrEF and 50% of women with HFpEF self-reported worsened symptoms. Overall, there were no statistical differences for worsened symptoms versus improved/stable in men according to HF subtypes (p=0.518). However, it was statistically significant in women (especially for women with HFpEF) (p=0.025). Based on the sensitivity analysis, sex and LVEF-based HF subtypes did not significantly interact with baseline and 12-month KCCQ symptom scores – see **Supplementary Table S2** for more descriptive data.

Correlates of worsening HF symptoms over 12-month

As shown in **Table 5**Error! Reference source not found., we tested a broad range of baseline correlates associated with worsened HF symptoms in men and women. Irrespective of gender, coronary artery disease (OR 2.01, 95%CI 1.21-3.31) and hypertension (OR 2.00, 95%CI 1.16-3.45) significantly correlated with worsened HF symptoms. Women were more likely to report worsening symptoms during the 12-month follow-up than men (OR 1.78, 95%CI 1.00-3.16). The higher LVEF range and those with HFpEF were more likely to report worsened symptoms in women but not men. Moreover, these sex-specific differences extended to other baseline characters, with primary English-speaking status (OR 2.30, 95%CI 1.02-5.20) and the presence of hypertension (OR 2.16, 95%CI 1.07-4.35) in men not women versus acute pulmonary oedema (OR 0.30, 95%CI 0.12-0.75) and cerebrovascular disease (OR 0.25 95%CI 0.08-0.79) in women not men also associated with worsening symptoms.

DISCUSSION

This study examined multifaceted factors associated with changes in symptoms in men and women living with different HF subtypes not typically examined in previously conducted studies. Subsequently, we report on three key findings relevant to the clinical management

of those hospitalised with the syndrome. Firstly, we observed baseline differences across LVEF-based HF subtypes for men and women, Secondly, here were potentially important differences in the symptom experiences and trajectory of symptom change among women across all HF subtypes (especially for HFpEF). Thirdly, different baseline characteristics correlated with a worsening symptomatic change at 12 months across the entire cohort and for both sexes. Overall, without being definitive, these findings suggest potentially important sex-stratified and LVEF-based HF subtypes differences in the symptomatic characteristics and symptom trajectory of those admitted and then discharged from hospital with the syndrome.

Previous studies that examined sex-related differences within HF subtypes (15-17, 27, 28) or HF subtypes in cohorts (18) have reported inconsistent findings. However, the present study showed that there are some key baseline differences by LVEF-based HF subtypes stratified by sex. Several baseline characteristics, including age, BMI, NYHA classification, elevated BNP, atrial fibrillation, and presence of comorbidities were different in the LVEF-based HF subtypes stratified by sex. In the European Society of Cardiology Guidelines (1), the medical management of HF differs by LVEF-based subtypes (noting that many elements and objective of multidisciplinary HF management/support remains the same). Building on the need for tailored treatment, our findings indicate that a combination of the sex and LVEF-based HF subtypes need to be considered when designing individualised treatment and follow-up/management strategies.

Reinforcing the above points, differences in symptom status at baseline were associated with LVEF-based HF subtypes in men and women separately. Also at baseline, KCCQ sub-category symptom scores were significantly different among women based on LVEF-based HF subtypes, and the presence of bilateral ankle oedema was significantly different across

HF subtypes in both sexes. Walking problems were significantly different in women and depressive symptoms in men according to LVEF-based HF subtypes. In this study, these sex-stratified outcomes according to the three common HF phenotypes cannot be compared to any other studies due to the paucity of data available. Although there is a lack of information on how HF subtypes stratified by sex affect HF symptom status overall, some evidence has shown that sex and HF subtypes affect HF symptoms. Women with HFpEF have worse symptoms and lower quality of life than men with HFpEF (13, 14, 17). Women also self-report worse KCCQ overall summary scores than men (29). Men with HFrEF have higher median KCCQ total symptom, symptom frequency and symptom burden scores than women with HFrEF. This collectively suggests that men have less HF symptom burden than women (15). Consequently, it is very likely that LVEF-based HF subtypes are associated with different symptom characteristics for women and men.

Based on symptom changes over one year, KCCQ sub-category symptom scores (except symptom stability score for women) did not change significantly according to LVEF-based HF subtypes irrespective of sex. Women with HFpEF were more likely to have worsening symptoms compared to women with HFrEF and HFmrEF. The majority of HF patients in the high-risk community were women with HFpEF, particularly those over 70 years of age (18). Consistent with the findings reported in our study, women with HFpEF were older and had a longer-term severe worsened symptom than women with HFrEF/HFmrEF. Additionally, we found that women with HFpEF had higher comorbidity scores (according to Charlson Comorbidity Index). Comorbidities (but not the only explanation) are more common in patients with HFpEF, making diagnosis difficult in patients with this type of HF and nonspecific HF symptoms (including shortness of breath and fluid retention such as chronic obstructive pulmonary disease) (1, 18). Lastly, lower quality of life has also been shown to

be associated with being a woman, geographical region, greater number of comorbidities, severe symptom burden in HFpEF (29). In this present study, women with HFpEF had more comorbid conditions and worsening symptoms. In older patients with multimorbidity, symptoms of both men and women with HFpEF can be misclassified or overlooked because of inadequate assessment of this HF subtype in both in- and out-patient settings. This is important because current strategies to support women with HF may be misdirected by findings (such as symptoms, medications, self-care management etc.) generated from a minority of women living with HFrEF as opposed to those with a preserved EF (18, 28). Given the differences in the symptom characteristics and changes of HFpEF in women, there is heterogeneity among this patient population, which requires greater clinical attention for treatment and diagnosis (18).

Correlates of worsening symptoms were different among the entire cohort as well as among men and women. At baseline, we found that HFpEF significantly predicted worsening symptoms at 12 months for the entire cohort and for women. In a previous study, there were significant differences in BNP level, HF symptoms (dyspnoea and fatigue), and pulmonary oedema presence between worsening HF groups and complicated and uncomplicated hospital groups (4). Another study found that older age, increased LVEF, and higher BNP were independently related to the development of worsening HF among hospital inpatients (30). Compared to our finding, this suggested that influencing factors of worsening HF progression can be different among different study cohorts. However, in our cohort, men and women also had different correlates of worsening HF symptoms. Therefore, factors influencing symptom changes in men and women in each cohort should be considered.

Early detection of worsening symptoms in outpatient settings could help improve long term

outcomes and reduce healthcare cost (5, 8, 9). Post-hospital discharge, severe episodes of worsening HF may be prevented with prompt and targeted follow-up care (according to sex and HF subtypes). Due to a lack of research data reporting HFmrEF/HFpEF symptom profiles in men and women, we need be cautious in applying a homogenous maintenance and follow-up care (including telemonitoring tools) to manage individuals with different LVEF-based subtypes. If we can identify who, and at what point women and men with different HF phenotypes would need more care (pharmacological/device therapy), and with early detection of worsening symptomatic profile, then we can apply timely interventions to reduce severe episodes of worsening HF and the potential for unplanned admissions and even death (31). At this stage, in outpatient settings, HF specialist nurses need to improve person-centred care (including patient education, treatment, symptom monitoring, and follow-up care) by identifying sex-specific predictors of long-term worsening symptomatic course to prevent disease progression. Addressing the subjective needs of men and women in their specific socio-cultural worldviews will support well-structured patient-centred care in HF (32). Finally, assessment of symptoms should adapt to both sexes perspectives to reduce the risk of worsening symptomatic profile and improve quality of life. Further research is needed to understand sex differences that drive symptom changes and progressive worsening of HF.

LIMITATIONS

The study sample included older adults with HF, which limits the generalisability of its findings to the broader population. Although the original WHICH? II trial enrolled a nationally representative of women and men with chronic HF in Australia, not all participants were assessed at both time points, which may influence the sample representativeness. Our results also may not be generalisable due to inherent participant

characteristic bias, such that most participants were in the NYHA class II, mainly of European/Caucasian descent (>90%) and had high BMI. Also, participants may have under-reported their symptoms and quality of life because their activity level was limited, and their age was older which may influence their symptom experiences and quality of life. Self-reported symptom experiences and quality of life may be influenced by the contribution of the other cardiometabolic risk factors or concurrent comorbid conditions. In addition, we were blinded from the original intervention allocation during the secondary data analysis, hence we analysed the two groups together. This may have influenced the symptom score changes among the LVEF-based HF subgroups. Lastly, the definition of worsening symptoms was based on the change in KCCQ symptom stability score, and this score only includes the main symptoms (shortness of breath, swelling and fatigue). The KCCQ symptom stability score includes the last two weeks' evaluation of symptom changes, and this can be controversial in terms of time.

CONCLUSION

The current study showed that LVEF-based subtypes of HF were associated with different symptoms, symptom characteristics and changes in men and women separately. Women with HFpEF were more likely to develop worsening symptoms over one year compared to women with HFrEF/HFmrEF. A better understanding of the differences in worsening symptoms of both sex-stratified and LVEF-based HF subtypes will help prevent the adverse outcomes of HF. Healthcare providers and researchers need to consider, develop, and then deliver tailored interventions and follow-up strategies to address a high underlying burden of severe and persistent symptoms in those hospitalised with the syndrome. Critically, the underlying LVEF-based HF subtype, sex, and likely factors influencing symptom changes of each affected individual need to be carefully considered.

AUTHOR CONTRIBUTIONS

SS conceived and designed the study, YKC prepared the study data for analyses, MS analysed the data and draft the main body of the manuscript with inputs from SS and YKC. All authors critically revised sequential versions of the manuscript and approved the final version for publication.

ACKNOWLEDGEMENT

The authors thank the Ministry of National Education of the Republic of Turkey, the Republic of Turkey for supporting Muzeyyen Seckin's PhD. The first author is also grateful to her valued partners (public advisors-RP and NH) for all their guidance, assistance and sharing their experience and expertise during this work. We wish to thank everyone who took part in the WHICH? II Trial Study cohort.

FUNDING

The original WHICH ? II Study was funded by the National Health and Medical Research Council of Australia Project Grant (GNT 1049133). There is no funding for this secondary data analysis research.

CONFLICT OF INTEREST

None.

DATA AVALIBILITY

Deidentified aggregated data support the findings of this study are available from the corresponding author, upon reasonable request.

SUPLEMENTARY INFORMATION

Table S1 Baseline characteristics in men and women

Table S2 Interaction analysis of sex and LVEF-based HF subtypes in KCCQ symptom scores at baseline and 12-month

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FIGURE LENGENDS

Figure 1 Study flow diagram

Legend HF, Heart failure; HFrEF, Heart failure with reduced ejection fraction (LVEF ≤40%); HFmrEF, Heart failure with mildly reduced ejection fraction (LVEF 41-49%); HFpEF, Heart failure with preserved ejection fraction (LVEF ≥50%).

1 **Table 1** Baseline characteristics of men and women according to heart failure subtypes based on left ventricular ejection fraction

Variables		Men (n=302)				Women (n=226)			
		HFrEF (n=175)	HFmrEF (n=62)	HFpEF (n=65)	P-value	HFrEF (n=69)	HFmrEF (n=46)	HFpEF (n=111)	P-value
Sociodemographic characteristics									
Age, mean±SD (years)		68.6±12.4	74.3±8.9	74.5±11.6	**<0.0001**	74.4±12.4	75.6±10.3	79.5±9.2	**0.004**
Living alone, n(%)		56 (32.0)	20 (32.3)	29 (44.6)	0.170	36 (52.2)	28 (60.9)	59 (53.2)	0.612
Married-living with partner, n(%)		107 (61.1)	39 (62.9)	35 (53.8)	0.467	18 (26.1)	14 (30.4)	40 (36.0)	**0.044**
European/Caucasian ethnicity, n(%)		157 (89.7)	57 (91.9)	61 (93.8)	0.831	63 (91.3)	44 (95.7)	108 (97.3)	0.530
<12 years education, n(%)		114 (65.2)	41 (66.1)	42 (64.6)	0.065	56 (81.2)	39 (61.4)	95 (85.6)	0.070
English not first language, n(%)		27 (15.4)	8 (12.9)	13 (20.0)	0.532	7 (10.1)	11 (23.9)	32 (28.8)	**0.013**
Retired, n(%)		127 (72.6)	54 (87.1)	56 (86.2)	**0.014**	58 (84.1)	42 (91.3)	103 (92.8)	0.158
Risk characteristics									
BMI, mean±SD (kg/m^2)		29.1±5.5	30.5±5.5	31.6±9.2	**0.024**	28.0±5.8	31.5±9.1	32.3±8.4	**0.002**
>2.5-hour physical activity, n(%)		82 (46.9)	27 (43.5)	22 (33.8)	0.195	20 (29.0)	12 (26.1)	18 (16.2)	0.130
Non-smoker, n(%)		43 (24.6)	19 (30.6)	20 (30.8)	0.150	28 (40.6)	19 (41.3)	79 (71.2)	**<0.0001**
Diabetes, n(%)		77 (44.0)	35 (56.5)	32 (49.2)	0.232	25 (36.2)	15 (32.6)	51 (45.9)	0.215
Hypertension, n(%)		119 (68.0)	50 (80.6)	48 (73.8)	0.151	49 (71.0)	36 (78.9)	98 (88.3)	**0.014**
Heart failure characteristics									
HF duration, n(%)	0 to 2 years	27 (15.4)	13 (21.0)	8 (12.3)	0.291	21 (30.4)	8 (17.4)	22 (19.8)	0.101
	2 to 5 years	100 (57.1)	37 (59.7)	45 (99.2)		31 (44.9)	26 (56.5)	71 (64.0)	
	≥5 years	48 (27.4)	12 (19.4)	12 (18.5)		17 (24.6)	12 (26.1)	18 (16.2)	
LVEF, mean±SD (%)*		27.2±6.6	43.1±2.7	58.3±5.9	**<0.0001**	30.2±6.4	42.8±2.3	58.29±6.90	**<0.0001**
NYHA functional class III/IV, n(%)		31 (17.7)	9 (14.5)	17 (26.2)	**0.020**	15 (21.7)	8 (17.4)	29 (26.1)	0.607
Elevated BNP, n(%)		95 (56.2)	22 (36.1)	22 (34.4)	**0.002**	39 (59.1)	17 (37.8)	37 (33.9)	**0.004**
Raised JVP, n(%)		78 (44.8)	29 (46.8)	40 (62.5)	0.050	32 (46.4)	25 (54.3)	49 (44.1)	0.504
Prior HF admission (12 months), n(%)		94 (53.7)	34 (54.8)	39 (60.0)	0.682	31 (44.9)	29 (63.0)	72 (64.9)	**0.024**
Clinical characteristics									
Acute pulmonary oedema, n(%)		40 (22.9)	17 (27.4)	20 (30.8)	0.424	22 (32.4)	16 (34.8)	49 (44.1)	0.242
Atrial fibrillation, n(%)		81 (46.3)	38 (61.3)	43 (66.2)	**0.009**	23 (33.3)	24 (52.2)	70 (63.1)	**0.001**
Sleep Apnoea, n(%)		40 (22.9)	11 (17.7)	19 (29.2)	0.305	4 (5.8)	7 (15.2)	20 (18.0)	0.065
Heart rhythm disturbance, n(%)		46 (26.3)	18 (29.0)	11 (16.9)	0.227	6 (8.7)	4 (8.7)	11 (9.9)	0.952
Coronary artery disease, n(%)		119 (68.0)	41 (66.1)	37 (56.9)	0.274	40 (58.0)	30 (60.2)	45 (40.5)	**0.007**
Chronic pulmonary disease, n(%)		42 (24.0)	19 (30.6)	23 (35.4)	0.185	20 (29.0)	13 (28.3)	26 (23.4)	0.663
Cerebrovascular disease, n(%)		29 (16.6)	18 (29.0)	21 (32.3)	**0.013**	10 (14.5)	9 (19.6)	24 (21.6)	0.493
Cancer or tumour, n(%)		18 (10.3)	14 (22.6)	13 (20.0)	**0.028**	19 (27.5)	7 (15.2)	16 (14.4)	0.072
Charlson Comorbidity Score, mean±SD		5.99±2.30	7.19±2.81	7.08±2.16	**<0.0001**	6.80±2.32	6.78±2.10	7.15±1.93	0.432
Poor sleeping quality, n(%)		56 (32.0)	14 (22.6)	20 (30.8)	0.170	19 (27.5)	20 (43.5)	39 (35.1)	0.132
KCCQ scores, mean±SD	Total symptom score	49.0±24.7	47.4±25.5	43.7±25.3	0.347	45.9±23.6	43.3±24.7	40.6±23.6	**0.018**
	Symptom frequency	46.2±25.5	45.6±26.2	40.8±26.7	0.349	45.2±23.2	42.0±26.54	35.0±23.8	**0.020**
	Symptom burden	51.8±26.5	49.1±28.0	46.6±27.0	0.395	46.6±26.5	44.5±26.0	37.3±24.0	**0.039**
	Symptom stability	45.4±37.3	53.2±39.8	53.8±38.5	0.190	39.8±37.9	53.2±36.3	55.8±40.3	**0.025**
	Quality of life	38.7±22.4	40.1±22.6	43.8±23.5	0.306	38.2±25.1	35.3±17.4	34.6±20.4	0.529
EQ-5D-5L, mean±SD	Quality of life	0.7±0.1	0.7±0.1	0.6±0.2	0.672	0.7±0.1	0.6±0.1	0.6±0.2	**0.034**

Legend *n=178 for women and n=279 for men; HF, heart failure; BMI, Body mass index; LVEF, left ventricular ejection fraction; HFrEF,Heart failure with reduced ejection fraction (LVEF ≤40%);HFmrEF, Heart failure with mildly reduced ejection fraction (LVEF 41-49%); HFpEF, Heart failure with preserved ejection fraction (LVEF ≥50%); NYHA, New York Heart Association; BNP, b-type natriuretic peptide; elevated b-type natriuretic peptide (BNP) >6000pg/ml; JVP, jugular venous pressure; SD: standard deviation; KCCQ, Kansan City Cardiomyopathy Questionnaire; EQ-5D-5L scale, EuroQol 5-level 5-dimensional scale; Quality of life was assessed by KCCQ and EQ-5D-5L scales; depressive symptoms were calculated by a two-item ARROL tool. ANOVA for continuous variables and chi-square (X^2) tests for categorical variables were used for a comparison between men and women.

Table 2 Baseline self-reported symptoms in men and women according to heart failure subtypes based on left ventricular ejection fraction

	Men (n=302)				Women (n=226)			
Symptoms	**HFrEF (n=175)**	**HFmrEF (n=62)**	**HFpEF (n=65)**	**P-value**	**HFrEF (n=69)**	**HFmrEF (n=46)**	**HFpEF (n=111)**	**P-value**
Shortness of breath, n(%)	159 (90.9)	59 (95.2)	60 (92.3)	0.558	66 (95.7)	43 (93.5)	107 (96.4)	0.720
Fatigue, n(%)	161 (92.0)	57 (91.9)	57 (87.7)	0.562	66 (95.7)	43 (93.5)	107 (96.4)	0.720
Bilateral ankle oedema, n(%)	97 (55.4)	38 (61.3)	49 (75.4)	**0.019**	36 (52.2)	32 (69.6)	96 (86.5)	**<0.0001**
Nocturnal cough, n(%)	73 (41.7)	24 (38.7)	22 (33.8)	0.537	30 (43.5)	16 (34.8)	43 (38.7)	0.634
Orthopnoea, n(%)	108 (61.7)	35 (56.5)	41 (63.1)	0.707	51 (73.9)	28 (60.9)	84 (75.7)	0.157
Paroxysmal nocturnal dyspnoea, n(%)	80 (45.7)	20 (32.3)	28 (43.1)	0.182	38 (55.1)	23(50.0)	53 (47.7)	0.632
Pain/discomfort, n(%)	75 (43.1)	24 (38.7)	26 (40.0)	0.807	27 (39.7)	23 (50.0)	51 (46.4)	0.518
Sleeping problems due to orthopnoea, n(%)	82 (46.9)	25 (40.3)	30 (46.2)	0.667	31 (44.9)	21 (45.7)	50 (45.0)	0.997
Walking problems, n(%)	91 (52.3)	35 (56.5)	44 (67.7)	0.102	43 (63.2)	32 (69.6)	90 (81.8)	**0.019**
Depressive symptoms, n(%)	121 (69.9)	36 (58.1)	33 (51.6)	**0.020**	48 (69.6)	32 (69.6)	73 (65.8)	0.830

Legend HF, heart failure; LVEF, left ventricular ejection fraction; HFrEF, Heart failure with reduced ejection fraction (LVEF ≤40%);HFmrEF, Heart failure with mildly reduced ejection fraction (LVEF 41-49%); HFpEF, Heart failure with preserved ejection fraction (LVEF ≥50%). The chi-square (X^2) tests were used to compare the presence of symptoms in men and women separately.

Table 3 Changes in KCCQ sub-category symptom scores from baseline according to heart failure subtypes based on left ventricular ejection fraction

KCCQ Heart Failure Symptom Score Change	Men (n=302)									
	HFrEF (n=175)			HFmrEF (n=62)			HFpEF (n=65)			
	Baseline	12-month	Baseline to 12 Months	Baseline	12-month	Baseline to 12 Months	Baseline	12-month	Baseline to 12 Months	P-value
Total Symptom	49.0±24.7	78.3±21.4	29.3(24.8,33.7)	47.4±25.5	76.8±23.8	29.4(21.2, 7.6)	43.7±25.3	72.9±24.0	29.3(22.50,36.2)	1.000
Symptom Stability	45.4±37.3	52.2±19.1	6.8(0.8,12.8)	53.2±39.8	47.1±16.3	-6.0(-16.2,4.1)	53.8±38.5	52.3±18.2	-1.9(-12.1 8.2)	0.062
Symptom Frequency	46.2±25.5	76.2±23.2	29.9(25.3,34.5)	45.6±26.2	75.5±23.9	29.8(21.4,38.3)	40.8±26.7	69.7±26.4	29.1(21.7,36.5)	0.934
Symptom Burden	51.8±26.5	80.5±22.3	28.7(23.8,33.5)	49.1±28.0	78.2±25.3	29.0(20.3,37.7)	46.6±27.0	76.0±24.4	29.3(22.1,36.5)	0.990
	Women (n=226)									
	HFrEF (n=69)			HFmrEF (n=46)			HFpEF (n=111)			
	Baseline	12-month	Baseline to 12 Months	Baseline	12-month	Baseline to 12 Months	Baseline	12-month	Baseline to 12 Months	P-value
Total Symptom	45.9±23.6	76.0±22.2	30.1(24.4,35.8)	43.3±24.7	74.7±23.2	31.4(21.7,41.1)	40.6±23.6	69.5±23.8	33.3(28.0,38.6)	0.749
Symptom Stability	39.8±37.9	48.9±16.8	9.0(1.0,17.1)	53.2±36.3	48.3±20.6	-4.89(-17.5,7.7)	55.8±40.3	48.8±19.1	-6.9(-15.2,1.2)	**0.033**
Symptom Frequency	45.2±23.2	75.4±22.3	30.2(24.3 36.1)	42.0±26.5	74.1±24.0	32.1(22.8,41.3)	35.0±23.8	66.4±25.3	31.3(25.4,37.2)	0.940
Symptom Burden	46.6±26.5	76.6±24.2	30.0(23.4,36.7)	44.5±26.0	75.3±25.3	30.7(19.5,42.0)	37.3±24.0	72.5±25.6	35.2(29.6,40.9)	0.492

Legend Symptom scores are presented as mean±SD (standard deviation) at baseline and 12-month; changes in symptom scores from baseline to 12-month are presented as mean difference (95% Confidence Interval [CI] upper and lower). HF, Heart Failure; LVEF, Left ventricular ejection fraction; HFrEF, Heart failure with reduced ejection fraction (LVEF ≤40%); HFmrEF, Heart failure with mildly reduced ejection fraction (LVEF 41-49%); HFpEF, Heart failure with preserved ejection fraction (LVEF ≥50%); KCCQ, Kansan City Cardiomyopathy Questionnaire. Repeated ANAVO was used to compare the symptom scores between baseline and 12-month in men and women separately.

Table 4 Baseline to 12-month symptoms change in men and women according to heart failure subtypes based on left ventricular ejection fraction

	Men (n=302)			Women (n=226)		
Symptoms change	HFrEF (n=175)	HFmrEF (n=62)	HFpEF (n=65)	HFrEF (n=69)	HFmrEF (n=46)	HFpEF (n=111)
Improving, n(%)	84 (48.0%)	23 (37.1%)	24 (37.5%)	38 (55.1%)	15 (32.6%)	39 (35.1%)
Persistent, n(%)	32 (18.3%)	10 (16.1%)	14 (21.9%)	15 (21.7%)	11 (23.9%)	17 (15.3%)
Moderate Worsening (25-49), n(%)	24 (13.7%)	10 (16.1%)	9 (14.1%)	5 (7.2%)	8 (17.4%)	20 (18.0%)
Severe Worsening (≥50), n(%)	35 (20.0%)	19 (30.6%)	17 (26.6%)	11 (15.9%)	12 (26.1%)	35 (31.5%)
		0.518			**0.025**	

Legend Symptoms change is calculated by change in KCCQ symptom stability scores from baseline to 12-month. LVEF, left ventricular ejection fraction; HF, Heart failure; HFrEF, Heart failure with reduced ejection fraction (LVEF ≤40%); HFmrEF, Heart failure with mildly reduced ejection fraction (LVEF 41-49%); HFpEF, Heart failure with preserved ejection fraction (LVEF ≥50%); KCCQ, Kansan City Cardiomyopathy Questionnaire. The chi-square (X^2) tests were used to compare the presence of stable/improved/worsened symptoms change between baseline and 12-month.

1 **Table 5** Correlates associated with worsening symptoms in the entire cohort, men, and women

Variables	Cohort						Men						Women					
	B	S.E.	Sig.	Exp(B)	95 C.I. for EXP(B)		B	S.E.	Sig.	Exp(B)	95 C.I. for EXP(B)		B	S.E.	Sig.	Exp(B)	95 C.I. for EXP(B)	
					Lower	Upper					Lower	Upper					Lower	Upper
Sex (women)	**0.579**	**0.292**	**0.047**	**1.785**	**1.006**	**3.166**												
Age	0.014	0.016	0.370	1.015	0.983	1.047	0.013	0.021	0.524	1.014	0.972	1.056	0.010	0.030	0.735	1.010	0.952	1.072
Living alone	-0.356	0.279	0.202	0.701	0.406	1.210	-0.224	0.379	0.554	0.799	0.380	1.679	-0.677	0.519	0.192	0.508	0.184	1.405
Married-living with partner	0.341	0.368	0.354	1.406	0.684	2.890	0.349	0.475	0.463	1.417	0.559	3.596	0.507	0.723	0.484	1.660	0.402	6.850
Education level	-0.001	0.287	0.998	0.999	0.569	1.755	0.106	0.391	0.786	1.112	0.516	2.395	-0.167	0.504	0.741	0.846	0.315	2.273
English not first language	0.590	0.317	0.063	1.804	0.969	3.359	**0.836**	**0.416**	**0.044**	**2.307**	**1.021**	**5.209**	0.054	0.629	0.932	1.055	0.308	3.619
Retired	0.198	0.358	0.580	1.219	0.604	2.461	0.291	0.422	0.490	1.338	0.585	3.057	-0.301	0.872	0.730	0.740	0.134	4.091
BMI	0.019	0.019	0.307	1.020	0.982	1.058	0.037	0.031	0.226	1.038	0.977	1.102	0.016	0.030	0.587	1.016	0.959	1.077
>2.5-hour physical activity	-0.435	0.26	0.094	0.647	0.389	1.077	-0.200	0.329	0.542	0.818	0.430	1.559	-0.884	0.526	0.093	0.413	0.147	1.159
Smoking	-0.324	0.465	0.487	0.724	0.291	1.800	-0.307	0.553	0.578	0.735	0.249	2.175	-0.657	1.105	0.552	0.518	0.059	4.519
Diabetes	-0.187	0.28	0.505	0.830	0.479	1.437	-0.120	0.379	0.752	0.887	0.422	1.864	0.081	0.510	0.874	1.085	0.399	2.947
Hypertension	**0.696**	**0.278**	**0.012**	**2.005**	**1.163**	**3.458**	**0.772**	**0.357**	**0.030**	**2.164**	**1.076**	**4.352**	0.150	0.590	0.799	1.162	0.366	3.690
LVEF	**-0.044**	**0.020**	**0.023**	**0.957**	**0.921**	**0.994**	-0.043	0.027	0.107	0.958	0.908	1.009	**-0.089**	**0.037**	**0.016**	**0.915**	**0.851**	**0.984**
HFpEF	**-1.352**	**0.658**	**0.040**	**0.259**	**0.071**	**0.940**	-1.155	0.968	0.233	0.315	0.047	2.102	**-2.407**	**1.149**	**0.036**	**0.090**	**0.009**	**0.856**
NYHA	-0.134	0.296	0.651	0.875	0.489	1.564	-0.361	0.425	0.396	0.697	0.303	1.605	-0.042	0.543	0.938	0.959	0.331	2.781
Elevated BNP	0.451	0.243	0.064	1.569	0.974	2.528	0.477	0.324	0.141	1.612	0.854	3.043	0.715	0.448	0.110	2.044	0.850	4.916
Raised JVP	-0.053	0.229	0.818	0.949	0.605	1.486	-0.124	0.304	0.684	0.884	0.487	1.603	-0.322	0.444	0.469	0.725	0.304	1.731
Hospital admission	0.081	0.102	0.428	1.085	0.887	1.326	0.180	0.16	0.261	1.197	0.875	1.638	-0.077	0.185	0.678	0.926	0.644	1.331
APO	**0.518**	**0.252**	**0.040**	**1.679**	**1.025**	**2.750**	-0.426	0.357	0.233	0.653	0.324	1.315	**-1.182**	**0.458**	**0.010**	**0.307**	**0.125**	**0.752**
AF	0.100	0.232	0.668	1.105	0.701	1.741	0.081	0.299	0.786	1.085	0.603	1.950	0.032	0.442	0.941	1.033	0.434	2.457
Sleep apnoea	0.065	0.304	0.831	1.067	0.588	1.936	0.116	0.393	0.768	1.123	0.520	2.424	-0.279	0.629	0.657	0.757	0.221	2.594
Heart Rhythm Disturbance	0.532	0.301	0.078	1.702	0.943	3.072	0.419	0.353	0.236	1.521	0.761	3.040	1.123	0.713	0.115	3.073	0.760	12.424
Coronary Artery Disease	**0.698**	**0.255**	**0.006**	**2.010**	**1.219**	**3.314**	0.671	0.359	0.062	1.956	0.967	3.956	0.593	0.433	0.170	1.810	0.775	4.225
Cerebrovascular Disease	-0.253	0.301	0.401	0.777	0.430	1.401	0.185	0.404	0.647	1.203	0.545	2.655	**-1.351**	**0.569**	**0.018**	**0.259**	**0.085**	**0.791**
Cancer or tumour	0.479	0.374	0.200	1.615	0.776	3.360	0.355	0.519	0.493	1.427	0.516	3.942	0.916	0.684	0.180	2.500	0.654	9.549
Adjusted Charlson Index	0.080	0.083	0.334	1.083	0.921	1.274	0.126	0.116	0.278	1.134	0.904	1.422	0.093	0.147	0.527	1.098	0.822	1.465
Depressive symptoms	0.156	0.245	0.525	1.168	0.723	1.887	0.145	0.326	0.656	1.156	0.611	2.188	0.683	0.475	0.150	1.981	0.780	5.028
EQ-5D-5L	0.104	0.097	0.286	1.109	0.917	1.343	0.244	0.130	0.061	1.276	0.989	1.645	-0.194	0.187	0.301	0.824	0.571	1.189

2

Legend HF, heart failure; LVEF, left ventricular ejection fraction; HFrEF, Heart failure with reduced ejection fraction (LVEF ≤40%);HFmrEF, Heart failure with mildly reduced ejection fraction (LVEF 41-49%); HFpEF, Heart failure with preserved ejection fraction (LVEF ≥50%); BNP, b-type natriuretic peptide; QoL: quality of life, b-type natriuretic peptide; elevated (BNP) >6000pg/ml; NYHA, New York Heart Association; BMI, Body mass index; JVP, jugular venous pressure, AF: Atrial Fibrillation, APO: Acute pulmonary oedema, KCCQ, Kansan City Cardiomyopathy Questionnaire; EQ-5D-5L scale, EuroQol 5-level 5-dimensional scale. Binary logistic (entry model) was used to identify the independent correlates of a worsened symptoms change in the cohort, men, and women separately.

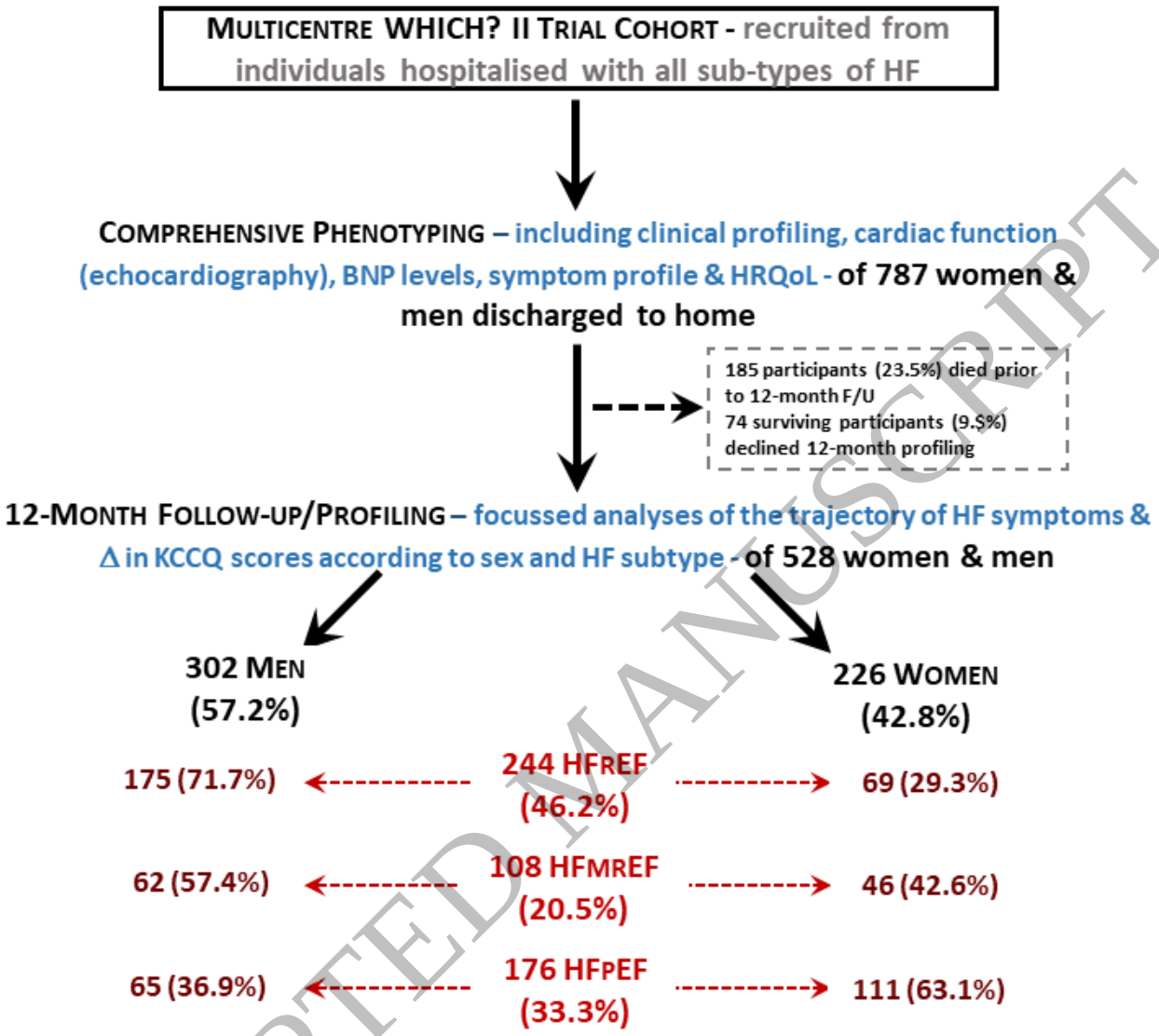
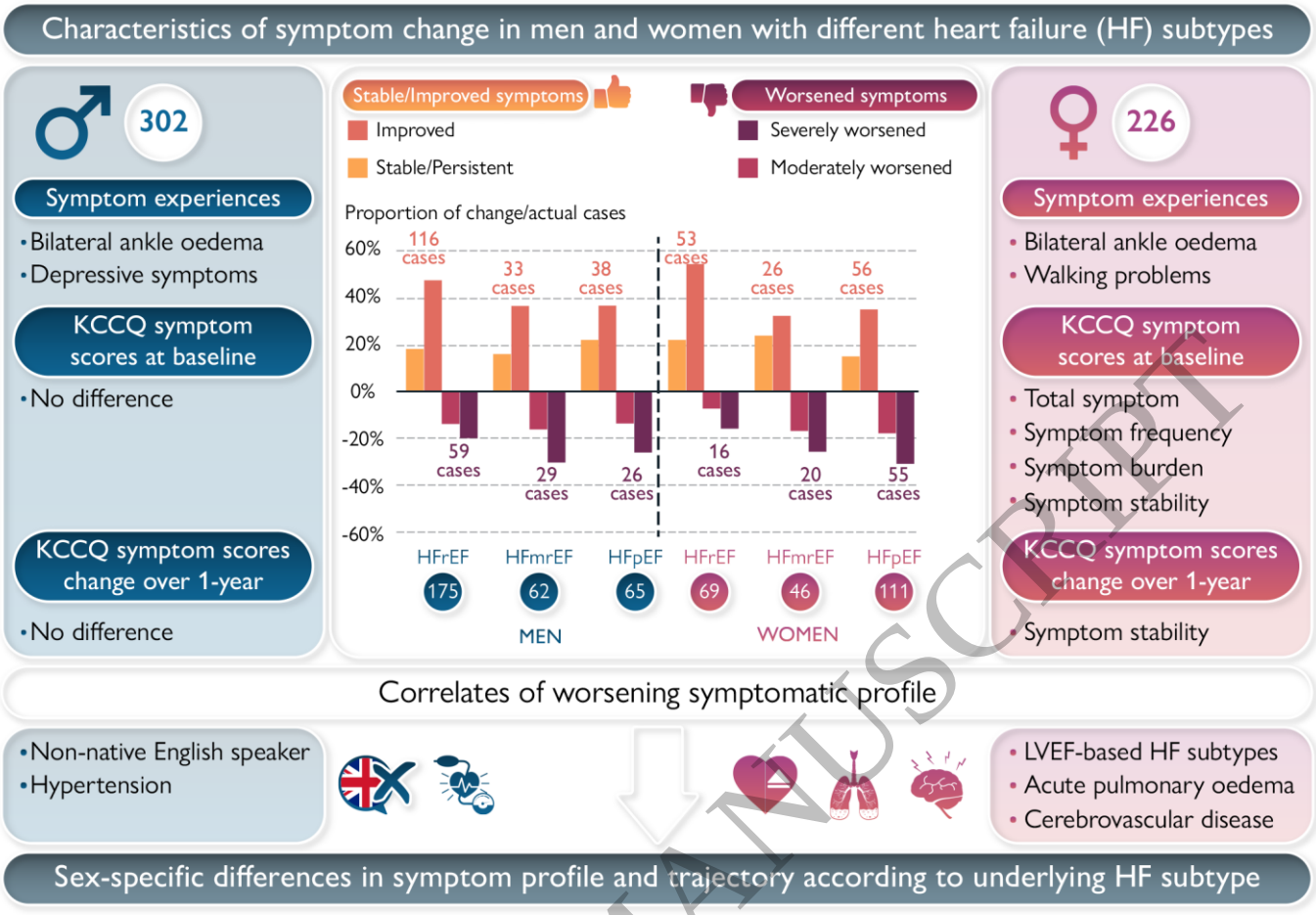


Figure 2 Study flow diagram



Graphical Abstract