Prevalence of palliative care needs in patients admitted to hospital with heart failure

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Summary

Background

The syndrome of heart failure is common, and is associated with high morbidity and reduced life expectancy. Patients can experience high symptom burden, low mood, and impaired quality of life. Repeated, and often prolonged, hospitalisations due to exacerbations of heart failure and other co-morbidities are common. Over the last 25 years, the evidence base for the treatment of heart failure has increased, with an associated improvement in prognosis. However, many patients with heart failure still have a poor prognosis. International guidelines for the treatment of heart failure now suggest referral to palliative care services, particularly in patients thought to have a poor prognosis and impaired quality of life. Despite these recommendations, few patients with this condition have access to specialist palliative care services in the United Kingdom. However, not every patient with heart failure will have palliative care needs, therefore the extent of the problem of unmet palliative care needs in patients with heart failure is unknown.

I systematically reviewed the published literature to identify studies describing the palliative care needs, including prevalence, of patients with heart failure. Although my search identified over 60 publications describing the palliative care needs of patients with heart failure, most of the studies were of highly selected cohorts, did not include descriptions of therapy, or descriptions of severity of heart failure such as ejection fraction, natriuretic peptides, prognostic scores or clinical outcomes. Most studies used a cross-sectional approach to describe the potential palliative care needs, and therefore, were unlikely to appreciate the variable clinical course of patient with heart failure. Although the studies identified were informative, a definitive description of the prevalence of palliative care needs in a well described, contemporary cohort of patients with heart failure is lacking. My systematic review also identified a number of preliminary randomised controlled clinical trials, assessing the effect of early palliative care in patients with heart failure. However, these studies included small numbers of

participants, and only had qualitative endpoints such as change in quality of life measures without assessment of clinical outcomes such as death or hospitalisation. Again, although these preliminary trials are informative, a definitive evidence base comparing palliative care to standard care in heart failure is not available.

Aims

The primary aim of this study was to inform the design of a randomised controlled clinical trial of palliative care in patients with heart failure. The first step in this process was to define the clinical problem and identify a suitable target population by describing the prevalence of patients with heart failure who have palliative care needs. I then aimed to describe whether these patients could be identified from data collected during an index hospital admission. The final aim of my study was to identify useful outcome measures which could be used in a randomised controlled clinical of palliative care in heart failure.

Methods

This was a prospective, longitudinal study of the prevalence of possible palliative care needs, defined using quantifiable patient reported outcome measures. An unselected cohort of patients admitted to hospital with a primary diagnosis of heart failure were recruited and extensively characterised. The World Health Organisation definition of palliative care was used to identify patients with heart failure who had palliative care needs. I made objective assessments of quality of life (using the Kansas City Cardiomyopathy and Short Form 12 questionnaires), mood disturbance (using the Hospital Anxiety and Depression Scale), symptom burden (using the Edmonton Symptom Assessment Scale), and caregiver strain (using the Zarit Burden Interview questionnaire). These assessments were made at baseline and repeated every four months for the duration of the study. Patients were identified as having palliative care needs if they had persistently severe impairment of any patient reported outcome measure without improvement, or severe impairment of any patient reported outcome measure followed by death. End-of-life care was assessed using the Views Of Informal Caregivers Evaluation of Services questionnaire, and by comparing preferred place of end of life care to

actual place of death. Multivariate logistic regression analysis was used to determine if baseline prognostic markers, physician completed assessments, or patient reported outcome measures could identify patients with palliative care needs.

Results

Between January 9th 2013 and December 1st 2014, 313 near consecutive patients with heart failure were enrolled in the study. Of these, 272 (86.9%) completed patient reported outcome measures at baseline and agreed to attend study visits. Patients were elderly, with a median [interquartile range] age of 76 [70-82] years, and 47% of participants were female. 56% of patients did not have a previous diagnosis of heart failure. Most participants had heart failure with reduced ejection fraction (67.3%) compared to heart failure with preserved ejection fraction (32.7%). Use of disease modifying pharmacotherapy was high, especially in participants with heart failure with reduced ejection fraction.

Participants suffered from a number of physical and psychological symptoms, as recorded using patient reported outcome measures. The most common physical symptoms were shortness of breath and fatigue, followed by drowsiness and lack of appetite. Although less frequent, pain and nausea were also common. Participants reported higher scores for depression and anxiety compared to studies using similar mood assessments in the general population. Quality of life was impaired in most participants at baseline, with 77.9% of participants being classified as having moderate or severe impairment as assessed by the Kansas City Cardiomyopathy questionnaire. At baseline, 114 (41.9%) participants scored severe in at least one patient reported outcome measure. Of these, 95 (83%) participants scored severe on the Kansas City Cardiomyopathy Questionnaire.

Participants were invited to attend study visits, or have home study visits, every four months for the duration of the study. The minimum number of study visits offered was two for the last participant enrolled. A total of 691 study visits were performed. 37% of these assessments were home visits. Participants were also followed up passively using record linkage to report number and cause of

hospitalisations, and cause and location of any deaths. Participants were followed up for a minimum of one year. During follow-up, 217 (79.8%) participants were re-admitted to hospital. The median number of admissions was 3. Most hospitalisations were due to non-cardiovascular causes. During passive follow-up until December 1st 2015, there were 103 (37.8%) deaths. Most (60.2%) deaths were due to cardiovascular causes.

73 (26.8%) participants met my criteria for having palliative care needs. These patients had worse summary scores at baseline for all patient reported outcome measures. Patients who met my definition of palliative care needs spent fewer days alive and out of hospital than the group who did not meet the definition of palliative care needs. The median [IQR] days alive out of hospital in the group meeting the definition of palliative care needs was 394 [172-586], compared to 638 [420-809] in the group not meeting the definition of palliative care needs ($p<0.001$). After adjusting days alive out of hospital for quality of life, patients in the palliative care needs group had fewer days of good health as a percentage of total follow-up, median 12 [3-22] % of potential follow-up, compared to 47 [25-68] % in those not meeting my definition of palliative care needs ($p<0.001$).

Most participants expressed a wish to spend the end of their life at home, but despite this, most died in hospital. 17 caregivers completed the Views Of Informal Caregivers Evaluation of Services questionnaire. Overall care in the last few months of life was assessed as fair or poor by 35.3%. Of the 272 participants who participated in the whole study, 33 (12.1%) had access to specialist palliative care services. Of the 73 participants who met the definition of PC needs, 19 (26.0%) accessed specialist PC services. 6 (2.2%) participants used hospice care during the duration of the study.

Using multivariate logistic regression analysis, a low Kansas City Cardiomyopathy Questionnaire summary score and a low Australia Modified Karnofsky Performance Scale (a physician completed assessment) score, were predictive of patients with palliative care needs. Conventional prognostic markers, such as natriuretic peptides or ejection fraction, were not predictive of patients with palliative care needs. Physicians, using their clinical judgement, were only modestly accurate at

predicting patients with heart failure who had or would go on to develop palliative care needs. Physicians were better at predicting prognosis than need for palliative care.

Conclusions

Palliative care needs were common in patients with heart failure admitted to hospital with heart failure, with 26.8% of participants meeting my definition of palliative care needs. This study has shown there is an unmet need for palliative care in many patients with heart failure, with a marked discrepancy between the patients who met the definition of palliative care needs and those who accessed specialist palliative care services. I have also shown that patients with heart failure who go on to develop palliative care needs can be identified during a hospitalisation, using a combination of a patient reported outcome measure and a physician completed assessment. Patients who met my definition of palliative care needs had 40% fewer days alive and out of hospital than those who did not. The quality of days alive out of hospital was much worse. This thesis also provides important pilot data describing the quality of life adjusted days alive out of hospital of a "real life", unselected, and therefore, generalisable cohort of patients with heart failure. I hope that these data, including the detailed description of a suitable target population, will inform the design of a randomised controlled clinical trial assessing the benefit of early palliative care in patients with heart failure.

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Publications containing work undertaken in this thesis

1. **Campbell RT**, Jackson CE, Wright A, Gardner RS, Ford I, Davidson PM, Denvir MA, Hogg KJ, Johnson MJ, Petrie MC, McMurray JJ. Palliative care needs in patients hospitalized with heart failure (PCHF) study: rationale and design. ESC Heart Fail 2015; 2: 25-36.

Presentation to Learned Societies

1. **Campbell RT**, Jackson CE, Wright A, Hogg KJ, Denvir MA, Gardner RS , Johnson MJ, Petrie MC, McMurray JJV. Prevalence of palliative care needs in patients admitted to hospital with heart failure. British Society of Heart Failure Autumn Meeting; November 2016

2. **Campbell RT**. Palliative care in heart failure: can we do more? Oral presentation, ESC Heart Failure Congress; Seville, May 2015.

3. **Campbell RT**, Jackson CE, Wright A, Hogg KJ, Denvir MA, Johnson MJ, Petrie MC, McMurray JJV. Heart failure with preserved ejection fraction: not as common as you think. Poster presentation, ESC Heart Failure Congress; Seville, May 2015.

4. **Campbell RT**, Jackson CE, Wright A, Kristensen SL, Hogg KJ, Denvir MA, Johnson MJ, Petrie MC, McMurray JJV. Discrepancy between preferred and actual place of death in patients with acute heart failure. ESC Heart Failure Congress; May 2014.

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I dedicate this thesis to my family. I would like to thank my parents for their life-long support. Lastly, and most importantly, I thank my eternally patient and amazing wife Lucy, and our beautiful daughter Emma. You have always been my greatest advocate, and this work would not have been possible without your endless support, love and encouragement.

Declaration

The work presented in this thesis was performed during my employment as a Clinical Research Fellow at the Glasgow Cardiovascular Research Centre, in the College of Medicine and Veterinary Life Sciences, at the University of Glasgow. I was supervised by Professor John McMurray and Professor Mark Petrie.

I performed the screening and recruitment, including attaining signed, informed consent, of all patients who participated in this study. I performed all of the echocardiograms, and these were blindly analysed by Dr Piotr Sonecki. I completed all case report forms from the index admission. Study visits and study visit case report forms were performed and completed by myself and Sister Ann Wright. Biochemical and haematological analyses were performed in the Western Infirmary biochemistry and haematology departments. I was helped with the more complex statistical analyses in this study were performed by Ms Paula McSkimming, under the supervision of Dr Alex McConnachie.

Work relating to this thesis has been presented at international conferences including the European Society of Cardiology Heart Failure Congress in 2014 and 2015, and published in the peer reviewed journal, European Society of Cardiology Heart Failure in 2015.

This writing of this thesis constitutes my own work, written entirely by myself. This thesis has not been submitted for a higher degree.

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Definitions/ abbreviations

ACEI	Angiotensin-Converting– Enzyme Inhibitor
ACP	Anticipatory Care Plans
A-HeFT	African American men in the African-Americans with Heart Failure Trial
AHF	Acute Heart Failure
AKPS	Australia-Modified Karnofksy Performance Scale
ANP	Atrial Natriuretic Peptide
ARNI	Angiotensin Receptor–Neprilysin Inhibitor
ATLAS	Assessment and Treatment with Lisinopril and Survival
AUROC	Area Under Receiver Operator Curve
BNP	Brain-type Natriuretic Peptide
CCB	Calcium Channel Blockers
CHARM	Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
CHF	Chronic Heart Failure
CIBIS II	Cardiac Insufficiency Bisoprolol Study II
CNP	C-type Natriuretic Peptide
CONSENSUS	Co-operative North Scandinavian Enalapril Survival Study

COPD	Chronic Obstructive Pulmonary Disease
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival
CRT	cardiac resynchronization therapy
CPR	Cardiopulmonary Resuscitation
CTU	Clinical Trials Unit
CV	Cardiovascular
CXR	Chest X-Ray
DAOH	Days Alive and Out of Hospital
DIG	Digtitalis Investigation Group
ECG	Electrocardiography
ECHOES	Echocardiographic Heart of England Screening
eGFR	Estimated Glomerular Filtration Rate
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EOL	End of Life
EQ-5D	Euro Quality of life
ESAS	Edmonton Symptom Assessment Scale
ESC	European Society of Cardiology

EVEREST	Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan
FACIT-SP	Functional Assessment of Chronic Illness Therapy- Spiritual well-being
GWTG	Get With The Guidelines
HADS	Hospital Anxiety and Depression Scale
HF-PEF	Heart Failure with Preserved Ejection Fraction
HF-REF	Heart Failure with Reduced Ejection Fraction
ICDs	Implantable Cardioverter Defibrillators
IQR	Interquartile Range
ISD	Information Services Division
KCCQ	Kansas City Cardiomyopathy Questionnaire
KPS	Karnofksy Performance Scale
LBBB	Left Bundle Branch Block
LVAD	left sided Ventricular Assist Device
MADIT-II	Multicentre Automatic Defibrillator Implantation Trial II
MERIT-HF	Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure
MLHFQ	Minnesota Living with Heart Failure questionnaire

MRAs	Mineralocorticoid Receptor Antagonists
NAT-PD-HF	Needs Assessment Tool Progressive Disease Heart Failure
NHS	National Health Service
NYHA	New York Heart Association
OPTIMIZE-HF	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure
PARADIGM-HF	Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial
PC	Palliative Care
PPS	Palliative Performance Scale
PROMS	Patient Reported Outcome Measures
QOL	Quality Of Life
RAAS	Renin-angiotensin aldosterone system
RALES	Randomized Aldactone Evaluation Study
RCB	Robertson Centre for Biostatistics
RCTs	Randomised Controlled Trials
REMATCH	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure
RRR	Relative Risk Reduction

SCD-HeFT	Sudden Cardiac Death in Heart Failure
SF-12	Short Form 12
SOLVD	Studies of Left Ventricular Dysfunction
SUPPORT	Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments
TAPSE	tricuspid annular plane systolic excursion
Val-HeFt	Valsartan Heart Failure
VOICES	Views Of Informal Carers for the Evaluation of Services
WHO	World Health Organisation

Chapter 1 Introduction

1.1 What is heart failure?

Heart failure is a clinical syndrome, the definition, management, and prognosis of which has changed dramatically over the years. Although one of the first descriptions of heart failure in the medical literature was in 1930s by Thomas Lewis, who described heart failure as "a condition in which the heart fails to discharge its contents adequately" , it was not until as recently as the 1980's that a fuller understanding of some of the aetiologies and pathophysiological processes led to the description of heart failure as a clinical syndrome .[1] The classical definition of heart failure by Eugene Braunwald describes heart failure as "the pathophysiological state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues."[2] The clinical syndrome of heart failure has been further defined by the European Society of Cardiology (ESC) as the presence of typical symptoms and signs (see Table 1-1) resulting from an abnormality of cardiac structure or function.[3]

Table 1-1 Typical signs and symptoms of heart failure

Symptoms	Signs
Typical	**More specific**
Ankle swelling	Elevated jugular venous pressure
Orthopnoea	Hepatojugular reflux
Paroxysmal nocturnal dyspnoea	Third heart sound (gallop rhythm)
Reduced exercise tolerance	Laterally displaced apical impulse
Breathlessness	Cardiac murmur
Fatigue, tiredness, increased time to recover after exercise	
Less Typical	**Less Specific**
Nocturnal cough	Peripheral oedema (ankle, sacral, scrotal)
Wheezing	Pulmonary crepitations
Weight gain (>2 kg/week)	Reduced air entry and dullness to percussion at lung bases (pleural effusion)
Weight loss (in advanced heart failure)	Tachycardia
Bloated feeling	Irregular pulse
Loss of appetite	Tachypnoea (>16 breaths/min)
Confusion (especially in the elderly)	Hepatomegaly
Depression	Ascites
Palpitations	Tissue wasting (cachexia)
Syncope	

1.1.1 Aetiology and pathophysiology of heart failure

The syndrome of heart failure can be caused by a number of conditions.[4] Ischaemic heart disease (especially in myocardial infarction) is by far the most common and best-understood cause of heart failure in developed countries, particularly in the context of left ventricular systolic dysfunction. Other common causes of heart failure include hypertension, valve disease, inherited cardiomyopathies (dilated, hypertrophic, arrhythmic right ventricular cardiomyopathy, and left ventricular non-compaction), and congenital heart disease. Rarer causes of heart failure include arrhythmia, infection, infiltrative conditions such as amyloidosis or sarcoidosis, iatrogenic causes such as chemotherapy, pericardial diseases, metabolic diseases, endocardial disease, conduction disorders, and high output states.

As there are many causes of the syndrome of heart failure, there is no unifying pathophysiological process. However, a number of pathological mechanisms and pathways have been described in detail, particularly in the context of heart failure with a reduced ejection fraction (HF-REF). Following an insult and reduction in cardiac output and/or increased wall stress of the left ventricle, caused by one of the aforementioned aetiologies of heart failure, a number of compensatory mechanisms are activated to maintain sufficient cardiac output and reduce ventricular wall stress. These compensatory mechanisms include activation of the adrenergic nervous system with increased circulating levels of noradrenaline, the renin-angiotensin aldosterone system (RAAS), and the cytokine system.[5, 6] Consequently there are increased levels of neuro-hormonal and autocrine/paracrine mediators of hypertrophy such as noradrenaline, angiotensin II, endothelin 1, fibroblast growth factor, transforming growth factor-ß, tumour necrosis factor-α, and interleukin-1ß amongst others.[6] Sustained up-regulation of these systems results in hypertrophy of the cardiac myocytes.[7] Although initially protective, many of these mechanisms and pathways eventually result in pathological structural changes to the left ventricle, known as ventricular remodelling.[8] As well as increased levels of the vasoconstrictors noradrenaline and angiotensin II, both of which directly stimulate myocyte hypertrophy but also increase afterload on the ventricle, there is, over time, loss of the beneficial effects of the endogenous counter

regulatory vasodilators such as nitric oxide, natriuretic peptides, prostaglandins, and kinins.[5, 6, 9]

There have been three broad patterns of ventricular remodelling described: concentric remodelling, caused by increased myocyte thickness in response to increased pressure load on the left ventricle; eccentric remodelling, caused by myocyte lengthening in response to increased volume load on the left ventricle; and myocardial infarction, where tissue is dilated, damaged, and stretched, resulting in a combination of pressure and volume load on the rest of the ventricle.[8] In eccentric remodelling and the remodelling changes seen post-myocardial infarction there is progressive left ventricular dilation, sphericity, left ventricular wall thinning, and mitral valve incompetence.[5] These changes to left ventricular geometry, particularly eccentric remodelling, can result in further pressure and volume load to the left ventricle, with resultant exacerbation of the afore mentioned compensatory mechanisms. Other pathological changes that occur in failing hearts include changes to the extra-cellular matrix, with increased collagen and fibrous deposition, reduced myocyte contractile function, cell apoptosis and death. The pathological processes involved in heart failure with preserved ejection fraction (HF-PEF) are not as clearly described, although concentric left ventricular remodelling and hypertrophy in response to increase pressure load, with resultant impaired diastolic function and impaired left ventricular filling are thought to be important.[10] Although left ventricular hypertrophy alone does not explain the presence of the heart failure syndrome in those with a preserved ejection fraction.[11]

All of these changes result in a progressive spiral of reducing cardiac function and worsening of the pathological processes. This spiral of ventricular remodelling was once thought to be un-modifiable, and thus palliative. However, some contemporary treatments have been shown to impede[12-15] and in some instances reverse[16] both eccentric left ventricular remodelling and concentric remodelling (when caused by aortic stenosis).[17]

1.1.2 Incidence, prevalence and prognosis of heart failure

Prevalence of heart failure in the community

Heart failure is common, affecting between 1-2% of the general population.[18-21] The prevalence of heart failure increases with age, with over 10% of the general population over the age of 80 suffering from heart failure.[19, 21] A number of studies have used echocardiography and symptom status to estimate the prevalence of heart failure in the general population. The first of these studies was carried out in Glasgow in the mid-1990s, where a cross-sectional sample of 2000 men and women from the community were assessed using echocardiography, biomarkers, questionnaires, and medical examination.[18] They found the prevalence of left ventricular dysfunction was 2.9% overall, and those with signs and symptoms of heart failure and left ventricular dysfunction was 1.5%. These data were similar to the Echocardiographic Heart of England Screening Study (ECHOES), where 6286 randomly selected patients over the age of 45 had an echocardiogram, history and examination.[19] Prevalence of heart failure (based on symptoms and signs) was present in 2.3%, with 41% of these patients having an ejection fraction less than 40%. Redfield et al performed a similar cross-sectional study of 2042 randomly selected adults over 45 years in Olmstead County.[20] Each participant had an echocardiogram and the Framingham criteria for diagnosis of heart failure was applied to confirm the diagnosis.[22] Using these methods, 2.2% of the study population had confirmed heart failure, with 56% having a reduced ejection fraction. The Rotterdam Study enrolled 7983 participants from a potential population of 10275 in the town of Ommoord, in the Netherlands.[21] They found the prevalence of heart failure in this cohort to be between 6-7%, perhaps reflecting the older age cut-off used as inclusion criteria. The prevalence of heart failure ranged from 0.9% in subjects aged 55-64, to 17.4% in those aged over 85 years.

Incidence of heart failure

Incidence rates of heart failure have been reported in a number of community studies.[21, 23] The Rotterdam Study reported an incidence rate of 14.4 per 1000 person-years, with a much higher rate in men versus women with rates of 17.6 and 12.5 per 1000 person-years respectively. The incidence increased with age,

with those aged 55-59 having a rate of 1.4 per 1000 person-years compared to 47.4 per 1000 person-years in those over the age of 90. This trend was seen in both men and women. The Hillingdon epidemiology study recorded incident cases of heart failure identified through referral to a heart failure diagnostic pathway. They reported much lower incidence rates of 1.3 cases per 1000 person-years. Incidence again was higher in elderly subjects, with rates of 0.02 per 1000 person-years in those ages 25-34, and 11.6 in those over 85 years. The discrepancy between these two studies can perhaps be explained by the methodology used, where the Rotterdam Study attempted to screen a whole population, and thus unselected cohort, the Hillingdon Study was a much more selected population by utilising a referral pathway. Two population studies in the United States reported incident rates at several time points and allow observations to be made regarding the possible changing incidence of heart failure.[24, 25] Levy et al reported incidence rates of heart failure in The Framingham Heart Study between 1950-69, 1970-79, 1980-89, and 1990-99. The incident rate for development of heart failure did not change significantly in men over these time periods, although there was a significant reduction in incident rate for women of 30-40%.[24] The Rochester Epidemiology Project, conducted in Olmsted County, Minnesota, recorded incident cases of heart failure over a time period of 20 years.[25] The incidence rate was higher amongst men (378 per 100 000 persons) compared to women (289 per 100 000 persons), and did not change over time amongst men or women. Jhund *et al* studied the incidence rates of first hospitalisation for heart failure by analysing the electronic record system in Scotland between 1986 and 2003.[26] All discharge diagnoses and causes of death were coded according to the International Classification of Diseases. The age adjusted incidence rate per 100 000 persons for men increased between 1986-1994, from 124 to 162. This trend changed after 1994, with a falling incidence rate for first hospitalisation for heart failure. A similar trend was seen in both men and women. Similar trends for first hospitalisation for heart failure have been observed in other countries, such as The Netherlands, Sweden, and England.[27-29] This fall in incidence of hospitalisation for heart failure, but not for incidence of community heart failure, could be as a result of improved prescribing of heart failure therapy and the introduction of heart failure nurses.[26] Although community incident rates have not declined, the ageing population, combined with better survival from

myocardial infarction and heart failure itself, will likely result in an overall increase in prevalence of heart failure, particularly in the elderly.[30]

Prognosis of patients with heart failure

Short and long-term prognosis for patients diagnosed with heart failure remains poor, although with each successive new therapy survival has improved. In the Co-operative North Scandinavian Enalapril Survival Study (CONSENSUS), published in 1986, which enrolled 253 patients with New York Heart Association (NYHA) class IV and reduced ejection fraction, 44% and 52% of the placebo arm were dead at 6 and 12 months, respectively.[31] This is a stark contrast to the most recent large randomized controlled trial in heart failure with reduced ejection fraction (HF-REF), the Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting– Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF), which was published in 2014 and enrolled 8442 patients with NYHA II-IV and HF-REF.[32] In this study participants were on good contemporary therapy, with over 90 %, 54%, and 14% of participants receiving a beta-blocker, mineralocorticoid receptor antagonist, and implantable cardioverter defibrillator, respectively, at baseline. All participants were on an ACEI during the run in phase of the study. The overall mortality for both treatment groups was under 30% after 3.5 years of follow up. Although randomised controlled clinical trials (RCTs) are useful in terms of estimating prognosis in patients with heart failure, they do not adequately reflect real-world patients in the community, who are generally older and with more co-morbidities. One contemporary study that provides important prevalence and mortality data in a community population is the ECHOES study.[33] This prospective study screened over 6000 members of the public in England with echocardiograms and performed detailed characterisation of each participant. These patients were followed up for over 10 years for vital status, thus providing useful insight into prognosis of community patients with heart failure in the United Kingdom. They found that patients with heart failure, both HF-REF and HF-PEF, had much worse 5 and 10 year survival rates. 54% of those with heart failure were alive after 5 years follow up, compared to 90% of those without heart failure. When these patients were followed up to 10 years, only 28% of

those with heart failure compared to 76% of those without heart failure were alive. Patients admitted to hospital because of heart failure are at even higher risk of death. Using hospital discharge records linked to death certificates through Information Services Division (ISD) of the National Health Service (NHS) Scotland, Jhund et al were able to describe 30 day, 1 year, and 5 year mortality following a hospitalisation for heart failure. They were also able to describe change over time between 1986 and 2003 in Scotland.[26] In 1986, 30 day mortality for men and women was 24 and 21 %, respectively, 1 year mortality for men and women was 33 and 31 % respectively, and 5 year mortality was 74 and 70 % respectively. These mortality rates improved over time, and in 1999, 30 day mortality for men and women was 20 and 19 % respectively, 1 year mortality for men and women was 28 and 28 %, respectively, and 5 year mortality was 66 and 64 % respectively. Although these trends for improving mortality were highly statistically significant, clearly the prognosis for patients with heart failure is still poor.

The natural history of heart failure is unpredictable at an individual patient level. Some patients will respond very well to therapy and will have a life expectancy approaching that of the normal population, whereas others will remain highly symptomatic and experience multiple hospital admissions with AHF and a shortened life expectancy. There are numerous risk prediction models for both patients in the community and those hospitalised because of heart failure, however, although these models are good at predicting prognosis at population level, they are not good at predicting individual patient prognosis.[34]

Where and how do patients with heart failure die?

Most patients with heart failure die from cardiovascular (CV) causes and the majority due to either worsening heart failure or sudden death.[35] There is some evidence that patients with more severe symptoms of heart failure are more likely to die from worsening heart failure, whereas less symptomatic patients are more likely to suffer a sudden death from arrhythmia.[36, 37] The majority of heart failure patients die in hospital. Place of death was recorded in the Assessment and Treatment with Lisinopril and Survival (ATLAS) trial and more than 50% of patients died in hospital and those who died out of hospital were

more likely sudden deaths.[38] This was similar to the results of the Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial where 58% died in hospital, 29% died at home, and 7% in an extended care facility.[39] Although these clinical trials are informative, they had a number of exclusion criteria and were not based on consecutive patients. Therefore, they are not truly reflective of the general population with heart failure. A recent analysis of data gathered from death certificates from England and Wales reported over 60% of patients dying from heart failure died in hospital and less than 20% died at home.[40] However, as heart failure is potentially under-reported on death certificates, this may not be truly reflective of patients with HF in the general population.[40, 41] Preferred place of death was described in a study of 80 patients hospitalised with heart failure which reported that 50% wished to be cared for at home when recovery seemed unlikely, and 40% wished to remain in hospital.[42] Data from prospective follow up of unselected, consecutive patients comparing preferred place of death to actual place of death is lacking in patients with heart failure. Patient preference for end of life care has been identified as a priority for research into palliative care (PC) need in patients with heart failure.[43, 44] Previous studies suggest that patients often change their mind about preferred place of death and there is also poor agreement with their carer on this issue.[45] Patients also change their mind about resuscitation status.[46, 47] A recent study has confirmed that patients with heart failure are willing to discuss end of life issues and also found that patients change their mind regarding resuscitation.[48] The same group also found that patients in this trial were willing to trade quality of life for length of life, which is contrary to previous studies. Although these studies are informative, they are based on clinical trial cohorts, and therefore represent a selected population.

1.1.3 Types of heart failure syndromes

Acute versus chronic heart failure

The syndrome of heart failure can present in two ways, as an emergency requiring hospital admission, often termed 'acute heart failure' (AHF), or in a more insidious fashion in the community, often called 'chronic heart failure' (CHF). Patients presenting to hospital with AHF are often known to have a diagnosis of CHF which has acutely deteriorated with worsening symptoms. The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry included data describing over 48 000 AHF hospitalisations in 259 hospitals across the United States.[49] 52% of patients in this registry were known to have heart failure prior to admission.[50] Common precipitating factors identified in those patients presenting with AHF included: arrhythmia (14%); uncontrolled hypertension (11%); ischaemia (15%); worsening renal function (7%); pneumonia (15%); non-adherence to medication (9%); non-adherence to diet (13%). Many patients had more than one factor that precipitated admission. Patients presenting to hospital with AHF often have signs and symptoms of pulmonary or peripheral oedema or congestion, or a combination of both of these. In extreme cases, patients can present in extremis and in cardiogenic shock. Acute pulmonary oedema is extremely distressing for patients and often a medical emergency. Acute pulmonary oedema results when increased left ventricular end-diastolic pressure, which is initially compensatory and increases pre-load and cardiac output, causes increases in pulmonary venous and ultimately capillary pressure. When the capillary pressure raises above the point where colloid osmotic pressure and alveolar basement membrane can keep fluid within the arterial and venous system, then fluid starts to accumulate in the pulmonary interstitium, alveoli, and ultimately airways.[51] Pulmonary oedema is often acute onset, on a background of a few days of increasing dyspnoea. Treatment with oxygen, diuretics, and vasodilators, usually resolves acute pulmonary oedema quickly over a few hours. However, some patients do not respond to these treatments and acute pulmonary oedema can be a terminal event. Other patients with AHF present with a more insidious deterioration with peripheral fluid accumulation over weeks or months, which ultimately gets to a point where this cannot be managed at home. The pathophysiological mechanisms of peripheral fluid

accumulation of cardiac origin are thought to be related to the heightened neurohormonal response seen in heart failure and to reduced renal perfusion.[52] Ultimately elevated levels of renin, aldosterone, natriuretic peptides, growth hormone, anti-diuretic hormone and cortisol result in sodium and water retention and oedema.[52] Peripheral oedema usually develops in the feet and ankles first, then as more sodium and water retention occurs, this increases to thigh level and ultimately ascites and pleural effusions. Patients often have many litres of excess fluid. Patients presenting to hospital with gross oedema and fluid overload require treatment with intravenous diuretics and are often hospitalised for numerous days. During the most recent audit of over 40 000 heart failure admission in England and Wales between 2012 and 2013, the median length of stay was 8 days.[53]

To determine the common presentations of patients with AHF, 452 consecutive admissions were retrospectively analysed at the Brigham and Women's Hospital between 1996 and 1999.[54] The authors found four common types of presentation in AHF based on the presence or absence of adequate perfusion and the presence or absence of congestion. Congestion was deemed present if patients had orthopnoea, jugular venous distention, pulmonary rales, hepatojugular reflux, ascites, peripheral oedema, leftward radiation of the pulmonic heart sound, or a square-wave blood pressure response to the Valsalva manoeuver. Patients were classified as either adequate perfusion (warm), inadequate perfusion, congested, or uncongested. 27% were well perfused and uncongested, 49% were well perfused and congested, 20% were congested and under-perfused, and 4% were under-perfused and uncongested. Patients that presented with signs and symptoms of congestion had a poorer prognosis.

CHF is a state where patients have been relieved of congestion, usually with adequate treatment with diuretics, and have been started on long-term therapy for heart failure. The typical symptoms experienced by patients with CHF are predominantly dyspnoea and fatigue, although a variety of other symptoms can be experienced including chronic oedema. Severity of symptoms is often graded using the NYHA classification, Table 1-2.[55] Although this scoring system is the most widely used and is predictive of prognosis, there are limitations. Namely, the scoring system does not equate to ventricular function at rest and often it not clear if NYHA classification has been applied by the physician or the patient.

Often there is a discrepancy between physician and patient estimates of functional limitation.[56]

Table 1-2 NYHA classification

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest.

As previously discussed, patients with heart failure who are admitted to hospital with AHF have a worse short and long term prognosis than those in the community. This higher mortality risk is not entirely related to the acute presentation, as most patients survive to discharge, but more reflects that these patients are a much higher risk group perhaps with more advanced disease. In the OPTIMIZE-HF registry, there were 1834 (3.8%) deaths during the index admission.[49] Although this was lower than that seen in England and Wales, where in hospital mortality was reported at 9.4%.[53]

Heart failure with reduced versus preserved ejection fraction

Heart failure is now further categorised by both the ESC and the American Heart Association according to cardiac function.[3, 57] Specifically, patients are categorised according to the most widely used estimate of ventricular systolic function, called ejection fraction. This is most commonly measured using echocardiography. HF-REF is defined by the ESC as an ejection fraction of less than 50% and HF-PEF as greater than or equal to 50%. Analysis of community, hospitalised and RCT cohorts reveals a distinctive difference in phenotype between these two groups.[58] Patients with HF-PEF are generally older, more often female and tend to have a higher body mass index. The number and type of co-morbidities in these two types of heart failure would appear to differ as well. Hypertension, atrial fibrillation, and chronic lung disease appear to be more common in patients with HF-PEF compared to HF-REF, where the converse is true regarding coronary artery disease. Other commonly reported medical conditions such as chronic kidney disease and anaemia appear to have similar prevalence between HF-PEF and HF-REF. Historically, the perception has been that HF-PEF is a more benign phenotype than HF-REF, although two large cohorts

(one community and one hospital) have suggested that not only is HF-PEF as common as HF-REF, but associated with a similar prognosis.[59, 60] Although, a meta-analysis of over 41 000 patients from a variety of cohorts showed that HF-REF has a poorer outcome.[61] The most striking and clinically relevant difference between the two phenotypes of heart failure is the response to therapy, where HF-REF has one of the strongest evidence bases for treatments which reduce mortality, there has been no therapy proven to improve survival in HF-PEF.[3]

1.1.4 Management of heart failure

1.1.4.1 HF-REF

The management of HF-REF has changed dramatically over the past 25 years, with a resultant increase in survival for patients. Many of the key treatments in HF-REF are aimed at interrupting the pathological neurohormonal cascade that occurs in heart failure, namely increased noradrenaline and the RAAS system. The first agent to be shown to reduce mortality in these patients was the ACEI enalapril. This was used in the key RCTs CONSENSUS and Studies of Left Ventricular Dysfunction (SOLVD)- Treatment trials, which enrolled 256 and 2569 participants with NYHA IV and II/III, respectively.[31, 62] There was a relative risk reduction (RRR) in mortality of 27 and 16% with use of an ACEI in CONSENSUS and SOLVD-Treatment, respectively. Further improvements in survival in patients with HF-REF were demonstrated in large RCTs of beta-blockers. These landmark trials were the Cardiac Insufficiency Bisoprolol Study II (CIBIS II), Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), and Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trials.[63-65] Further improvements in survival were demonstrated through use of the mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone in the Randomized Aldactone Evaluation Study (RALES) and Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trials.[66, 67] These studies enrolled 1663 and 2737 patients with HF-REF and NYHA class III and II respectively. There was a RRR in mortality of 30% in RALES and a RRR in cardiovascular mortality of 37% in EMPHASIS-HF. In the Valsartan Heart Failure (Val-HeFt) and Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Added and Alternative trials, angiotensin receptor blockers were effective at reducing heart

failure hospitalisation in patients intolerant of ACEI, or in addition to ACEI, but did not reduce all-cause mortality.[68-70] Another therapy for HF-REF which has been shown to reduce heart failure hospitalisation but not mortality is the I_f channel blocker ivabradine.[71] In the Digitalis Investigation Group (DIG) trial of 6800 participants with HF-REF, digoxin was shown to reduce heart failure hospitalisation, but not mortality.[72] The combination of hydralazine and isosorbide dinitrate was shown to reduce mortality in a selective population in the African-Americans with Heart Failure Trial (A-HeFT).[73]

These dramatic reductions in mortality in HF-REF with pharmacotherapy, particularly ACEI, beta-blockers and MRAs, have been further improved upon with the addition of device therapy. Implantable cardioverter defibrillators (ICDs) are one such device, which detect malignant ventricular arrhythmias and deliver an electrical shock, aimed at cardioverting the patient back to sinus rhythm. The SCD-HeFT trial enrolled 2521 patients with HF-REF (ejection fraction ≤ 35%), NYHA class II/III, no history of ventricular arrhythmias, and either non-ischaemic or ischaemic cardiomyopathy.[74] Treatment with ICD, in addition to ACEI (96%) and beta-blocker (69%) therapy resulted in a 23% RRR compared to treatment with amiodarone. These results were supported by the Multicentre Automatic Defibrillator Implantation Trial II (MADIT-II), which enrolled 1232 patients with a previous myocardial infarction and a low ejection fraction (<30%).[75] Participants were randomised to receive conventional medical therapy or ICD, and those receiving ICD had a 31% RRR in mortality. Patients with HF-REF (ejection fraction ≤ 30%), in sinus rhythm, a prolonged QRS duration, and left bundle branch block (LBBB) morphology have improved survival with the addition of cardiac resynchronization therapy (CRT) by pacing both sides on the heart.[76, 77] The improved survival seen CRT use in NYHA class III/IV patients was also seen in addition to ICD therapy in patients with HF-REF and NYHA I-III.[78, 79] Patients with advanced heart failure, who have severe symptoms despite optimal medical therapy should be considered for heart transplantation.[80] For those who are ineligible, there is evidence from the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure (REMATCH) study that ventricular assist devices improve survival.[81] This study randomised 129 patients with NYHA class IV heart failure, ejection fraction less than 25%, a peak oxygen consumption of ≤ 12 ml per kilogram of

body weight per minute or a need for continuous intravenous inotropic support, decreasing renal function or worsening pulmonary congestion. Patients randomised to long-term left sided ventricular assist device (LVAD) had a 48% RRR of death compared to medical therapy. However, the survival for the LVAD group was only 25% at two years.

Unlike the dramatic improvements in mortality seen over the last 25 years in HF-REF, no study has shown a survival benefit in HF-PEF, despite numerous large RCTs.[82-86] A similar trend has been also been seen in RCTs of therapies for patients with AHF, where no survival benefit has been demonstrated.[87-94]

1.2 What is palliative care?

The PC movement in many ways originated from the hospice movement. The modern hospice movement was founded by Dame Cicily Saunders when she founded St Christopher's Hospice in 1967.[95] Dame Saunders developed the principle of "total pain" and essentially incorporated holistic practice by assessing and managing physical, emotional, social, and spiritual distress. As well as developing the principle of total pain, she developed the principles of good end of life (EOL) care, where dying patients should be treated with compassion, dignity and respect. In the 1980's, the PC movement began to develop formally, building on the experiences of those in the hospice movement. This involved the establishment of a scientific journal,[96] a medical association, and ultimately formal recognition of the specialty of palliative medicine in 1987.[97]

Perhaps the most widely used and accepted definition of PC is provided by the World Health Organisation (WHO), in which PC is defined as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."[98] The complete definition of PC by the WHO is detailed in Table 1-3.

Table 1-3 WHO definition of PC

WHO definition of palliative care[98]
Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care: • Provides relief from pain and other distressing symptoms; • Affirms life and regards dying as a normal process; • Intends neither to hasten or postpone death; • Integrates the psychological and spiritual aspects of patient care; • Offers a support system to help patients live as actively as possible until death; • Offers a support system to help the family cope during the patients illness and in their own bereavement; • Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated; • Will enhance quality of life, and may also positively influence the course of illness; • Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

The Scottish Palliative Care Guidelines, published on-line in 2014, provide a complimentary description of PC, highlighting the use of PC early on in a patient's illness and not just at the end of life: "Good palliative care is not just about supporting someone in the last months, days and hours of life, but about enhancing the quality of life for both patients and families at every stage of the disease process from diagnosis onwards. A palliative care approach should be considered alongside active disease management from an early stage in the disease process. Palliative care focuses on the person, not the disease, and applies a holistic approach to meeting the physical, practical, functional, social, emotional and spiritual needs of patients and carers facing progressive illness and bereavement."[99]

1.3 Palliative care in other conditions

PC is more established in other terminal conditions in the United Kingdom (UK), particularly cancer. Of all of the patients accessing hospice care or specialist PC services in the England and Wales in 2013-14, 88% had a diagnosis of cancer.[100]

Improving EOL and access to palliative care has been established as a priority by the Department of Health in the UK. EOL care was recently assessed in England using the Views Of Informal Carers for the Evaluation of Services (VOICES) questionnaire.[101, 102] This specifically designed questionnaire is sent to bereaved relatives and asks for their opinion regarding different areas of EOL care. The latest EOL survey in England, was in November 2015. The VOICES questionnaire was sent to 49 558 adults who had registered a death between 4 and 11 months previously.[103] 21 320 (43%) responses were received. 25% of patients died from cardiovascular disease, 28% from cancer, and 46% from other conditions. Place of death was recorded as part of the questionnaire: 21% died at home, 46% died in hospital, 27% died in a care home and 6% died in a hospice. Overall quality of care in the last three months was reported in 95% of responses. 12% reported this care as outstanding, 30% as excellent, 33% as good, 15% as fair and 10% as poor. Patients with cancer were more likely to receive better overall quality of care, as assessed by their caregiver, and were more likely to die in their preferred place of EOL.

While the use of PC in terminal conditions is intuitive, designing and executing an RCT to formally investigate the pros and cons is challenging. IN cardiology very few therapeutic approaches are adopted without RCT evidence. RCTs have been performed in other terminal conditions, namely cancer. Temel *et al* performed a single centre RCT of 151 participants with metastatic non-small-cell lung cancer to receive either early PC in conjunction with standard therapy or standard therapy alone.[104] The main outcome measures were change in quality of life (QOL) and mood as assessed by the Functional Assessment of Cancer Therapy-Lung and the Hospital Anxiety and Depression Scale (HADS) questionnaires, at 0 and 12 weeks, respectively. Patients assigned to early PC had better QOL and fewer depressive symptoms. Interestingly, patients in the early PC arm had statistically significant better median survival, at 11.6 versus 8.9 months in the standard care arm. These preliminary results were followed up by Zimmerman et al, who performed a multi-centre cluster-RCT of early referral to PC plus standard care versus standard care alone in patients with cancer.[105] Patients were considered eligible if they had advanced cancer and an estimated clinical prognosis of 4- 24 months. 461 participants were randomised (228 to early PC and 233 to standard care). Outcome measures were QOL,

symptom severity (as measured by the Edmonton Symptom Assessment Scale [ESAS]), satisfaction with care, and problems with medical interactions. These patient reported outcome measures (PROMS) were assessed at baseline and monthly for 4 months. The primary outcome measure was change in QOL, as measured by the Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being scale, at 3 months. This study did not corroborate the previously described study by Temel *et al*, as there was no significant difference in the primary end point of change in QOL.

1.4 Palliative care use in heart failure

There is little doubt that, for some patients, heart failure is a terminal condition associated with poor QOL and high morbidity with multiple hospitalisations. The poor prognosis in heart failure has led to comparisons with cancer, and heart failure has been described as "more malignant than cancer".[106] Again, it would seem intuitive that these patients would benefit from a palliative approach. Indeed, guidelines and consensus documents from both the ESC and American Heart Association recommend referral to palliative care services for certain patients, although these recommendations are based on expert opinion rather than evidence.[3, 107] Despite these recommendations, very few patients in the United Kingdom access PC. The latest National Heart Failure Audit of England and Wales, between April 2012 and March 2013, included over 43 000 patients admitted to hospital due to heart failure .[108] The median age of these patients was 80, and most patients were highly symptomatic, 44 and 35% were NYHA class III and IV respectively. Overall, these patients were a high risk group, with 30 day and 1 year mortality rates of 15 and 25%. Despite these patients having high symptom burden and reduced life expectancy, only 4% were referred to PC. These findings are different to those reported from the Rochester Epidemiology Project from Minnesota, USA.[109] The Rochester Epidemiology Project enrolled 1369 Southeastern Minnesota residents with heart failure into a longitudinal cohort study between 2003 and 2011. During this time there were 698 deaths. Over the time period studied, the proportion of patients with heart failure who were referred to palliative care increased from 10.8% between 2003-2006 to 43.6% between 2010-2012. There was also an increase in hospice access from 28.6% to 42.2% from between 2003-2006 and 2010-2012, respectively. This was associated with a reduction in patients with heart failure who died in hospital,

with 32.8% between 2003-2006 and 22.4% between 2010-2012. This study provides a stark contrast to the National Heart Failure Audit, reflecting a difference in healthcare practice.

Chapter 2 Systematic review of PC needs in patients with HF

The main aim of this systematic review was to critically analyse and appraise the current evidence base describing the palliative care needs of patients with heart failure. Specifically, I wanted to assess the available quantifiable data describing what the potential PC needs are in patients (and their caregivers) with heart failure and assess the prevalence of these needs. The secondary aim of this systematic review was to describe the evidence base, specifically RCTs, for a palliative intervention in this population.

2.1 Methods

Data sources and searches

I collected data from observational study and trial data, where available, which described patient and caregiver perceived experiences and PC needs. I searched the online databases Medline, Embase, CINAHL, and PsycINFO using the terms "heart failure" or "congestive cardiac failure" or "advanced heart failure" or "end stage heart failure" in abstracts, titles, or as keywords. This search was combined with the search terms "palliative care" or "end of life" in abstracts, titles, or as keywords. Citations of studies identified, review articles and guidelines were searched for any potential additional studies. The search was initially performed on the 27th October 2013, and updated on 7th May 2014. A summary of the search is provided in Figure 2-1.

Study selection

Studies were limited to those of adult humans, and published in English. Titles and abstracts were then reviewed to exclude duplicates and studies not assessing patients with heart failure. The search was further limited to include only original research by excluding letters, editorials, reviews, guidelines, case reports, and conference abstracts (Figure 2-1). As this systematic review aimed to assess patient and caregiver perceived needs, surveys of health professionals and publications describing service provision were excluded. Studies assessing a PC intervention were included if a description of PC needs was provided. Full

text was then reviewed of the remaining articles to assess inclusion and exclusion criteria, Figure 2-1.

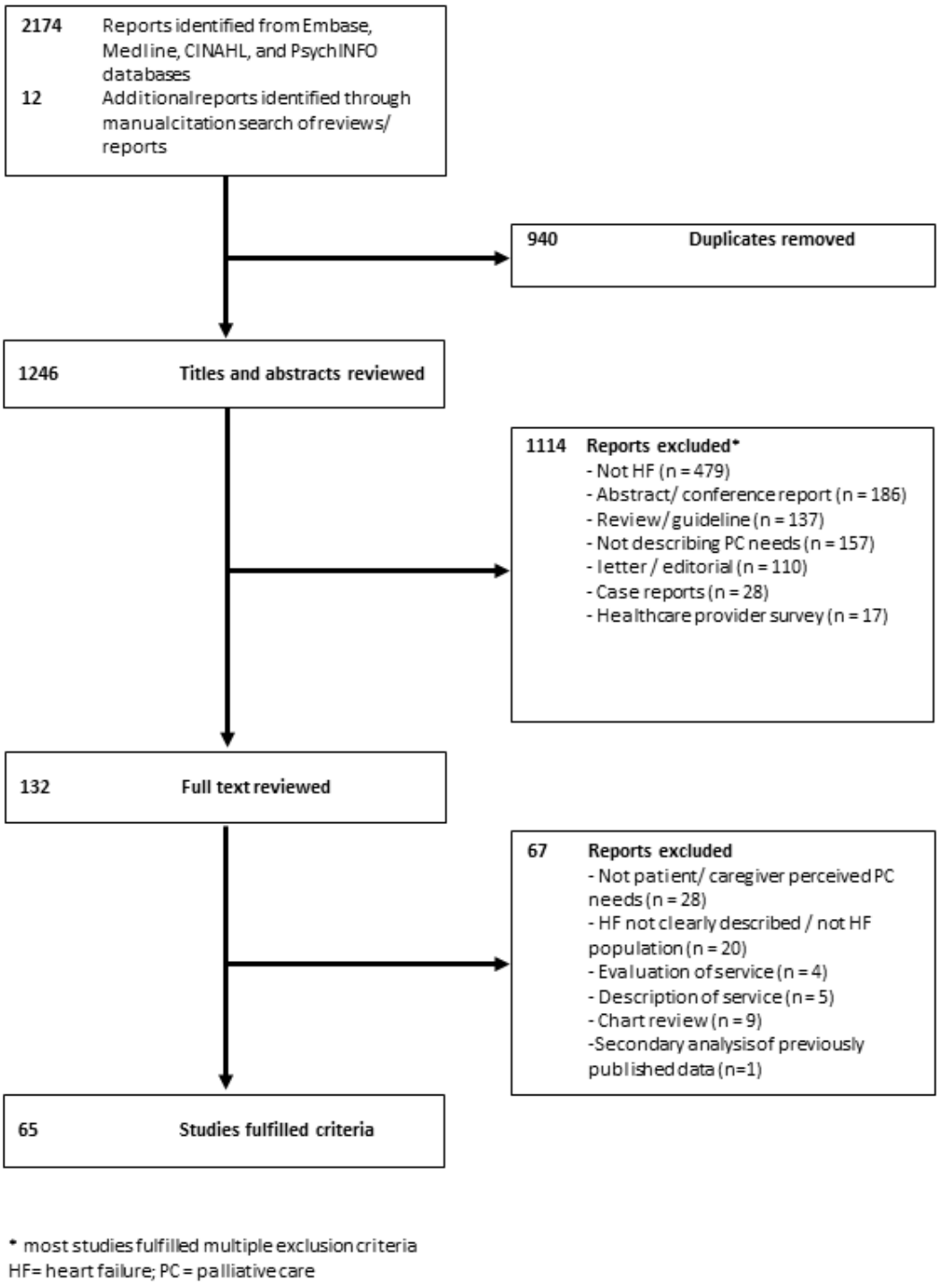


Figure 2-1 Systematic review and study selection

Data extraction and quality assessment

Data from the methods and results section of each publication was reviewed and tabulated. Authors' comments and opinions were not included in data extraction or synthesis. Specifically, the number of participants with heart failure, number of caregivers (where relevant), mean age, sex, proportion of participants according to NYHA status, and mean ejection fraction were extracted and assessed. Other data collected from the methods section included the setting of recruitment of each patient, whether the recruitment was selected or unselected, whether a description of the diagnostic criteria used to define heart failure was used, and whether HF-PEF was included in the cohort. The study design and outcome measures were recorded.

2.2 Results

2.2.1 Study characteristics

The search criteria identified 65 original research publications primarily aimed at assessing PC needs of patients (and their caregivers) with heart failure.[46, 110-172] Of these, 32 studies used quantitative outcome measures and research methodology (supplementary table 1-A), and a further 33 used qualitative outcome measures (supplementary table 1-B). The majority of the studies were carried out in the USA, UK, or Europe. Studies were published between 1997 and 2014. Overall, the median number of patients with heart failure studied was 45 (interquartile range [IQR] 20-76). For studies using quantitative outcome measures, the median number of participants was 60 (IQR 46-111). The studies using qualitative outcomes had a median number of participants of 24 (IQR 13-45). Weighted mean age for all studies identified was 71 (SD 7.4). The weighted mean age for those enrolled in qualitative studies was 72 (SD 7.1), and for those enrolled in quantitative studies was 71 (SD 7.4). 12 studies did not provide a mean or median age. Most of the participants were male (weighted mean overall 65%), although 8 studies did not report sex of participants. Of the 65 studies identified, only 19 reported an ejection fraction, 12 reported how the diagnosis of heart failure was made, and only 5 mentioned whether patients with HF-PEF were included in their sample. Only 4 studies used an unselected cohort

of patients, with three of these studies using prospective recruitment. The majority of studies targeted patient population that were thought to have higher PC needs, such as exclusively NYHA class III/IV, physician's estimated limited life expectancy, or elderly patients.

2.2.2 Qualitative studies

Although results from qualitative studies are less generalisable than quantitative studies, important preliminary themes can be identified through such research, therefore it is important to critically assess these studies also. 33 of the studies identified utilised qualitative methodology. Of these, 8 performed assessments longitudinally, with the rest utilising a cross-sectional approach. As described above, most of the qualitative studies were highly selected cohorts, with small numbers of participants. Only 3 studies enrolled over 100 participants.

A number of common themes were identified in these studies. One of the most common themes was the issue of communication between healthcare practitioner and patients and caregivers. Patients and caregivers often reported a need for greater disclosure of information regarding their diagnosis, treatment options, and particularly prognosis.[115, 119, 135, 155, 159, 162] Patients with heart failure, and their caregivers, had less of an understanding of their prognosis and fewer discussions regarding EOL care than patients with cancer.[155, 171] Understanding prognosis was considered an important aspect of having a 'good death',[171] as was dying at home.[164] Preference, when asked, for where EOL care should take place was often at home.[42] Many patients asked would not want active resuscitation,[46, 42] although the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) study investigators found that when patients were asked this question serially, they often (40%) changed their mind. A common sub-theme within the overall theme of communication was the lack of EOL care discussions in patients with heart failure. Patients with heart failure were less likely to discuss EOL care, wishes, or anticipatory care plans than patients other conditions such as cancer.[138, 145, 162, 167, 172] Although many studies drew attention to the potential EOL care needs in heart failure, rarely was the opinion of EOL care, following death, from the relatives and caregivers reported. One notable exception was the study by Formiga et al, who asked the caregivers of deceased relatives with heart failure

to reflect on the standard of care received at the EOL.[133] Although 67% were satisfied with the EOL care received, 45% felt symptoms could have been better managed.

Another common theme identified was the effect heart failure had on patient and caregivers' daily lives. Patients with heart failure often experienced feelings of hopelessness, isolation, and loss of confidence and independence.[154, 170] Patients reported feeling like a burden to relatives or caregivers, and caregivers themselves also felt socially isolated and struggled with the physical demands of caregiving.[123, 139]

Physical symptoms were commonly experienced by patients with heart failure and included dyspnoea, falls, fatigue, insomnia, headaches, oedema, palpitations, and fatigue. Less common symptoms included pain.[119, 126, 139, 160]

The unpredictable nature, and fluctuant course of heart failure was often highlighted in the studies identified. Murray *et al* assessed, qualitatively, changes in social, spiritual, psychological wellbeing every 3 months in patients with heart failure and cancer thought to be in the last year of life. They found no clear terminal phase in heart failure, as opposed to cancer, but greater fluctuation in spiritual and psychological wellbeing.[155]

2.2.3 Quantitative studies

32 studies assessing PC needs in patients with heart failure which utilised quantitative outcome measures were identified. Of these studies, 21 (65%) used a cross-sectional approach and the remaining 11 (34%) used a longitudinal methodology. A number of different aspects of PC needs were assessed using quantitative outcome measures. These included physical symptom assessment, quality of life, mood assessment, spiritual well-being, performance status, caregiver burden and care dependency, and EOL care. Most studies assessed one or two of these individual components, but no study assessed all components.

Physical symptom assessment

13 of the 32 quantitative studies made an assessment of physical symptoms using PROMs. The PROMs used included: Edmonton Symptom Assessment Scale (ESAS) (6 studies); Memorial Symptom Assessment Scale (3 studies); Brief Pain Inventory (one study); Visual Analogue Scale (one study); and the McCorkle Symptom Distress Scale (one study). One study used an investigator-designed questionnaire, specifically designed for the study to assess physical symptom burden, which had not validated in an external cohort. Physical symptoms were common, and often reported as severe by patients.[168, 169] The classic symptoms of heart failure, dyspnoea and fatigue, were commonly reported in the quantitative studies identified, although dyspnoea perhaps not as frequently as expected. Reported dyspnoea ranged from 25-76% of patients in the studies identified. Fatigue was more commonly reported (50-85%). Pain and anorexia were also frequently reported (41-78% and 30-50%, respectively). Pain was more commonly reported in those with higher NYHA class.[131] When compared to cancer populations, patients with heart failure had a similar distribution of physical symptom burden.[120, 156]

Quality of life

QOL was measured using heart failure and generic PROMs in 13 and 7 studies respectively. The heart failure specific questionnaires included Minnesota Living with Heart Failure questionnaire (four studies) and the Kansas City Cardiomyopathy Questionnaire (KCCQ) (9 studies). The generic QOL PROMs used were the Short Form-36 (four studies), the Short Form-12 (SF-12) (two studies), and the Quality of Life Index questionnaire (one study). 4 studies utilised both a generic and a heart failure specific questionnaire. Generally QOL was reported as poor, particularly on the subscales of physical function and general health. Evangelista *et al* showed that patients who experienced pain were more likely to suffer from poor QOL.[131] Studies that compared QOL in patients with heart failure and cancer found similar QOL, although better social function sub-scores were found in patients with heart failure.[156] Allen *et al* monitored QOL longitudinally in 1458 patients admitted to hospital because of heart failure and found that in this high risk population (33% 6 month mortality), 13.2% suffered from persistently unfavourable QOL as measured by the KCCQ.[112] Brunner La

Rocca *et al* asked 622 patients with heart failure (as part of a RCT) if they would consider trading time (life expectancy) for improved QOL, and found that most (74%) would not be willing to trade any time which is perhaps contrary to popular belief.[48]

Mood assessment

13 studies used a quantifiable patient reported outcome measure to report mood disturbance. The measures used were Geriatric Depression Scale (four studies), Hospital Anxiety and Depression Scale (four studies), Patient Health Questionnaire (four studies), and the Mental Health Inventory questionnaire (one study). Anxiety and depression were common in the patients studied, reported levels ranging between 33-50% and 30-50% respectively. Fitzsimmons *et al* reported common depression, but not at clinically significant levels.[132] This was contrary to Bekelman *et al*, who reported 30% prevalence of clinically significant levels of depression.[117] Studies that compared mood disturbance between patients with heart failure and cancer found no difference in prevalence of anxiety or depression.[117, 156] Scott *et al* assessed mood disturbance in 20 highly selected patients, receiving out-patient infusions of inotropes, and 18 caregivers using the mental Health Inventory.[161] They showed that not only was depression and anxiety common in patients, 45 and 50% respectively, but more so in their caregivers at 65 and 55% respectively.

End of life care

Of the 7 studies using quantifiable or semi-quantifiable outcome measures to describe EOL care, most focused on documentation of anticipatory care plans (ACP), cardiopulmonary resuscitation (CPR) preferences, and preference for ICD deactivation at EOL. Strachan *et al* asked 106 patients with heart failure their preferred place of death, resuscitation preference, and their preference for knowledge about their prognosis.[165] Most patients, when asked, would prefer to die at home. Patients thought obstacles to achieving this preferred place of death were no caregiver available, uncontrolled pain, and lack of home services. 46% of patients would want to know their predicted prognosis, and 50% of patients wanted to discuss CPR preferences. Dunlay *et al* assessed documentation of ACP by reviewing 608 unselected patients' case records

retrospectively.[128] Of these, 249 had an ACP documented in the case record. However, less than half of these addressed CPR, haemodialysis or mechanical ventilation. Many patients would want to have discussions regarding ICD deactivation at the EOL, although most had no recollection of having any such discussion.[140, 141, 158] Herman *et al* reported that of 109 selected patients with HF attending a tertiary referral centre, only 7% had any recollection of discussing ICD deactivation at EOL, although 40% would have wanted more information, 26% refused to have any further discussions on the topic.

Caregiver burden / strain

The influence of heart failure on the caregiver's well-being or strain/ burden was assessed by quantifiable measures in four studies identified through the search criteria. The quantifiable PROMs used to assess caregiver strain were the Caregiver Reaction Assessment (one study), Care Dependency Scale (one study), Family Appraisal of Caregiving Questionnaire for Palliative Care (one study), and the Zarit Burden Interview (one study). Scott *et al* studied 20 patients with end stage heart failure attending secondary care for outpatient inotrope infusions and their caregivers (n= 18), and found not only high levels of depression and anxiety in caregivers, as described above, but reported one third of caregivers felt unprepared for the stress associated with caring for someone with heart failure.[161] Not all studies focused on the negative aspects of caregiving, Jansen *et al* and Malik *et al* reported on the positive aspects of caregiving, with many participants reporting caregiving positively.[148, 152] Furthermore, Malik *et al* compared caregiver strain between caregivers of patients with heart failure and cancer, and found that most caregivers (90%) reported no or only mild levels of caregiver burden.[152] Janssen *et al* further described dependency on care, using the Care Dependency Scale, and found similar levels of dependency in patients with heart failure and chronic obstructive pulmonary disease (COPD).[148] Patients with COPD were more likely to develop increasing care dependency over time compared to patients with heart failure.

Other assessments- spiritual well-being and palliative performance scale

Spiritual well-being was assessed in two studies using quantifiable PROMs, both studies using the Functional Assessment of Chronic Illness Therapy- SPiritual

well-being (FACIT-SP) questionnaire. Greater spiritual well-being was associated with less depression as measured by the Geriatric Depression Scale.[116] Patients with heart failure were found to have similar scores for spiritual well-being when compared to patients with cancer, and regardless of ejection fraction.[120]

Two studies measured functional capacity using the Palliative Performance Scale (PPS), of these two studies one described the proportion of patients with low functional levels.[151] Kaveralitos *et al* compared 334 selected patients with heart failure to 697 patients with cancer attending a PC service, all of which had a PPS assessment performed. This assessment rates functional capacity across five domains. Patients with heart failure had similar functional levels to patients with cancer. 28 and 46% of patients with heart failure had low and medium functional levels respectively, whereas 34 and 42% of patients with cancer had low and medium functional levels respectively.

2.2.4 Randomised controlled trials

3 RCTs that assessed an early PC intervention in patients with heart failure were identified. The first published study in 2007 recruited terminally-ill, housebound patients with either heart failure, cancer, or COPD.[173] 297 patients were enrolled (97 with heart failure), with 145 being randomised to early PC and 152 to standard care. The main outcome measures were satisfaction with care, healthcare utilisation, and place of death. Patients in the early PC group were less likely to die in hospital, had higher patient satisfaction, and less secondary care healthcare utilisation. Patients with heart failure were not analysed separately from the whole cohort and there was no clear description of how the diagnosis of heart failure was made or influence of ejection fraction or other prognostic markers on outcomes.

In 2014 72 patients with chronic heart failure, from a single centre in Sweden, were randomised to either standard care or early PC.[122] The primary endpoint was change in QOL as measured by the KCCQ and Euro Quality of life (EQ-5D) questionnaires, and symptom burden as measured by the ESAS. A good description of the participants, including ejection fraction was provided. The standard care group differed from the early care by being significantly older at baseline. There was no statistically significant difference between the groups in

mean symptom burden as measured by the ESAS or in QOL as measured by the KCCQ. However, there were greater improvements in nausea (measured by ESAS), physical symptom burden (measured by KCCQ), self-efficiency (measured by KCCQ), or QOL (measured by KCCQ) in the early PC group. NYHA functional class was significantly better in the early PC group when assessed at 6 months. There was less resource utilisation in the early PC group, in particular hospitalisations (15 vs 53, p = 0.009).

When the literature review was performed, the most recent RCT of an early palliative intervention in patients with heart failure was reported by Sidebottom *et al* in 2014.[163] The study recruited patients admitted to hospital with heart failure and randomised participants to early PC before discharge or standard care. The primary outcome measures were change in symptom burden (as measured by ESAS), QOL (as measured by MLHF), and mood (as measured by patient health questionnaire). Secondary endpoints included use of anticipatory care planning, repeat hospitalisation at 30 days, hospice use, and death. The study was powered for 500 patients, but only managed to recruit 232 patients, the most common reason for screening failure being refusal of consent. There was very little baseline characterisation of patients with heart failure. There was no description of NYHA class, distribution of ejection fraction, how the diagnosis of heart failure was made, or mention of whether patients with HF-PEF were included. At baseline, patients in the early PC arm were statistically older, by a mean of 5 years, than the standard care arm. Despite being underpowered, patients in the early PC arm had significantly better symptom burden, QOL, and mood, at both one and three months. Patients in the early PC arm were more likely to have an anticipatory care plan than standard care, but there was no other difference in the other secondary endpoints. This study suffered from loss to follow up, with only 79% of patients who were known to be alive completing study assessments at both study visits.

2.3 Discussion

2.3.1 Summary of literature describing potential palliative care needs in patients heart failure

The primary purpose of this systematic review was to critically appraise the available literature describing PC needs in patients with heart failure, with a secondary aim of reviewing the current evidence base for a palliative intervention. The number of publications describing PC needs has increased, particularly in the last ten years. Over half of the studies identified through my search criteria used qualitative methodology. Although less generalisable than studies using quantitative methodology, these studies are none the less informative, particularly in identifying common themes which can be further studied using quantifiable methods. The common themes highlighted from these studies include the variety of physical and psychological symptoms experienced by not only patients, but also by their care-givers. Poor communication, particularly about disease prognosis and EOL care and issues was consistently flagged as an issue.

The quantitative studies provide further insights into the potential PC needs in this patient population. A number of studies described and quantified the frequency and severity of physical symptoms, and also psychological mood disturbance in these patients. Many made comparisons to similar terminal conditions, such as cancer, COPD, and renal failure, and found similar symptom burden. EOL communication and planning was assessed using quantifiable measures and often there was a lack of anticipatory care planning in patients with heart failure. Some patients with heart failure were found to have impaired QOL, similar to other terminal conditions such as COPD or cancer.

2.3.2 Summary of randomised controlled clinical trial evidence

The three studies identified through the search criteria provide good preliminary, although tentative, evidence that an early palliative intervention in heart failure is possible and potentially effective. Brumley *et al* showed that PC for housebound terminally ill patients can potentially reduce unplanned hospital admissions, and cost of care, while improving patient satisfaction with care, and increasing the likelihood of a home death.[173] The study by Brannstrom *et al* did

not show a statistically significant difference in the primary outcome measures of QOL and symptom burden at 6 months, although the early PC group used less healthcare resources including hospitalisations.[122] In contrast to this study, Sidebottom *et al* showed statistically significant better scores in QOL, symptom burden and mood at 3 months.[163]

2.3.3 Limitations of current evidence base

Most studies, both qualitative and quantitative, recruited highly selected patients based on known or expected poor prognosis or because of the established presence of predictors of poor prognosis, such as NYHA status. Other studies recruited exclusively from patients already attending PC services. These studies are therefore, although informative, less generalisable than an unselected, real-world cohort. Therefore, the prevalence of PC needs in the general population with heart failure cannot be extrapolated from these studies. Most of the studies identified were small, with a median of 45 participants. Many studies did not describe in detail the heart failure population that was studied. Specifically, ejection fraction, NYHA class, whether patients with HF-PEF were included, or what criteria was used to make the diagnosis of heart failure, were rarely described. It is important to describe these findings for a number of reasons. Firstly, a description of factors which may influence prognosis is crucial when describing the PC needs of a population, and therefore ejection fraction and NYHA status, amongst other characteristics, should be included in the description of the cohort. Another limitation of the current evidence base describing the PC needs of patients with heart failure is the lack of longitudinal data. When this was described, e.g. by Murray *et al* or Barnes *et al*,[114, 155] patients with heart failure were found to have a fluctuating course, and a single one off assessment seems unlikely to describe the needs adequately in these patients. A further limitation of the evidence base was the number of facets of PC needs assessed. Although many different aspects were assessed using quantitative measures, such as QOL, symptom burden, EOL care, caregiver burden, and mood disturbance, no one study assessed all of these.

The RCTs were limited in terms of size, particularly the study by Sidebottom *et al*, who failed to meet their target sample size by over 50%.[163] Although Brumley *et al* enrolled almost 300 participants, only 97 had heart failure, and like many

of the studies describing potential PC needs, there was no description of the heart failure cohort.[173] Two of the three studies had statistically significant differences between groups at baseline, namely large differences between mean ages, possibly as a result of small numbers of participants and under-recruitment. An adequate description of the inclusion of HF-PEF was also lacking in all three studies, again potentially limiting the generalisability of the results.

2.3.4 Conclusion

There are a number of studies describing the PC needs of patients with heart failure, and a fledgling evidence base evaluating benefit of early PC intervention in RCTs in this group. Patients with heart failure can suffer from a variety of physical symptoms, not just dyspnoea and fatigue. The patients described in the studies often suffered from psychological disturbance as well, particularly anxiety and depression, sometimes at clinically significant levels. Mood disturbance was also reported at high levels in caregivers, although caregiving was not universally seen as a negative experience. Communication breakdown in EOL planning was a common theme in both qualitative and quantitative studies. Despite the number of studies identified in this systematic literature review, there were no systematic studies with detailed descriptions of the patients with heart failure, describing the prevalence of PC needs. Furthermore, there were no studies using quantitative measures which assessed all of the different potential facets of PC needs. This study and thesis will provide these essential data, which will both describe whether there is a need for further RCTs, by describing the extent of the problem, and also help inform the design of any future trials.

Chapter 3 Methods

Although there have been descriptions of unmet supportive and PC needs of patients with heart failure, these needs have not been described using reproducible and quantifiable measures in a 'real world' heart failure population. Any such description should take into account the WHO definition of PC (Table 1-1),[98] and therefore not only make an assessment of EOL care needs, but also the QOL of patients and their caregivers, mood and symptom burden. In this section I will describe how I will make objective, quantitative assessments and describe the rationale for using each chosen patient reported outcome measure. I will then describe the target study population, how the diagnosis of heart failure was confirmed, and then describe the study protocol used in detail.

3.1 Study Aims

1. Describe the prevalence of PC needs, and what these needs are including EOL issues, in a contemporary cohort of patients (and their caregivers) with heart failure.

2. Assess whether patients who have, or are likely to develop, PC needs can be identified.

3. Explore potential outcome measures which could be used as end-points in a RCT of PC use in heart failure.

3.2 Study population

I studied patients admitted to hospital with a primary diagnosis of heart failure. This group of patients, rather than community based or patients with chronic heart failure, were chosen as they are at particularly high risk of readmission and death.[26] To reduce selection bias, I recruited prospectively, and aimed to recruit a near consecutive population. A truly consecutive, prospective cohort is not possible, due to refusal or inability of some patients to participate. Therefore, I screened all patients identified as possibly having a primary diagnosis of heart failure and invited those who met the inclusion criteria to participate.

3.2.1 Confirming the diagnosis of heart failure

Making the diagnosis of heart failure is difficult. The criteria required to diagnose heart failure have changed over the past two decades, with more of an emphasis on demonstrating, using objective measures, abnormalities in the structure and function of the heart, particularly the left ventricle. The ESC sets different criteria for different phenotypes of heart failure based upon ejection fraction.[3] The 2012 ESC guidelines were used as these were the most up to date when participants were enrolled. Patients with HF-REF require the following three conditions to be met: typical symptoms of heart failure; typical signs of heart failure; and reduced left ventricular ejection fraction (<50%). The diagnosis of HF-PEF is met if the following criteria are met: presence of typical symptoms of heart failure; typical signs of heart failure; normal or mildly reduced ejection fraction ($\geq$ 50%); and relevant structural heart disease indicating diastolic dysfunction
(Table 3-1). As well as the typical symptoms and signs of heart failure, investigations are crucial in making the diagnosis, particularly in confirming the presence of structural and functional abnormalities of the heart. First line investigations, as directed by the ESC, in the assessment of suspected heart failure include electrocardiography (ECG) and chest x-ray (CXR). An ECG may reveal evidence of structural heart disease such as left ventricular hypertrophy, previous myocardial infarction with pathological q waves, inter-ventricular conduction delay, or arrhythmias. Although CXR is not deemed to be as useful in chronic heart failure, it is an important test in acute heart failure. Firstly, CXR can exclude other conditions which could be causing a patient's symptoms, for example pneumonia. Secondly, CXR can provide objective evidence of congestion and pulmonary oedema, which are often pathognomonic of acute heart failure. Other findings that may support the diagnosis of heart failure include cardiomegaly and pleural effusions.

Echocardiography allows assessment of heart structure through two-dimensional measurement of left ventricular wall thickness, chamber volumes, and valve structure. Assessment of systolic and diastolic function of the left ventricle, either or both of which must be abnormal to meet the ESC definition of heart failure, are possible through two dimensional and Doppler echocardiography.

Use of Doppler echocardiography also allows estimation of left ventricular filling pressure. Echocardiography allows identification of pericardial disease, which can mimic the presentation of heart failure. A summary of the echocardiography features which are commonly found in heart failure and make the diagnosis more likely are detailed in Table 3-1.

Another important test that can aid the physician in making the diagnosis of heart failure is natriuretic peptide testing.[174] Natriuretic peptides are released by the heart in response to pressure and volume overload of the atria and ventricles.[174] There are three major natriuretic peptides, atrial natriuretic peptide (ANP), Brain-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). ANP and BNP are released from the heart and act as circulating hormones which have beneficial vasodilatory, natriuesis and diuretic properties.

Table 3-1Echocardiography protocol

Window	Protocol: Doppler	Protocol: 2D / M-mode	Measurement
Parasternal			
Long axis	MV & AV colour flow	IVSd, LVEDD, LVPWd IVSs, LVESD, LVPWs, LVOT, LA	LV end diastolic dimension (cm/m^2) LV end systolic dimension (cm/m^2)
RV inflow	TV CW + colour flow		
Short axis			
Base	AV, TV & PV colour flow		
MV	MV colour flow		
Papillary muscle apex		2D endocardial & epicardial area	LV mass index (g/m^2)
Apical			
4 chamber	MV annulus TDI + LV inflow PW MV colour flow, TV colour flow	LV volume diastole + systole, LAA	LV EF (%) LV diastolic volume (ml/m^2) LV systolic volume (ml/m^2) LV stroke volume (ml) Cardiac output (L/min) LV diastolic parameters (E, E/e', IVRT, E/A) Left atrial volume (ml/m^2) Valve assessment of structure and function
2 chamber	MV colour flow	LV volume diastole + systole, LAA	LV EF (%) Left atrial volume (ml/m^2) LV diastolic volume (ml/m^2) LV systolic volume (ml/m^2)
5 chamber	AV CW + PW + IVRT, AV colour flow		
Long axis	MV colour flow		
RV		TAPSE, RAA	TAPSE RAA (mm^2)
Subcostal			
4 chamber			
IVC & hepatic veins		IVC diameter	RVSP

AV= aortic valve; CW= continuous wave; E= early diastolic filling; e'= early lengthening velocity; E/A= IVC+ inferior vena cava; IVRT= isovolumic relaxation time; IVSd= intraventricular septal diastole; IVSs= intraventricular septum systole; LVEDd= left ventricular end-diastolic dimension; LVESD= left ventricular end-systolic dimension; LVOT= left ventricular outflow tract; LVPWd= left ventricular posterior wall diastole; LVEDs= left ventricle posterior wall systole; EF = ejection fraction; LAA= left atrial area; LV= left ventricle; MV= mitral valve; PV= pulmonary valve; PW= pulsed wave; RAA= right atrial area; RV= right ventricle; RVSP= right ventricular systolic pressure; TAPSE = tricuspid annular plane systolic excursion; TV= tricuspid valve.

BNP is particularly useful in the diagnosis of heart failure, as it is synthesised and secreted in bursts in response to volume and/ or pressure overload of the left ventricle. The use of BNP has been incorporated into guidelines on the basis of a number of observational studies and randomised controlled trials.[3] In the landmark Breathing Not Properly Multination Study, BNP was measured in 1586 patients presenting to the emergency department with acute shortness of breath.[175] This study showed that BNP measurement on admission had a higher area under the receiver-operating characteristic curve than the emergency physician at diagnosing heart failure. This study demonstrated a cut-off of 100 pg/ml had a sensitivity and specificity for the diagnosis of acute heart failure of 90% and 76% respectively. The ESC stipulate a rule-out value of BNP of <100 pg/ml in the setting of suspected acute heart failure.[3] Other conditions can also cause elevation of natriuretic peptide including: increasing age; renal dysfunction; acute coronary syndromes; pulmonary disease (acute respiratory distress syndrome or cor pulmonale); pulmonary embolism; high output states (anaemia, cirrhosis, hyperthyroidism); and atrial fibrillation. Therefore, the combination of natriuretic peptide and echocardiography are recommended by the ESC, taking into consideration signs and symptoms of heart failure.[3] I used this evidence based and objective approach to confirm the diagnosis of heart failure in every participant in this study.

3.3 Outcome measures

I have chosen to use quantifiable PROMs as the main outcome measures in this study. This will enable me to make generalisable, objective assessments of PC need. PROMS are outcomes reported directly by the patient, without interpretation or influence from the clinician, caregiver, or researcher. PROMs inform researchers and clinicians regarding the influence of disease, or the response of treatment, on morbidity and disease burden on individual patient lives. More importantly, these outcome measures reflect the patients' opinion of their own health and potential suffering, rather than the investigators'. The ESC has recently released a position statement recommending that PROMs be incorporated into not only clinical trial design and reporting, but also clinical practice, as well as RCT design.[176]

3.3.1 Assessing Quality of Life in heart failure

It is unclear which QOL tool is best in patients with heart failure, although a combination of a heart failure specific and a generic questionnaire may be optimal.[177] Both generic and heart failure specific QOL PROMs have recently been systematically reviewed by the Oxford Patient Reported Outcome Group, on behalf of the UK Department of Health.[178] A number of different PROMs were identified in the systematic review, and the evidence base describing construct validity, test-retest reliability, and responsiveness was also critically appraised. Another important aspect of any PROM is acceptability to the patient, this was also reviewed. One of the more commonly used HF specific questionnaires is the KCCQ.[179] The KCCQ was one of two disease specific QOL PROMs recommended, the other being the Minnesota Living with Heart Failure questionnaire (MLHFQ).[180] Although both of these assessments are well validated, there is a suggestion that the KCCQ may be more sensitive to change in QOL than the MLHFQ.[178] The KCCQ is a 23-item, self-administered questionnaire that quantifies symptoms (including severity, frequency, and change), self-efficiency, knowledge, physical function, and QOL. The KCCQ generates an overall summary score derived from combining each of the afore mentioned domains. Each sub-set score and overall summary scores are out of 100, with higher scores indicating better function.

Over 34 studies describing the use, construct validity, reliability, and responsiveness of the KCCQ are available.[178] This strong evidence base has shown The KCCQ have excellent test-retest reliability, with an interclass correlation coefficient (ICC) of 0.88, in a study testing the psychometric properties of the KCCQ in patients with both anaemia and heart failure.[181] Assessment of construct validity of the KCCQ has been demonstrated previously with a strong correlation between NYHA class and KCCQ overall score, lower KCCQ overall scores associated with worse NYHA class.[182] The KCCQ overall score has been shown to discriminate between patients with and without symptoms of depression.[117, 183] The KCCQ overall score has also been shown to be predictive of prognosis, with those scoring less than 25 being five times more likely to die at one year than those scoring over 75. The responsiveness of the KCCQ has been demonstrated in a multi-centre study of 476 patients with heart failure, where the KCCQ was found to have the highest C-statistic for monitoring

individual patients, followed by NYHA class and 6-minute walk test.[182] Responsiveness of KCCQ was also demonstrated in an analysis of the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, where change in KCCQ summary score had a linear association with all-cause mortality.[184] This linear relationship was also true for each 5 point reduction in KCCQ summary score. Patient acceptability of the KCCQ is good, and in one study there was an 80% response rate to a posted questionnaire survey.[185]

A variety of generic QOL assessment tools are available and one of the more widely used is the SF-36,[186] which has been validated in a variety of populations including HF.[187, 188] This has been shortened to a 12 question format, while retaining construct validity, in the form of the SF-12.[189, 190] The SF-12 is a 12-item questionnaire which assesses both physical and mental components of QOL. Test-retest reliability is assessed as moderate, with a ICC of 0.59.[191] Responsiveness of the SF-12 has been shown to be good, particularly for the physical component score.[192] One particular advantage of utilising the SF-12 questionnaire is the high acceptability, particularly when compared to the more extensive SF-36. One study found completion rate of 99%.[191] SF-12 also has normative data and data from patients with heart failure for comparison and interpretation purposes.[193]

HF not only affects patients' QOL, but also that of their caregivers.[194] Caregiver QOL can be readily assessed using a generic tool, such as SF-12, but assessing 'caregiver burden' within a family as a result of heart failure can also be assessed using the Zarit Burden Interview.[195] This is the most widely used and validated caregiver assessment tool.[196] The validity and reliability of the Zarit Burden Interview has been demonstrated in caregivers of patients with heart failure.[197] This tool also includes an assessment of financial strain placed on the caregiver. This is an important question, as patients within the last 6 months of life are potentially entitled to financial support in some countries.

3.3.2 Assessing mood disturbance

The WHO definition of PC states that PC should identify and treat psychosocial as well as physical problems. Therefore, any assessment of PC needs should detail how QOL, symptom burden, and EOL care potentially affect a patient's

mood. The review of PROMs undertaken by the Oxford Patient Reported Outcomes Group in 2009 highlighted that neither of the preferred disease specific PROMS (KCCQ or MLHFQ) adequately covered the psychological domain or the whole range of symptoms.[178] They therefore suggest concomitant use of a dimension-specific measure of psychological well-being. This has become standard practice in other conditions, and in one RCT of PC use in lung cancer, mood assessment was used as an outcome measure.[104] Depression, which is common in HF,[198] can affect QOL[199] and is associated with higher morbidity and mortality.[200-202] A validated screening questionnaire for depression is the HADS.[203] HADS is a 14-item screening questionnaire, comprised of 7 questions relating to anxiety and 7 to depression. A summary score is generated for both anxiety and depression, which are interpreted independently. The HADs questionnaire can be administered by an interviewer or self-administered. Summary scores for anxiety and depression can categorise patients as normal, mild, moderate, or severely impaired. The test-retest reliabilty, internal consistency , and validity of the HADS have been assessed and supported by previous reviews.[204, 205] HADS has been used in a variety of populations,[205] and is validated in HF.[206] This, together with the reduced patient burden, combines two aspects of psychological assessment into one PROM and make HADS an appropriate and objective tool for this study.

3.3.3 Assessing symptom burden

Assessing on-going symptoms should also form part of an assessment of potential PC needs in patients with heart failure. Heart failure RCTs tend to focus on the symptoms of dyspnoea, fatigue and oedema. However, my systematic review highlighted that patients with HF can suffer from other symptoms including pain, anxiety, low mood, constipation, anorexia, nausea, insomnia, and persistent cough.[207, 208] There are recognised tools to help make an objective measurement of symptom burden but these have not been extensively evaluated in heart failure (although they have been in other diseases). The ESAS[209] is one such PROM which has been validated in cancer[210, 211] and has previously been used in a studies of patients with heart failure.[157] The ESAS comprises 10 separate questions regarding different symptoms, where respondents mark a score between 0 and 10 for each symptom, with zero being no symptom and 10 representing the worst. There is also the possibility to generate a total score

out of 100, with higher scores representing higher overall symptom burden. Scrutiny of the content of the ESAS and prior studies suggest that it can quantify many of the symptoms experienced in HF, and importantly, has low patient burden.

3.3.4 Assessing end of life care

Assessment of EOL care is essential in making any assessment of PC need. For this reason, I made an assessment of the patients' preferences for EOL care and also a retrospective assessment of the caregivers' (where available) opinion of EOL care. Patient preference for EOL care has been identified as a priority for research into PC need in heart failure.[3, 43] Previous studies suggest that patients often change their mind about preferred place of death and there is also poor agreement with their caregiver on this issue.[45] Patients also change their mind about resuscitation status.[46, 47] A recent study showed that patients with heart failure were willing to discuss EOL issues and that patients were willing to trade QOL for length of life,[48] which is contrary to previous studies.[212, 213] Although these studies are informative, they are based on selected cohorts of patients and this issue requires further research.

In this study I asked participants, in a sensitive way, to consider their preferred place of care, death and resuscitation preference. Specifically patients were asked " If your health was to deteriorate in the future, such that you required other people to care for you, where would you prefer that care to take place?" Patients were then given the following options to choose from (after explaining this was a hypothetical discussion): in their own home; a nursing or care home; hospital; hospice; or undecided. Patients were then asked to consider their preferred place of care for EOL treatment, specifically, patients were asked "If you were to think about the last few days of hours of life, would you have a strong opinion or preference for where that care took place?" Patients will then be given the following options to choose from (again, after explaining this is a hypothetical discussion): in their own home; a nursing or care home; hospital; hospice; or undecided. Finally, patients were asked, after an explanation of what resuscitation is, to consider their preference for resuscitation. Specifically, patients were asked "Do you have a strong opinion or preference to be resuscitated or not to be resuscitated in the event of a cardiac arrest".

Patient were asked to pick an option from "for active resuscitation, not for resuscitation, or undecided".

Any EOL assessment should not only assess preference for and actual place of death, but also the patient and caregiver experience of dying, wherever that occurs. The VOICES postal questionnaire has been designed to evaluate relative's experience of EOL care of the patients in the last few months of life.[101] A recent review by the Department of Health has identified the VOICES questionnaire as the tool of choice in a survey of EOL care.[214] I used this questionnaire to assess the caregivers' (where available) perspective on EOL care. The VOICES questionnaire was posted to relatives of deceased participants between 6 and 12 months after a death.

3.3.5 Identification of patients with palliative care needs

Before a RCT of PC use in HF can be planned, there is a need to further explore how patients with PC needs can be identified and which patients require the additional services of a specialist PC service. Heart failure guidelines suggest using the following factors to identify patients PC needs: frequent admission to hospital with decompensated heart failure; weight loss and cachexia; the need for frequent or on-going intravenous therapy; chronic poor QOL with NYHA class IV symptoms; and a clinical judgement that the patient is close to the EOL.[3, 44] However, predicting prognosis (and specifically mortality) is notoriously difficult and is recognised as a barrier to PC referral in heart failure.[215] A number of prognostic models for mortality have been described from various heart failure cohorts.[34] Unfortunately, most models were developed in chronic ambulatory populations (as opposed to acutely hospitalised patients) and many were based on patients not receiving contemporary pharmacotherapy or did not include important prognostic factors such as renal function, BNP[216] (or NT pro BNP) or troponin.[217, 218] Use of prognostic models has been suggested as a way of identifying patients with heart failure who are approaching EOL.[219] However, while these models may predict death there is no evidence to suggest that prognostic models for mortality correlate well with PC needs.[220] For example, patients who are clinically stable and then die suddenly probably are not candidates for PC. This question requires further exploration.[221]

One approach to try and specifically identify and assess the PC needs of patients with heart failure is to use tools currently in development for cancer patients, acknowledging that these require validation in patients with heart failure. The Needs Assessment Tool (Progressive Disease – Cancer) (NAT-PD-C),[222] has been designed specifically to assess and monitor PC needs in cancer patients. It was designed based upon a literature review of needs of patients and their caregivers. This assessment is made on a single page and completed by the patient's healthcare professional. The NAT-PD-C has been validated in cancer patients[223, 224] and has been adapted for use in heart failure with the creation of the Needs Assessment Tool Progressive Disease Heart Failure (NAT-PD-HF), with reliability testing and construct validation.[225] However this tool has yet to be evaluated in a substantial cohort of patients with heart failure and its value in identifying PC needs in patients with heart failure is as yet unconfirmed. I will assess the usefulness of the NAT-PD-HF as part of this study.

Performance status has been used by PC clinicians in both clinical practice and research as an indication for the likely need for PC services.[226-228] The Karnofksy Performance Scale (KPS)[229] is regarded by many as the gold standard tool for use in cancer patients.[227, 228] This instrument has been simplified and validated in the form of the Australia-Modified Karnofksy Performance Scale (AKPS).[230] The AKPS has been developed for use in cancer, and review of it suggests that it should also provide a suitable assessment of performance status in patients with heart failure.

Current guidelines suggest using the physician's own assessment of prognosis and need for PC to guide who to refer to PC services.[3, 43, 219] I therefore, where available, asked the treating physician to estimate whether the patient had a prognosis of more or less than one year, and also to estimate whether they thought the patient had PC needs.

3.4 Study protocol

This was a prospective observational study of near-consecutive patients admitted to hospital with a primary diagnosis of heart failure. Patients were extensively characterised during their inpatient stay by collecting echocardiographic, demographic, biomarker and physiological data, as well as a detailed past medical history, (Appendix 3). Patient symptom burden, mood and QOL were assessed during the index admission and repeatedly at study visits using PROMs as described above (Appendix 4). The burden on caregivers assessed using the Zarit Burden Interview PROM (appendix 4). Patient preference for place of care and death, as well as resuscitation preference, were recorded during the index admission.

Patients had study assessments performed at baseline during their index admission to hospital, and then at 4 monthly intervals for a minimum of 8 months and a maximum of 2.5 years.

3.4.1 Patient recruitment and consent

Near-consecutive patients admitted to the Western Infirmary in Glasgow with suspected HF were screened for inclusion in the study. The Western Infirmary acted as a community hospital for the North and West of the city, serving a population of about 250,000. I screened all case notes of patients admitted to the medical receiving and cardiology wards at the Western Infirmary. All new patients admitted through the medical receiving wards, unless admitted directly to the coronary care unit, were screened. I screened medical admissions every morning, Monday to Friday. On a Monday, I reviewed a list of admissions from the previous two days and case notes reviewed. In addition to reviewing case records, I reviewed CXRs and ECGs of any potentially eligible patients. I also screened echocardiogram referral requests and referrals to the Heart Failure Liaison Service, to ensure a rigorous screening process. Any patients with signs and symptoms suggestive of heart failure were invited to participate in the study and have a BNP screening test performed.

I used a two-staged consent process. The patient information sheets and consent forms are detailed in Appendix 2. The first stage involved asking permission to access patients' medical records and to link their record through NHS Scotland Information Services Division (ISD), allowing identification and cause of hospital readmission and death (including place of death), and to allow a sample of plasma to be tested for BNP. A finger prick (12 microlitre) sample of blood was analysed for BNP using a validated, point of care, capillary blood sample analysis (Alere HeartCheck System). Those with a BNP less than 100 pg/mL were excluded.[3] In addition to elevated BNP, patients had to meet the ESC echocardiographic criteria for the diagnosis of HF.[3, 231] Patients with a confirmed diagnosis of HF were invited to participate in the study and asked to complete the PROMs. A full echocardiographic examination was carried out according to the European Association of Echocardiography guidelines and assessment of known prognostic variables were recorded (Table 3-1).[232] Left ventricular ejection fraction was measured using Simpson's biplane method.[233] Echocardiograms were blindly analysed by two cardiologists to ensure validity of the diagnosis and findings. If an ejection fraction was not possible through poor echocardiographic acoustic window, an estimated ejection fraction was given. Inclusion and exclusion criteria are detailed in Table 3-2.

Table 3-2 Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria

• Admitted to hospital with a primary diagnosis of acute decompensated HF
• Age ≥ 18 years
• Fulfilling the ESC diagnostic criteria for the diagnosis of HF
• HF-REF, HF-PEF and valvular HF will be included.
	• Refusal to participate
	• Unable to provide informed consent/ complete study assessments
	  o Confusion/ dementia
	  o Learning difficulties
	  o Unable to read or write English language
	  o Moribund
	• Already in study
	• Geographical reasons, not from catchment area
	• Isolated cor pulmonale
	• Acute coronary syndrome complicated by pulmonary oedema

3.4.2 In-patient assessment

A representation of the patient flow through the study is shown in Figure 3-1.

I gathered detailed clinical data and data used in validated models of mortality prediction in HF during the index hospitalisation from history and examination of the patient, and review of the case record. Before discharge from hospital, patients completed the PROMs: the KCCQ and SF-12 questionnaires to assess QOL; the ESAS questionnaire to assess their current symptom burden; the HADS questionnaire to assess mood. Patients were given a questionnaire pack (Appendix 4) and given 24 hours to complete the questionnaires. Patients' caregivers, where available, were invited to complete the Zarit Burden Interview to assess caregiver burden. Performance status was evaluated using the AKPS. The NAT-PD-HF was used to assess the palliative needs of the patient.

3.4.3 Study visit

Following discharge patients with HF-REF were reviewed at an outpatient clinic by a cardiologist, a Heart Failure Liaison Nurse (HFLN), or both, where evidence-based therapy were optimised in accordance with ESC guidelines.[3] Patients were invited to attend for study assessments at 4 monthly intervals following discharge for a maximum follow-up period of 2.5 years. Participants were also offered the option of a home visit instead of attending in person, to increase study retention. At these visits the PROMs were completed, to detail any potential change in QOL, mood, and symptom burden over time. At these study assessments, prognostic markers were updated and the NAT-PD-HF was reassessed. A physical examination and assessment of medications and symptoms was also made (Appendix 3).

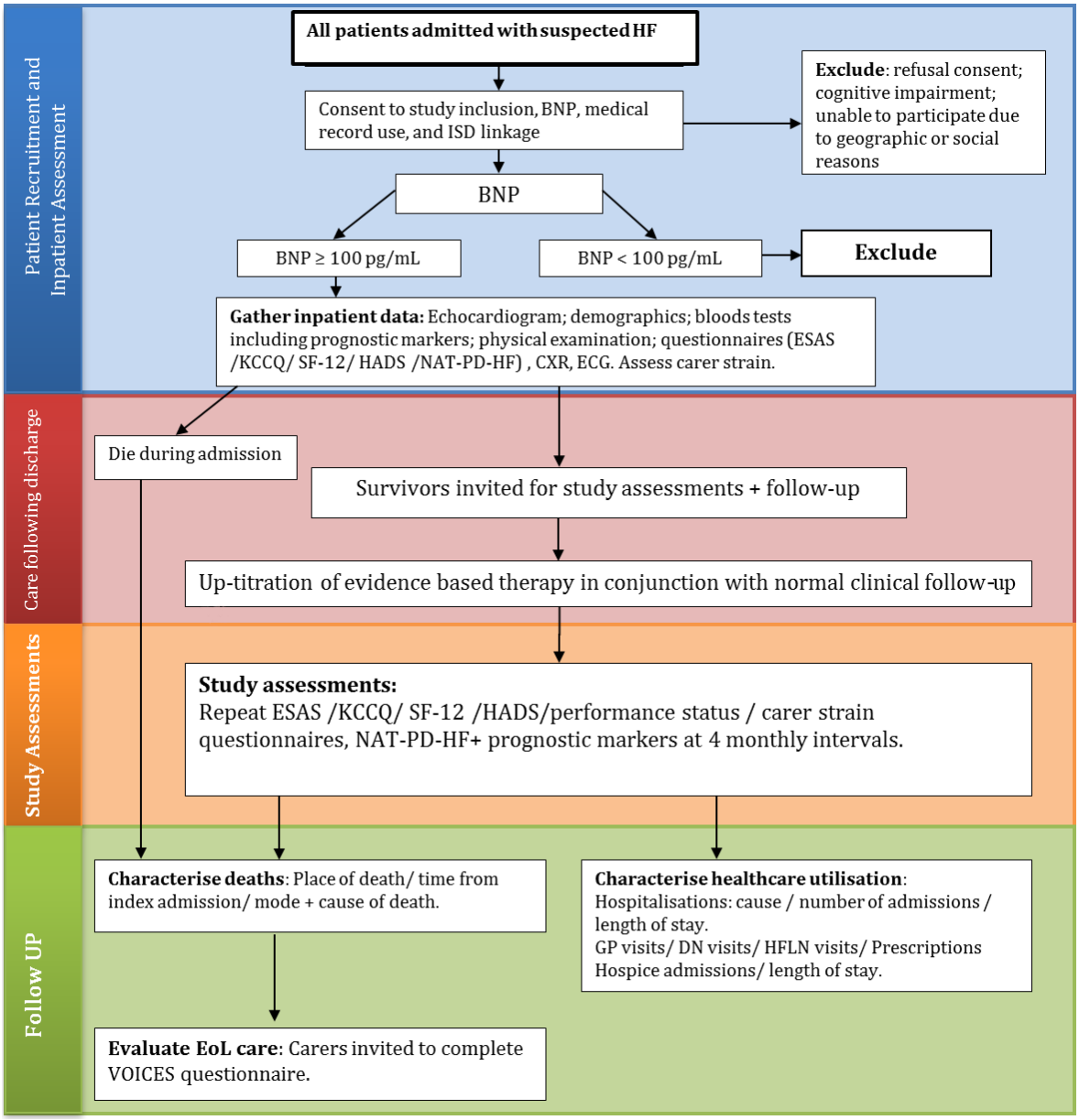


Figure 3-1 Study schedule
BNP= Brain type natriuretic peptide; ESAS= Edmonton Symptom Assessment Scale; DN= district nurse; GP= general practitioner; HFLN= heart failure liaison nurses; KCCQ= Kansas City Cardiomyopathy Questionnaire; SF-12= Short Form 12; HADS= Hospital Anxiety and Depression Scale; NAT-PD-HF= Needs Assessment Tool- Progressive Disease- Heart Failure; VOICES= Views Of Informal Carers Evaluation of Service.

3.4.4 Follow up

All consenting patients were followed-up passively using record linkage though Information Services Division and the Safehaven record linkage services at NHS Scotland and NHS Greater Glasgow and Clyde, respectively. This ensured as complete follow-up as possible. All participants were followed up for a minimum of 12 months. The number of hospital admissions, length of stay, date, cause and location of death were extracted. Cause of hospital admission and death were determined using the primary cause of death or discharge diagnosis. These were coded using the International Classification of Diseases version 10 classification.

Relatives of deceased patients were asked to complete the VOICES EOL postal questionnaire. This was posted to relatives between 6 months and 1 year following the death of a patient. This recommendation (from the questionnaire's authors) on timing of posting the questionnaire is aimed to reduce any potential upset caused by receiving an EOL questionnaire too soon after a death, but not so long after the death as to reduce recall of the events surrounding the death. Relatives were written to and given the opportunity to opt out prior to the questionnaire being posted to minimise any potential emotional upset from this questionnaire.

3.4.5 Data handling

All data were managed by the Robertson Centre for Biostatistics (RCB) at the University of Glasgow, the Data and Biostatistics Centre of the UK Clinical Research Collaboration Glasgow Clinical Trials Unit (CTU). Baseline and follow-up data (including patient and carer PROMs) was entered into case report forms (appendix 3) and then into the study database by experienced data entry staff. All data was stored, and managed according to CTU standard operating procedures that comply with appropriate legal and regulatory requirements.

3.5 Statistical analysis

Much of the analyses in this study are descriptive. Normally distributed continuous variables are expressed as mean with associated standard deviation described. Nonparametric continuous variables were summarised and expressed

as median with associated interquartile range. Comparison of categorical variables was performed using Fisher's exact test, and comparison of non-parametric continuous variables using the Mann-Whitney U test. To test the relationship between baseline prognostic variables, baseline PROMs, and physician completed assessment, multivariate logistic regression analysis was used. Time to event analysis for mortality were analysed using the Kaplan-Meier survival analysis. This analysis was used to determine if patients who went on to meet the definition of PC needs could be identified from the baseline dataset. Statistical analysis were made using STATA 13 (College Station, TX, USA).

3.5.1 Severity of patient reported outcome measures

Summary scores from each PROM were categorised according to severity. Where available, cut-offs used were based upon published normative data. Cut-offs used are detailed in

Table 3-3. KCCQ overall summary score was categorised as none/mild, moderate, and severe impairment of QOL using the scores 51-100, 25-50, and less than 25 respectively. An overall score of less than 25 has previously been shown to not only correlate with severe symptom burden according to NYHA classification, but also with poorer prognosis.[181, 184, 234] Furthermore, a summary score of less than 25 has recently been shown to be associated with higher likelihood of persistently impaired QOL or death at 12 weeks following discharge.[112] Indeed, this was the strongest predictor of any variable in a multivariable model. SF-12 summary scores for physical and mental component scores are based upon normative data of more than 8000 individuals in the United Kingdom, with moderate and severe impairment being classified as one and two standard deviations from the mean respectively.[193] Summary scores for both anxiety and depression HADS PROM can be used to categorise patients into severity of mood impairment with scores of <8 indicating normal, 8-10 mild, 11-15 moderate, and >15 severe impairment. These cut-offs have been complimented and corroborated by normative data.[203, 235] There are no published data categorising ESAS overall scores by severity. However, as the ESAS is composed of 10 Likert scales for each individual symptom, with a

minimum of 0 and a maximum of 100, I chose to define mild symptom burden as ESAS total score of <34, moderate as 34-66, and severe as >66. As each individual PROM would not assess QOL, symptoms, or mood, and taking into account that patients could be severe in one, but not other PROMs, I made an overall assessment of severity. I defined severe overall as any patient who was categorised as severe in at least one PROM.

Table 3-3 Severity category patient reported outcome measures

Score	Severity	Cut-off
HADS Depression	None/mild	≤ 10
	Moderate	11-15
	Severe	≥ 16
HADS Anxiety	None/mild	≤ 10
	Moderate	11-15
	Severe	≥ 16
KCCQ Summary Score	None/mild	> 50
	Moderate	25-50
	Severe	< 25
ESAS Summary Score	None/mild	0-33
	Moderate	34-66
	Severe	67-100
SF-12 PCS	None/mild	> 40.28
	Moderate	30.56-40.28
	Severe	< 30.56
SF-12 MCS	None/mild	> 40.28
	Moderate	30.56-40.28
	Severe	< 30.56
Overall severity category	Severely impaired	Severe in any PROM category

ESAS= Edmonton Symptom Assessment Scale; HADS= Hospital Anxiety and Depression Scale; KCCQ= Kansas City Cardiomyopathy Questionnaire; SF-12= Short Form 12.

3.5.2 Defining palliative care needs

There is no tool currently available to classify the presence of absence of PC needs. I have therefore used the WHO definition of PC as a basis on which to categorise patients who likely had PC needs and those who were less likely to have palliative care needs. To do this, I have elected to identify those patients with the worst QOL, symptom burden, and mood. Given the fluctuating nature of heart failure, I have taken into account potential change in status over time. My definition of PC needs, which is a practical interpretation of the WHO definition of PC, is shown in Table 3-4. I have chosen to try to identify the patients with the worst symptom, QOL and mood burden as these are the patients who would likely benefit most from a palliative intervention.

Table 3-4 Definition of PC needs

Either

1- Severely impaired status* preceding death, without known improvement of status.
2- Persistently severely impaired status*, defined as two or more consecutive study visits, without known improvement.

*Severely impaired status = severe in any patient reported outcome measure

3.5.3 Days alive and out of hospital analysis

To test whether the definition described above was appropriate for identifying patients with PC, further analyses of the patient journey were performed. I used three different analyses. Firstly, I calculated the number of days spent alive and out of hospital (DAOH), as patients in the PC needs group would likely have a poorer prognosis and a higher morbidity (including longer length of initial hospitalisation and more subsequent hospitalisations), and therefore have fewer DAOH. DAOH is a useful metric as it provides a quantifiable combination of both morbidity and mortality. This allows comparison of the patient journey between two groups. DAOH was calculated by subtracting one day from the total time from recruitment to study completion, for each day spent in hospital or lost to death. I then calculated the proportion of DAOH compared to the potential DAOH for each participant. The second sensitivity analysis I used was to adjust DAOH for QOL. This metric assesses not only days lost due to death or hospitalisation, but estimates days lost due to poor QOL. This metric has been used to describe the patient journey in heart failure previously.[236] To calculate

QOL adjusted DAOH I first calculated the number of DAOH between each assessment. I then used the KCCQ overall summary score to weight each DAOH. For example, if a KCCQ summary score was 75, and there were 100 DAOH, this would be calculated as 0.75 x 100 days, resulting in 75 days of good health. I then calculated the proportion of QOL DAOH compared to the potential DAOH. The third sensitivity analysis performed was similar to the QOL adjusted DAOH calculation, but using symptom adjusted DAOH. I used the ESAS summary score to estimate the number of days lost to symptom burden. As a higher score on ESAS was associated with worse symptom burden, I subtracted the total ESAS score from 100 before calculating the symptom adjusted DAOH. For example, a patient with an ESAS summary score of 75 and 50 DAOH would have ((100-75)/100) x 50 DAOH, resulting in 12.5 symptom free DAOH. If the definition used for PC needs is robust, then the PC needs group should have lower DAOH, QOL adjusted DAOH, and symptom adjusted DAOH.

3.6 Ethical considerations

This study was conducted according to the principles outlined in the Declaration of Helsinki.[237] The study protocol was approved by the West of Scotland Research Ethics Committee. All participants were given over 24 hours to read the patient information letter and consider if they wish to participate before provide written consent. Patient burden and load were considered, and PROMs were specifically chosen to limit the burden placed on participants. Burden of follow up study visits was reduced by offering participants home visits or providing door to door transport.

Chapter 4 Recruitment and baseline characteristics

In this chapter I will describe the number of patients with suspected heart failure that I screened, and describe the proportion who met the inclusion criteria and agreed to participate in the study. I will also describe the baseline characteristics of the cohort recruited, including medical history, physical examination findings, laboratory findings, and results of baseline investigations including echocardiography. I will then compare the cohort recruited to other published hospitalised cohorts of patients with heart failure and reflect on the generalisability of this cohort.

4.1 Recruitment

4.1.1 Screening

All patients admitted to the medical receiving and cardiology wards at the Western Infirmary Glasgow, were screened for eligibility for inclusion. I discussed with the physicians and nurses on each ward to identify any possible new cases of suspected heart failure. I also reviewed the case notes for all new admissions, looking for any patients with potential signs or symptoms of heart failure. In addition to this, I reviewed the chest X-ray and ECG for each patient, again looking for any evidence of an underlying diagnosis of heart failure. As a further screening method, I reviewed all of the requests for echocardiography, looking for any requests that queried heart failure as a diagnosis.

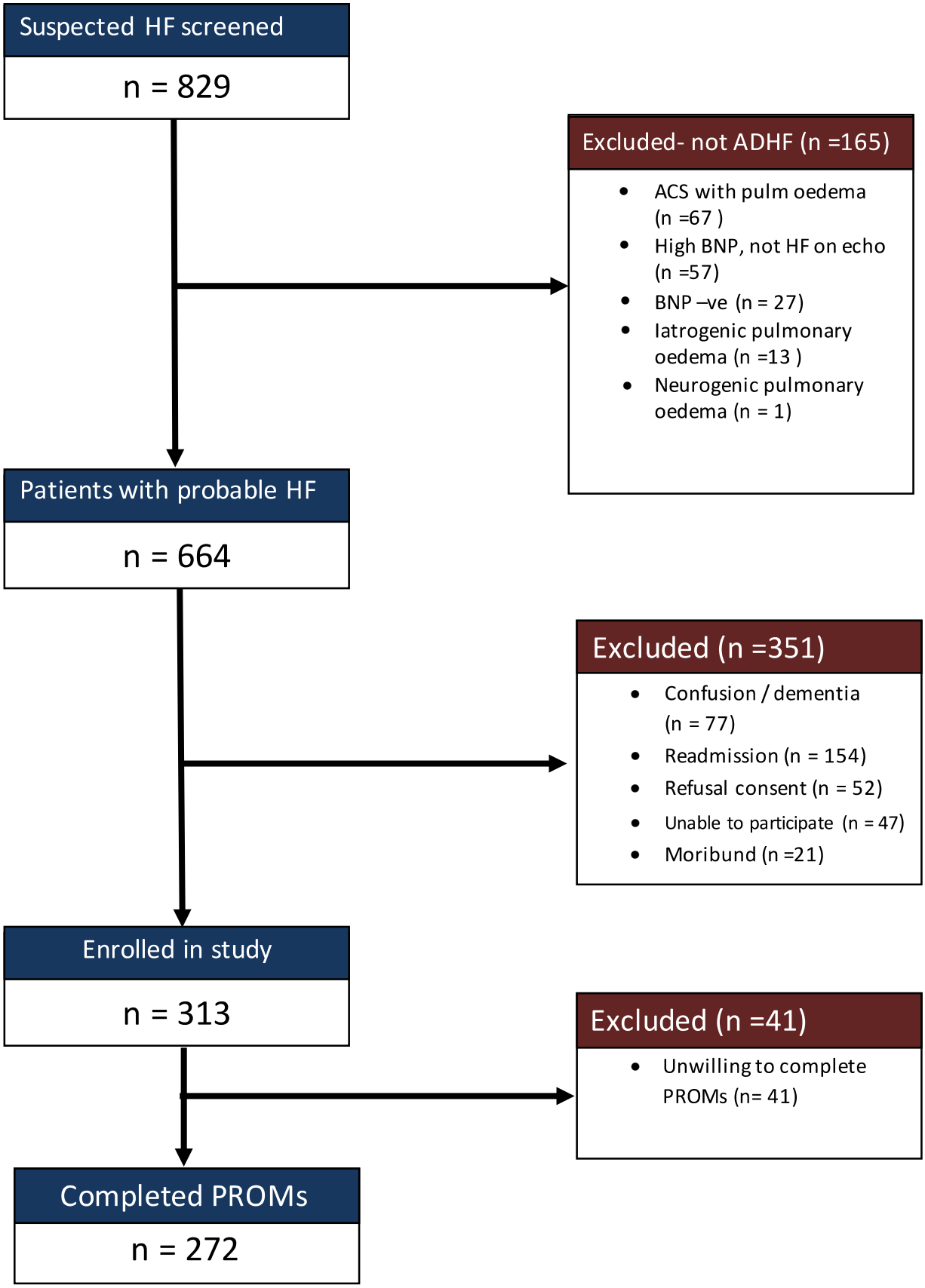
I screened new admissions between January 9th 2013 and December 1st 2014. I did not routinely screen on Saturday or Sunday, but attempted to review all potential patients admitted over this period each Monday morning. I screened an unselected population of patients admitted to hospital with suspected heart failure. Consecutive admissions were screened for inclusion in the study on the days that I was present. Using this method of screening patients, I was able to approach a near-consecutive, unselected population, thus increasing the generalisability of this study. Potentially eligible patients were initially approached and given preliminary information about the study and the potential diagnosis of heart failure. They were asked for consent to B-Type natriuretic

peptide testing and also for access to medical records and ISD record linkage. Patients were then given 24 hours to consider participation in the study. Those consenting to participate and with an elevated natriuretic peptide were invited to participate in the full study, including completing patient reported outcome measures and follow up assessments.

4.1.2 Screening log

I screened over 15 000 acute medical admissions to the Western Infirmary, Glasgow, between January 9th 2013 and December 1st 2014. Of these acute admissions, 829 patients had suspected heart failure based on the receiving physician's initial assessment, or from reading the case notes (Figure 4-1). During further screening through use of history, examination, natriuretic peptide, and echocardiography, 165 patients were excluded as they did not meet the inclusion criteria. That is, heart failure was not the primary reason for admission, or an alternative diagnosis was found.

The reasons for exclusion included: primary presentation with acute coronary syndrome complicated by pulmonary oedema; elevated natriuretic peptide, but no objective evidence of structural heart disease on echocardiography; low natriuretic peptide levels; iatrogenic pulmonary oedema caused by giving intravenous fluids; and one case of neurogenic pulmonary oedema in the context of a sub-arachnoid haemorrhage. Many of the patients with elevated natriuretic peptide, but no objective evidence of heart failure had a diagnosis of likely or confirmed cor pulmonale, others a diagnosis of pulmonary embolism, renal failure, or sepsis. Of a total of 664 patients identified as having probable heart failure, 351 patients were excluded. The most common reason included readmission and already in the study (n = 154). The next most common reason for exclusion was those that were unable to participate for language, geographical, or cognitive issues (n = 124). A further 52 patients refused consent to participate in the study. 21 patients were deemed too unwell, or were in fact, moribund, and thus not approached for inclusion.



ACS= acute coronary syndrome; ADHF= acute decompensated heart failure; BNP = brain type natriuretic peptide; HF= heart failure; PROM= patient reported outcome measure

Figure 4-1 Screening

A total of 313 patients met the inclusion criteria, and met the ESC definition of heart failure. Of these patients, 272 agreed to complete the questionnaire pack of PROMs and to attend study visits every four months for the duration of the study. On average, 3.6 patients were recruited per week over the duration of study enrolment (Figure 4-2).

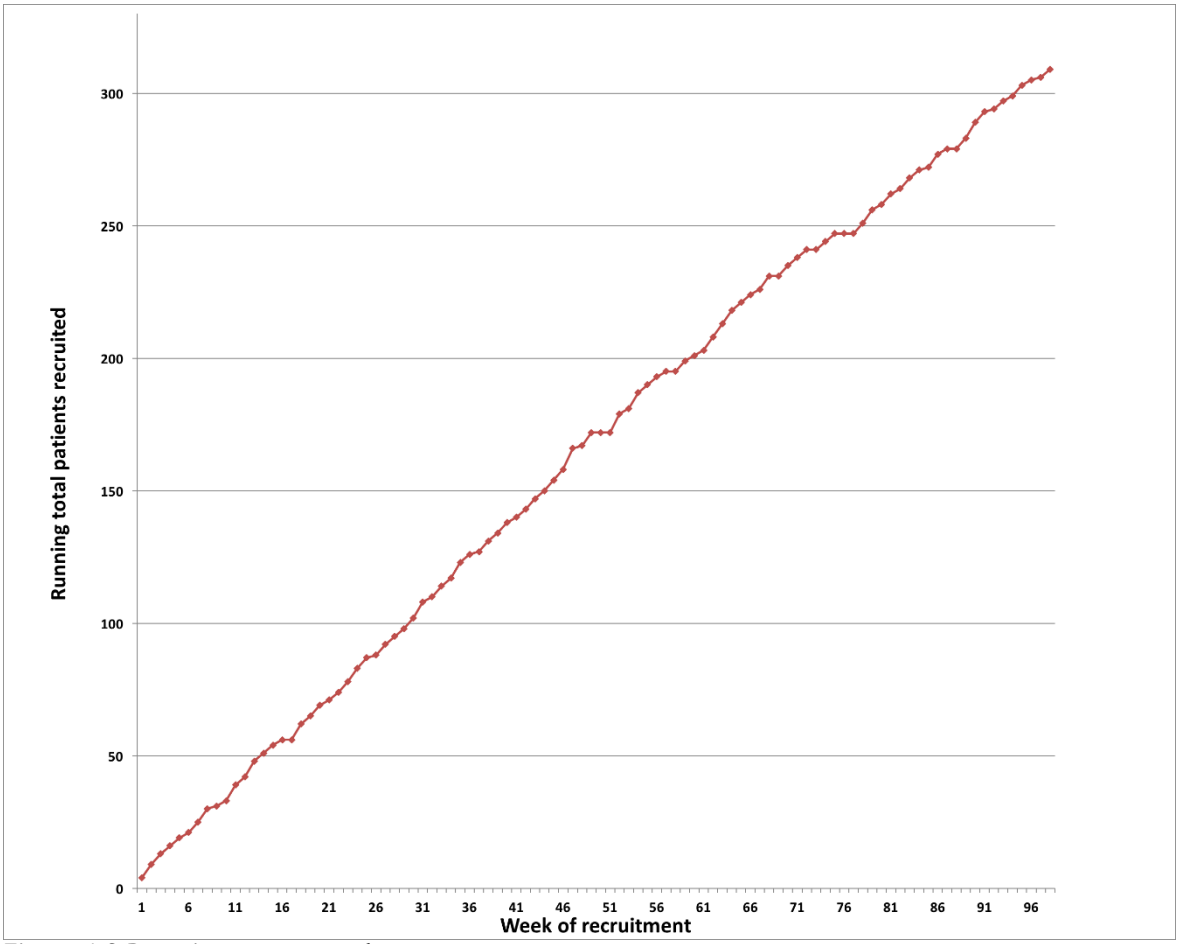


Figure 4-2 Recruitment per week

4.2 Baseline results

313 patients agreed to participate in the study. Of these, 272 agreed to complete PROMs and attend further follow-up visits. All 313 patients consented to long term follow up via electron records regarding vital status, cause of death, number and cause of hospitalisations. The median time from admission to recruitment was 2 days [IQR 2, 4]. Most patients survived until discharge, with only 4 deaths during the index admission for those that were able and willing to participate in the study. The median length of stay was 9 [5-15] days.

4.2.1 Baseline demographics clinical features

Demographics and past medical history are displayed in Table 4-1. Patients were elderly, with a median age of 77 [IQR 71-83] for the whole cohort. Patients who did not complete PROMs or consent to attend study visits were older than those who did with a median age of 84 [IQR 79-88] and 76 [IQR 70-82] respectively. Female sex was more common in patients who declined to participate in the questionnaire and active follow-up components of the study (63 versus 47%), although there was no statistically significant difference between groups. The majority of participants were of Caucasian decent, reflecting the patient population that attended the Western Infirmary, Glasgow. Many patients were hypertensive on admission, in keeping with acute heart failure, with the overall cohort having a median systolic blood pressure of 134 [IQR 117-155]. Patients who participated were similar physiologically in terms of blood pressure and pulse rate on admission. There was a statistically significant difference between the two groups in body mass index, with those not completing PROMs having a lower body mass index at 24 kg/m [IQR 21.3-27.1] versus 27.0 [IQR 23.5-31.6] in those who did.

As expected, common symptoms experienced in heart failure were extremely common in the overall cohort. The most prevalent symptom was ankle swelling (76%), followed by paroxysmal nocturnal dyspnoea (71%), and orthopnoea (74%). Patients participating in the full study with follow-up and PROMs reported a higher prevalence of these symptoms, although this was not statistically significant.

Table 4-1 Baseline demographics

	All participants n = 313	Completed PROMS n =272	Did not complete PROMS n = 41	p
Age- yr	77.1 [70.6, 83.4]	76.0 [69.8, 82.4]	84.2 [79.1, 87.8]	**< 0.001**
Female sex- n (%)	154 (49.2)	128 (47.1)	26 (63.4)	0.051
Race or ethnic group- n (%)				0.065
White	304 (97.1)	266 (97.8)	38 (92.7)	
Black	1 (0.3)	1 (0.4)	0 (0.0)	
Asian	7 (2.2)	5 (1.8)	2 (4.9)	
Other	1 (0.3)	0 (0.0)	1 (2.4)	
Systolic blood pressure- mmHg	134 [117, 155]	134 [118, 155]	129 [112, 154]	0.370
Diastolic blood pressure- mmHg	75 [63, 89]	75 [64, 90]	71 [61, 83]	0.111
Heart rate- beats/min	82 [68, 103]	82 [68, 102]	77 [67, 106]	0.536
Body-mass index- kg/m	26.5 [22.9, 30.9]	27.0 [23.5, 31.6]	24.0 [21.3, 27.1]	**0.001**
Symptoms- n (%)				
NYHA functional class				0.713
Class I	0 (0.0)	0 (0.0)	0 (0.0)	
Class II	95 (30.4)	82 (30.1)	13 (31.7)	
Class III	160 (51.1)	141 (51.8)	19 (46.3)	
Class IV	58 (18.5)	49 (18.0)	9 (22.0)	
HF symptoms				
Orthopnea	232 (74.1)	204 (75.0)	28 (68.3)	0.346
PND	221 (70.6)	194 (71.3)	27 (65.9)	0.467
Ankle swelling	237 (76.0)	208 (76.5)	29 (72.5)	0.558
Wheeze	65 (20.8)	62 (22.8)	3 (7.3)	**0.022**
Palpitations	11 (3.5)	10 (3.7)	1 (2.4)	1.000
Signs- n (%)				
Elevated JVP (> 4cm)	208 (74.0)	176 (73.0)	32 (80.0)	0.438
Third Heart Sound	63 (20.2)	59 (21.8)	4 (9.8)	0.094
Murmur	174 (55.8)	149 (55.0)	25 (61.0)	0.504
Pulmonary crackles	239 (76.8)	212 (78.5)	27 (65.9)	0.110
Basal§	237 (99.2)	210 (99.1)	27 (100.0)	1.000
Middle§	55 (23.0)	45 (21.2)	10 (37.0)	0.087
Apex§	10 (4.2)	9 (4.2)	1 (3.7)	1.000
Pleural effusion	107 (34.5)	95 (35.3)	12 (29.3)	0.486
Right	67 (62.6)	59 (62.1)	8 (66.7)	1.000
Left	66 (61.7)	59 (62.1)	7 (58.3)	1.000
Peripheral Oedema	236 (75.9)	206 (76.3)	30 (73.2)	0.696
Ankle*	236 (100.0)	206 (100.0)	30 (100.0)	NA
Knee*	141 (59.7)	125 (60.7)	16 (53.3)	0.551
Thigh*	72 (30.5)	64 (31.1)	8 (26.7)	0.678
Sacrum*	47 (19.9)	43 (20.9)	4 (13.3)	0.464
Abdomen*	38 (16.1)	35 (17.0)	3 (10.0)	0.432
Ascites	44 (14.1)	40 (14.8)	4 (9.8)	0.478

Continuous variables expressed as median [interquartile range].

HF= heart failure; JVP= jugular venous pressure; NYHA = New York Heart Association; PND= paroxysmal nocturnal dyspnoea.

§ percentage of patients with pulmonary crackles

* percentage of pateints with peripheral oedema

No patients were NYHA classification I by definition, as such patients would be symptom free and not present to hospital or have heart failure. Most patients were NYHA III (51%), with 30% NYHA II and 19% NYHA IV. This represents a very high disease and symptom burden when using the most commonly utilised functional assessment. Those completing PROMs and the full study were very similar in terms of NYHA classification compared to those who did not, with the exception of a numerically higher proportion of NYHA IV in those who did not complete the PROM component of the study (although this was not statistically significant).

Physical signs of heart failure were common. Signs of elevated venous pressure were particularly common, with 74% overall having an elevated jugular venous pressure. There was similar proportion of patients with elevated jugular venous pressure in both those who completed PROMs and those who did not (73 and 80%, respectively). Auscultation of the heart frequently identified a murmur (56%), although a gallop rhythm or third heart sound was only detected in 20% of patients. Clinical evidence of pulmonary congestion, in the form of pulmonary crackles or rales, was present in 77% of patients, with no statistically significant difference between those participating and those who did not. 27% of patients presented with marked signs of pulmonary congestion, with pulmonary rales to the mid-zones or more. 35% of patients had clinical evidence of a pleural effusion, either uni- or bi-lateral. Peripheral oedema was another common physical finding, present in 76% of patients at admission. Most of these patients presented with oedema extending to the knees (60%), whereas 20 and 16% presented with oedema extending to the sacrum and abdomen, respectively.

4.2.2 Past medical history

Overall, most patients had not been diagnosed with heart failure previously (57%); this was true for both patients completing the PROM aspect of the study (56%) and those who did not (61%). Of the 136 patients with a previous diagnosis of heart failure, 80 (59%) had previously been admitted to hospital with a primary discharge diagnosis of heart failure. Most were under the care, or had previously been under the care, of a cardiologist (77%). Only 24 patients had been admitted to hospital due to heart failure in the previous 6 months.

Co-morbidities were highly prevalent in the overall cohort, and those completing PROMs (Table 4-2). Ischaemic heart disease was particularly common, with 40% suffering from previous myocardial infarction, 13% having had percutaneous coronary intervention, and 15% coronary artery bypass grafting. Most patients had a previous diagnosis of, or were being treated for, hypertension (68%). A past history of atrial fibrillation was also common, reported in 53% of patients. Of these 165 patients, atrial fibrillation was persistent or permanent in 80% and paroxysmal in 19%. Other commonly reported cardiovascular co-morbidities included stroke (19%) and peripheral vascular disease (14%). Permanent pacemakers were uncommon, with only 21 patients with some form of pacing device. Of these 21 patients, only 8 had cardiac resynchronisation therapy. Implantable cardioverter defibrillators, either in combination with cardiac resynchronisation therapy or as a stand-alone system, were also very rare with only 10 patients having these devices. Non-cardiovascular co-morbidities were frequently reported, with 100 patients (32%) reporting a diagnosis of, or were treated for, diabetes. Of these, most were on oral hypoglycaemic medication (65%) or insulin (29%), with 23% being treated with di*et al*one. A history of anaemia was also prevalent at 28%. Many patients had a history of chronic lung disease, with 25 and 8 % reporting a history of chronic obstructive pulmonary disease and asthma, respectively. 43 patients reported, or were on treatment for, depression, with 28% of these patients reporting current depression.

Table 4-2 Past medical history

	All participants n = 313	Completed PROMS n =272	Did not complete PROMS n = 41	p
History of HF- n (%)				
HF diagnosis prior to admission	136 (43.5)	120 (44.1)	16 (39.0)	0.614
Previous HF hospitalisation	80 (25.6)	73 (26.8)	7 (17.1)	0.279
HF hospitalisation preceding 6 months	24 (7.7)	22 (8.1)	2 (4.9)	0.752
Cardiovascular- n (%)				
Treated Hypertension	212 (67.7)	184 (67.6)	28 (68.3)	1.000
Myocardial Infarction	126 (40.3)	111 (40.8)	15 (36.6)	0.733
PCI	42 (13.4)	38 (14.0)	4 (9.8)	0.624
CABG	47 (15.0)	42 (15.4)	5 (12.2)	0.814
Hypercholesterolaemia	94 (30.0)	88 (32.4)	6 (14.6)	0.027
Atrial Fibrillation/Flutter	165 (52.7)	144 (52.9)	21 (51.2)	0.868
Cerebrovascular disease (CVA/TIA)	59 (18.8)	52 (19.1)	7 (17.1)	1.000
Peripheral Vascular Disease	43 (13.7)	37 (13.6)	6 (14.6)	0.810
Primary prevention ICD	5 (1.6)	4 (1.5)	1 (2.4)	0.508
Pacemaker	21 (6.7)	18 (6.6)	3 (7.3)	
Conventional[§]	13 (61.9)	10 (55.6)	3 (100.0)	0.257
CRT-P[§]	3 (14.3)	3 (16.7)	0 (0.0)	1.000
CRT-D[§]	5 (23.8)	5 (27.8)	0 (0.0)	0.549
Valve replacement	16 (5.1)	11 (4.0)	5 (12.2)	0.044
Non-cardiovascular-n (%)				
Diabetes Mellitus	100 (31.9)	89 (32.7)	11 (26.8)	0.590
COPD	77 (24.6)	69 (25.4)	8 (19.5)	0.560
Asthma	24 (7.7)	23 (8.5)	1 (2.4)	0.339
Depression	43 (13.8)	37 (13.7)	6 (14.6)	0.811
Cancer	41 (13.1)	31 (11.4)	10 (24.4)	0.043
Hypothyroidism	44 (14.1)	35 (12.9)	9 (22.0)	0.145
Osteoarthritis	29 (9.3)	27 (9.9)	2 (4.9)	0.396
Anaemia	86 (27.5)	77 (28.3)	9 (22.0)	0.457

CABG= coronary artery bypass graft; COPD= chronic obstructive pulmonary disease; CRT-P= cardiac resynchronisation therapy- pace; CRT-D= cardiac resynchronisation therapy- defibrillator; CVA= cerebrovascular accident; HF= heart failure; ICD= implantable cardioverter defibrillator; PCI= percutaneous coronary intervention; TIA= transient ischaemic attack.

[§] percentage of patients with pacemaker

4.2.3 Drug history- medications started prior to admission

Drug history is detailed in Table 4-3. Polypharmacy was common. Although, only 43% of all patients had a known diagnosis of heart failure, many were already prescribed the common therapies used in chronic heart failure, although heart failure was not necessarily the indication for these medications. Over half of all participants were on an ACEi (41%), or an ARB (15%) prior to admission. The most commonly prescribed ACEi were ramipril (60%), followed by enalapril (17%), and lisinopril 16%). ARBs prescribed prior to admission were losartan (50%), candesartan (41%), and irbesartan (9%). Beta blocker therapy was also very common prior to admission, with 56% of participants taking this class of drug. Patients were prescribed bisoprolol (74%), atenolol (17%), carvedilol (9%), and metoprolol (1%). 25 (8%) of participants were already prescribed a MRA. Other heart failure therapies which have been shown to reduce morbidity were less commonly prescribed, with only 8 and 1 patients prescribed hydralazine and ivabradine, respectively. Drug therapy that is often used for symptomatic treatment in heart failure, loop diuretics (in the form of furosemide) and digoxin, were also frequently prescribed prior to admission, with 64 and 10% respectively taking these medications. Many patients were prescribed pharmacotherapy often used in the treatment of ischaemic heart and cerebrovascular disease, with 63% taking a statin, 42% taking aspirin, and 10% taking clopidogrel prior to admission. Calcium channel blockers (CCB) were often prescribed prior to hospitalisation, with 25% of participants on this class of medication. The most common CCBs were amlodipine (68%), verapamil (14%), and diltiazem (9%). The anti-anginal medications nicorandil and long-acting nitrates were prescribed in 9 and 12% of participants, respectively. Warfarin prescription was relatively low (28%) compared to the proportion of participants with a past history of atrial fibrillation (53%).

Unsurprisingly, a high proportion of participants were receiving some form of diabetic therapy, reflecting the high prevalence of diabetes mellitus in this cohort. 26% of all participants were taking some form of diabetic therapy. Of these, the most commonly prescribed were insulin (35%), sulphonurea (49%), or biguanide (57%).

Non-cardiovascular medications were common, again reflecting the high co-morbid burden in the cohort. The most common non-cardiovascular medications were respiratory medications/ bronchodilators and anti-depressants, at 30 and 16% respectively. 85% of patients on respiratory medications were prescribed a beta-agonist inhaler, with a further 58 and 54% prescribed steroid and anti-cholinergic inhalers respectively. The most frequently prescribed anti-depressants were selective serotonin reuptake inhibitors (37% of those taking anti-depressants) and tricyclic antidepressants (41% of those taking anti-depressants).

Table 4-3 Medications prior to admission

	All participants n = 313	Completed PROMS n =272	Did not complete PROMS n = 41	p
Cardiovascular - n (%)				
ACE-Inhibitor	128 (40.9)	108 (39.7)	20 (48.8)	0.308
ARB	46 (14.7)	40 (14.7)	6 (14.6)	1.000
Beta-blocker	176 (56.2)	152 (55.9)	24 (58.5)	0.866
MRA	25 (8.0)	23 (8.5)	2 (4.9)	0.756
Hydralazine	8 (2.6)	8 (2.9)	0 (0.0)	0.603
Ivabradine	1 (0.3)	1 (0.4)	0 (0.0)	1.000
Anti-arrhythmic	4 (1.3)	4 (1.5)	0 (0.0)	1.000
Calcium channel-blocker	79 (25.2)	68 (25.0)	11 (26.8)	0.847
Long-acting nitrates	37 (11.8)	33 (12.1)	4 (9.8)	0.799
Statin	197 (62.9)	171 (62.9)	26 (63.4)	1.000
Diabetic medication	82 (26.2)	70 (25.7)	12 (29.3)	0.703
Insulin§	29 (35.4)	27 (38.6)	2 (16.7)	0.198
Sulphonylurea§	40 (48.8)	33 (47.1)	7 (58.3)	0.543
Biguanide§	47 (57.3)	41 (58.6)	6 (50.0)	0.754
Glitazone§	3 (3.7)	3 (4.3)	0 (0.0)	1.000
Other§	9 (11.0)	8 (11.4)	1 (8.3)	1.000
Diuretics	199 (63.6)	172 (63.2)	27 (65.9)	0.862
Digoxin	31 (9.9)	26 (9.6)	5 (12.2)	0.577
Aspirin	130 (41.5)	112 (41.2)	18 (43.9)	0.737
Clopidogrel	32 (10.2)	26 (9.6)	6 (14.6)	0.403
Warfarin	89 (28.4)	78 (28.7)	11 (26.8)	1.000
Nicorandil	28 (8.9)	25 (9.2)	3 (7.3)	1.000
Non-cardiovascular -n (%)				
Bronchodilator	93 (29.7)	86 (31.6)	7 (17.1)	0.067
Steroid tablets*	9 (9.7)	9 (10.5)	0 (0.0)	1.000
Beta-agonist inhalers*	78 (84.8)	71 (83.5)	7 (100.0)	0.590
Anti-cholinergic inhalers*	50 (54.3)	45 (52.9)	5 (71.4)	0.448
Steroid inhalers*	53 (57.6)	48 (56.5)	5 (71.4)	0.695
Antidepressants	49 (15.7)	42 (15.4)	7 (17.1)	0.818
SSRI±	18 (36.7)	17 (40.5)	1 (14.3)	0.238
TCA±	20 (40.8)	19 (45.2)	1 (14.3)	0.216
MAOI ±	3 (6.1)	3 (7.1)	0 (0.0)	1.000
Other±	10 (20.4)	5 (11.9)	5 (71.4)	0.002
NSAIDs	11 (3.5)	8 (2.9)	3 (7.3)	0.163
Vitamins	32 (10.2)	28 (10.3)	4 (9.8)	1.000
Antihistamines	12 (3.8)	11 (4.0)	1 (2.4)	1.000
Osteoarthritis	29 (9.3)	27 (9.9)	2 (4.9)	0.396

ACE= angiotensin converting enzyme; ARB= angiotensin receptor blocker; MRA= mineralocorticoid receptor antagonist; MAOI= monoamine oxidase inhibitor; SSRI= selective serotonin reuptake inhibitor; TCA= tricyclic antidepressant.

§ percentage of diabetic medication

* percentage of bronchodilator medication

± percentage of antidepressant medication

4.2.4 Drug history- medications started during admission or on discharge

Almost all participants were treated with the loop diuretic furosemide (98%). Of these patients, most received intravenous furosemide. One bolus of intravenous furosemide was received by 22% and regular boluses on more than one day by 74%. 279 (90%) patients went on to have regular oral furosemide prescribed. Another loop diuretic that was prescribed was bumetanide (n= 17, 5%), often orally after intravenous furosemide. Intravenous vasodilators and inotropic agents were prescribed infrequently. Intravenous nitrate was prescribed in only 2% of participants, and only 3% and 1% received dobutamine and dopamine respectively.

ACEi and ARB prescription increased during hospital admission, with 70% of patients on one of these medications at discharge. The proportion of patients on ACEi which have been shown to reduce mortality in patients with heart failure was higher than admission, with 32% of patients who were on an ACEi being prescribed enalapril. Most other patients who were prescribed an ACEi were prescribed Ramipril (53%). The most common ARBs prescribed were candesartan (52%) and losartan (41%). Beta blocker prescription increased following admission, with 69% of being prescribed this class of medication. Again, cardio-selective beta blockers were favoured, with a higher proportion being prescribed specific beta blockers which have been shown to reduce mortality in patients with heart failure. By far the most commonly prescribed beta blocker was bisoprolol (84%), followed by carvedilol (11%). MRA prescription increased, with 32% of patients being prescribed either spironolactone (67%) or eplerenone (33%). A similar proportion of patients continued or were prescribed hydralazine and ivabradine compared to admission, with 9 and 1 patients respectively prescribed these medications. The number and proportion of patients prescribed digoxin increased from admission from 10% to 28%. Warfarin prescription saw a similar increase in prescription from admission from 29 to 37%.

There were no significant differences in prescription between patients who participated in the full study and those who did not, either on admission or medications prescribed during admission.

Table 4-4 Medications started in hospital or at discharge

	All participants n = 313	Completed PROMS n =272	Did not complete PROMS n = 41	p
Cardiovascular - n (%)				
ACE-Inhibitor	178 (56.9)	152 (55.9)	26 (63.4)	0.401
ARB	42 (13.4)	37 (13.6)	5 (12.2)	1.000
Beta-blocker	217 (69.3)	192 (70.6)	25 (61.0)	0.275
MRA	100 (31.9)	91 (33.5)	9 (22.0)	0.155
Hydralazine	9 (2.9)	9 (3.3)	0 (0.0)	0.612
Ivabradine	1 (0.3)	1 (0.4)	0 (0.0)	1.000
Anti-arrhythmic	7 (2.2)	7 (2.6)	0 (0.0)	0.600
Calcium channel-blocker	32 (10.2)	28 (10.3)	4 (9.8)	1.000
Long-acting nitrates	35 (11.2)	30 (11.1)	5 (12.2)	0.792
Statin	184 (59.0)	160 (59.0)	24 (58.5)	1.000
Diuretics (exc. Furosemide)	25 (8.0)	22 (8.1)	3 (7.3)	1.000
Furosemide	306 (97.8)	265 (97.4)	41 (100.0)	0.600
IV once-off	57 (18.2)	49 (18.0)	8 (19.5)	0.817
IV regular	209 (66.8)	182 (66.9)	27 (65.9)	0.893
Oral once-off	4 (1.1)	3 (1.1)	1 (2.4)	0.478
Oral regular	279 (89.1)	242 (89.0)	37 (90.0)	0.807
Digoxin	86 (27.5)	76 (27.9)	10 (24.4)	0.711
Aspirin	109 (34.9)	96 (35.4)	13 (31.7)	0.727
Clopidogrel	38 (12.2)	31 (11.4)	7 (17.1)	0.307
Warfarin	116 (37.2)	106 (39.1)	10 (24.4)	0.083
Nicorandil	23 (7.4)	18 (6.6)	5 (12.2)	0.203
Inotropes / vasodilators				
IV Nitrate	7 (2.2)	6 (2.2)	1 (2.4)	1.000
Dobutamine	4 (1.3)	4 (1.5)	0 (0.0)	1.000
Dopamine	10 (3.2)	9 (3.3)	1 (2.4)	1.000
IV other	6 (1.9)	6 (2.2)	0 (0.0)	1.000

ACE= angiotensin converting enzyme; ARB= angiotensin receptor blocker; MRA= mineralocorticoid receptor antagonist; IV= intravenous.

4.2.5 Investigations

Electrocardiogram

All participants had an ECG performed during admission, often within the first hour of admission. A summary of the ECG findings are detailed in Table 4-5. As expected, the ECG often suggested underlying structural heart disease and was often abnormal. Half of all participants were in atrial fibrillation, in keeping with the high prevalence of atrial fibrillation in the past medical history. A bundle branch block pattern was present in 29% of all participants, more often a left bundle branch block pattern (70%). QRS duration was 100 [IQR 88-128] ms and corrected QT duration was 468 [441-495] ms. Pathological Q waves were present in almost one quarter of patients (24%) and evidence of left ventricular hypertrophy in a further 19%. Patients who participated in the whole study and completed PROMs were similar to those who did not, other than a higher proportion of atrial fibrillation in those who did not.

Table 4-5 Electrocardiogram

	All participants	**Completed PROMS**	**Did not complete PROMS**	**p**
	n = 313	**n =272**	**n = 41**	
ECG during admission	313 (100)	272 (100)	41 (100)	
Sinus rhythm	151 (48.2)	138 (50.7)	13 (31.7)	0.029
AF/flutter	158 (50.5)	131 (48.2)	27 (65.9)	0.044
BBB	92 (29.4)	81 (29.8)	11 (26.8)	0.854
Right[§]	28 (30.4)	26 (32.1)	2 (18.2)	0.494
Left[§]	64 (69.6)	55 (67.9)	9 (81.8)	
Paced	19 (6.1)	16 (5.9)	3 (7.3)	0.724
Pathological Q waves	75 (24.0)	66 (24.4)	9 (22.0)	0.846
LVH	60 (19.2)	54 (19.9)	6 (14.6)	0.527
QRS duration	100 [88, 128]	102 [88, 129]	96 [88, 128]	0.488
QTc duration	468 [441, 495]	470 [441, 497]	458 [440, 490]	0.314

Values are expressed as n (%) or median [inter-quartile range].
AF= atrial fibrillation; BBB= bundle branch block; LVH= left ventricular hypertrophy.
[§] percentage of BBB

Chest X-ray

Most participants (98%) received a CXR as part of standard clinical care for patients admitted to hospital with suspected heart failure. A summary of the key findings from the CXR is detailed in Table 4-6. CXRs were often abnormal with signs suggestive of underlying cardiac disease and congestion in most.

Cardiomegaly was present overall in 91% of patients, with a higher proportion of cardiomegaly in the group completing the PROMs versus those who did not, 93 versus 81% respectively. Evidence of pulmonary congestion was common, but not universal. Most patients CXR showed upper lobe venous diversion (91%), with a further 42 and 38% showing evidence of interstitial oedema (with Kerley B-lines) and alveolar oedema (with patchy consolidation), respectively. Just over half of all patients who had a CXR had evidence of pleural effusions, with most (68%) being bilateral. Other than cardiomegaly, there were no statistically significant differences between those who participated in the full study and those who did not.

Table 4-6 Chest X-ray findings

	All participants n = 313	**Completed PROMS** n =272	**Did not complete PROMS** n = 41	**p**
CXR during admission	308 (98.4)	267 (98.2)	41 (100)	
Cardiomegaly (CTR > 0.5)	281 (91.2)	248 (92.9)	33 (80.5)	0.016
Upper lobe venous diversion	279 (90.6)	245 (91.8)	34 (82.9)	0.084
Interstitial oedema (kerley B lines)	128 (41.6)	112 (41.9)	16 (39.0)	0.865
Alveolar oedema (patchy consolidation)	118 (38.3)	104 (39.0)	14 (34.1)	0.608
Pleural effusions	160 (51.9)	140 (52.4)	20 (48.8)	0.738
Right§	33 (20.6)	31 (22.1)	2 (10.0)	0.468
Left§	19 (11.9)	16 (11.4)	3 (15.0)	
Bilateral§	108 (67.5)	93 (66.4)	15 (75.0)	

Values are expressed as n (%).
CTR= cardiothoracic ratio; CXR= chest X-ray.
§ percentage of patients with pleural effusions

Laboratory results

A summary of the laboratory results, which were collected on the day of enrolment, and often within 24-48 hours of admission, are detailed in Table 4-7. A detailed biochemistry and haematology profile was tested in every participant. This included known prognostic markers in heart failure including BNP, sodium, haemoglobin, haemoglobin A1c, urea, creatinine, estimated glomerular filtration rate, thyroid function, urate, troponin, and lymphocyte count. As a BNP value of >100 pg/ml was used as part of the inclusion criteria, as per ESC Guidelines, BNP was elevated in all participants. BNP is one of the most powerful prognostic marker in heart failure and is also a marker of congestion. BNP levels were

generally extremely high, as expected in patients presenting to hospital with acute decompensated heart failure, with a median BNP of 749 pg/ml [IQR 424-1424] for the whole cohort. Although the median BNP was higher in the patients who did not participate in the whole study and complete PROMs than those who did, 888 pg/ml versus 724 pg/ml respectively, this difference did not reach statistical significance.

Another powerful predictor of prognosis in heart failure, amongst other conditions, is troponin. Over half of all participants had detectable troponin on admission to hospital.[238-240] This was often at very low levels, with a median level of 0.04 µg/L (IQR 0.02-0.12). Although troponin is often associated with myocardial ischaemia and infarction, the levels seen in this cohort were much lower than would normally be seen when ischaemia is the main driver for admission. Chronic troponin leak is often seen in heart failure, particularly in the acute setting. Patients with extremely high troponin levels (> 1.0 µg/L) and a history or ECG consistent with ischaemia were excluded as per the inclusion / exclusion criteria.

Although sodium levels were within the normal range for most participants (normal range 136 -145 mmol/L) with a median level of 138 mmol/L, one quarter of all participants were hyopnatraemic with a level of 135 mmol/L or less. Hyponatraemia is the most common electrolyte abnormality in acute decompensated heart failure, with a number of pathophysiological processes identified.[241] These processes in heart failure can broadly be divided into dilutional and depletional hyponatraemia. Hyponatraemia is associated with worse outcomes including all-cause mortality in patients admitted to hospital with heart failure.[242] Impaired renal function is an independent prognostic marker in heart failure, both in patients with reduced and preserved ejection fraction.[243] Renal function was abnormal (estimated glomerular filtration rate [eGFR] < 60 mL/ min/ 1.73m^2) in 185 (59%) participants on admission blood testing. One quarter of the whole cohort had at least moderately impaired renal function assessed by eGFR. Liver function tended to be within the normal range for the whole population, and although there were statistically significant differences between those completing the PROMs and those who did not, median results for these values (and inter-quartile ranges) were within normal limits. Thyroid stimulating hormone levels were similar between those completing

PROMs and those who did not, however, there was a higher proportion of patients with low free T4 in the group completing PROMs. The significance of this is uncertain, as a recent analysis of a large randomised controlled trial data set has shown that thyroid status is not an independent predictor of outcome (all-cause mortality).[244] Serum Albumin levels were generally low in many patients with 50% of total participants having levels on or below the lower reference limit for serum albumin (reference range 35-50 g/l). Hyopalbuminaemia is common in heart failure with a prevalence of approximately 25%, and is associated with worse outcomes.[245-247] The cause of low albumin in acute heart failure is multifactorial, potentially reflecting a chronic disease state, advanced heart failure, or dilutional component secondary to volume overload.

Not only is diabetes an important, independent predictor of prognosis in heart failure, but so is HBA1c, even when not at diagnostic levels.[248] Many patients in this cohort had abnormal random serum glucose on presentation, with 50% of all participants having a random glucose of at least 6.5 mmol/l. HBA1c was also elevated in many patients and into the diagnostic range for diabetes in at least 25% of participants. Although there was a statistically significant difference (p= 0.032) between those participating in the whole study and those who did not, this likely reflects that only 14 (33%) of those who did not complete PROMs had HBA1c available, compared to 238 (88%) in the group who completed PROMs. This discrepancy was due to the two staged consent process, in which consent to draw additional blood samples was given. The high prevalence of abnormal random serum glucose and HBA1c are to be expected given the high prevalence of diabetes in heart failure in general and specifically this cohort.

Anaemia is an important and common co-morbidity in heart failure, and is an independent predictor of adverse outcomes.[249] Anaemia is multi-factorial in heart failure, with anaemia of chronic disease thought to play an important role. An analysis of the CHARM Program revealed a prevalence of anaemia of 25%, with similar prevalence between both HF-PEF and HF-REF phenotypes.[249] The median haemoglobin was 121 g/L (IQR 107-136). There were no significant differences between the group of patients who completed the whole study and those who did not.

Table 4-7 Laboratory results

	All participants n = 313	Completed PROMS n =272	Did not complete PROMS n = 41	p
Biochemistry				
BNP level (pg/ml)	749 [424, 1424]	724 [420, 1405]	888 [481, 1635]	0.333
TnI (ug/l)	0.04 [0.02, 0.12]	0.04 [0.02, 0.12]	0.05 [0.02, 0.09]	0.704
TnI ≥ 0.04 ug/L - n(%)	149 (50.5)	130 (50.0)	19 (54.3)	0.753
Sodium (mmol/l)	138 [135, 140]	138 [135, 140]	139 [137, 141]	0.108
Potassium (mmol/l)	4.2 [3.8, 4.6]	4.2 [3.8, 4.6]	4.2 [3.9, 4.6]	0.643
Chloride (mmol/l)	104 [99, 106]	103 [99, 106]	104 [100, 107]	0.580
Urea (mmol/l)	8.6 [6.4, 12.4]	8.5 [6.4, 12.4]	9.0 [6.5, 13.2]	0.589
Creatinine (umol/l)	99 [73, 133]	99 [73, 136]	101 [79, 120]	0.985
eGFR (ml/min/1.73 m^2)	59 [41, 80]	62 [40, 82]	57 [45, 68]	0.347
eGFR <= 60 ml/ min/1.73 m^2 - n(%)	185 (59.1)	159 (58.5)	26 (63.4)	0.611
Bilirubin (mmol/l)	15 [10, 23]	16 [10, 23]	13 [8, 21]	**0.044**
AST (mmol/l)	24 [18, 34]	24 [18, 34]	22 [17, 29]	0.228
ALT (mmol/l)	19 [13, 34]	20 [13, 36]	17 [11, 23]	**0.046**
Alk Phos (mmol/l)	95 [73, 127]	99 [76, 128]	82 [68, 112]	**0.047**
Albumin (g/l)	34 [31, 36]	34 [31, 36]	34 [31, 36]	0.967
TSH (mU/l)	1.55 [0.95, 2.60]	1.60 [0.94, 2.60]	1.49 [1.11, 2.08]	0.890
T4 (pmol/L)	14.00 [0.24, 16.00]	14.00 [0.19, 16.00]	15.50 [13.00, 16.90]	**0.006**
Urate (mmol/l)	0.51 [0.41, 0.65]	0.51 [0.41, 0.65]	0.49 [0.44, 0.64]	0.877
Glucose (mmol/l)	6.5 [5.6, 8.3]	6.5 [5.6, 8.3]	6.5 [5.3, 7.7]	0.424
Haematology				
Haemoglobin (g/L)	121 [107, 136]	122 [109, 136]	119 [103, 127]	0.120
WCC (x10/l)	8.1 [6.5, 10.6]	8.1 [6.4, 10.6]	8.3 [6.6, 10.7]	0.539
HbA1c (mmol/mol)	41 [38, 50]	41 [38, 48]	54 [40, 61]	**0.032**
MCV (fl)	91.0 [86.0, 95.6]	90.9 [86.1, 95.5]	92.1 [85.6, 96.6]	0.692
Platelets (x10)	216 [166, 270]	216 [164, 273]	222 [186, 250]	0.798
Lymphocytes (x10/l)	1.20 [0.85, 1.60]	1.20 [0.83, 1.60]	1.30 [0.92, 1.70]	0.252

Values are expressed as median [interquartile range] unless specified.

ALT= alanine aminotransferase ; AST= aspirate aminotransferase; eGFR= estimated glomerular filtration rate; HbA1c= haemoglobin A1c; MCV= mean corpuscular volume; BNP= Brain-Type natriuretic peptide; TnI= troponin I; TSH= thyroid stimulating hormone.

Echocardiography

I performed a detailed echocardiogram in every participant to confirm the diagnosis of heart failure. The protocol for the echocardiogram is detailed Table 3-1. In summary, detailed measurements based on standard echocardiographic views were performed to provide a systematic evaluation of left and right ventricular structure and function, valve structure and function, left and right atrial size, and left ventricular diastolic function. A summary of the key echocardiographic findings are detailed in Table 4-8. Overall, there were multiple abnormalities noted on echocardiography examination. This is entirely expected as abnormality of left ventricular systolic and or diastolic function is required to make the diagnosis of heart failure.[3]

Left ventricular systolic function is most commonly quantified by measuring ejection fraction, as described in chapter 3. Ejection fraction is calculated using the modified Simpson's Biplane method, which requires visualisation of the endocardial border in systole and diastole, in both apical four and two chamber views. This was attempted in every patient, however, due to body habitus, or poor acoustic window, a formal ejection fraction was possible in 245 (78%) of participants. The remainder of ejection fractions were estimated. The mean ejection fraction for the cohort was 39% (±16.55). When using the ESC definition of HF-PEF as ≥ 50%, 104 (33%) patients were in this category. This is much lower than the 50% of cases often quoted in the literature, although this is in keeping with the proportion of these patients that are seen in the catchment area from which the cohort was recruited.[59, 60] A similar proportion of HF-PEF was found in a previous study of near-consecutive patients with admitted to hospital in Glasgow.[250]

Table 4-8 Echocardiography

	All participants n = 313	Completed PROMS n =272	Did not complete PROMS n = 41	p
LV structure				
LViDDi, cm/m^2	2.97 ±0.56	2.96 ±0.56	2.98 ±0.54	0.829
LViSDi, cm/m^2	2 ±1	2 ±1	2 ±1	0.852
LVDVi, ml/m^2	74 ±31	75 ±32	67 ±27	0.216
LVSVi, ml/m^2	48 ±30	49 ±31	43 ±25	0.284
LV mass index, mg/ m^2	118 ±38	119 ±37	109 ±46	0.216
LV systolic function				
LVEF biplane assessment	245 (78.3)	218 (80.1)	27 (65.9)	**0.044**
LVEF estimated	68 (21.7)	54 (19.9)	14 (34.1)	**0.044**
LVEF, %	39.93 ±16.55	39.63 ±16.55	41.98 ±16.55	0.397
HF-PEF	104 (33.2)	89 (32.7)	15 (36.6)	0.722
S-Lateral, m/s	5.58 ±1.96	5.54 ±1.99	5.84 ±1.71	0.401
LV diastolic function				
E, m/s	1.05 ±0.35	1.05 ±0.34	1.05 ±0.41	0.926
a, m/s	0.75 ±0.35	0.73 ±0.34	0.91 ±0.37	0.053
E/a ratio	1.65 ±1.11	1.69 ±1.12	1.41 ±1.08	0.346
E'-Lateral, m/s	0.08 ±0.05	0.08 ±0.05	0.07 ±0.03	0.160
E'-Septal, m/s	0.05 ±0.05	0.06 ±0.05	0.05 ±0.02	0.498
E'-Average, m/s	0.07 ±0.07	0.07 ±0.08	0.06 ±0.02	0.117
E/E', cm/s	17.61 ±7.79	17.45 ±7.57	18.80 ±9.29	0.337
DT, ms	196.6 ±77.38	194.1 ±72.94	212.8 ±101.3	0. 271
LAVi, ml/m^2	57 ±19	57 ±18	62 ±24	0.210
RV structure/ function				
RViDD, cm	3.54 ±0.74	3.53 ±0.72	3.57 ±0.83	0.349
TV Peak Gradient, ms	2.86 ±0.57	2.85 ±0.57	2.96 ±0.58	0.852
RV Systolic Pressure, mmHg	48.47 ±14.73	48.29 ±14.34	49.63 ±17.21	0.622
IVC Diameter, mm	2.22 ±0.57	2.24 ±0.56	2.12 ±0.58	0.457
TAPSE, mm	18 ±6	18 ±6	17 ±5	0.629
RA Volume, ml	23 ±8	23 ±8	22 ±8	0.168
Valvular disease				
Valve disease	266 (85.0)	228 (83.8)	38 (92.7)	0.165
Significant Valve Disease*	74 (23.6)	65 (23.9)	9 (22.0)	1.000
Significant TR[§]	23 (7.3)	21 (7.7)	2 (4.9)	0.751

Continuous variables are expressed as mean ± standard deviation unless specified, categorical variables are expressed as n (%).
DT = deceleration time; HF-PEF= heart failure with preserved ejection fraction; IVC = inferior vena cava; LAV ; left atrial volume index; LV = left ventricle; LVEF ; left ventricular ejection fraction; LViDDi= left ventricular internal diastolic dimension indexed; LVDVi = left ventricular diastolic volume indexed; LVISDi= left ventricular internal systolic dimension indexed; LVSVi = left ventricular systolic volume indexed; RV = right ventricle; RViDD= right ventricular internal diameter diastole; TAPSE = tricuspid annular plane systolic excursion; TV= tricuspid valve;
* Defined as ≥ moderate-severe left sided valve disease.
[§] defined as ≥ moderate-severe left tricuspid regurgitation.

Mean left ventricular size, assessed by measuring left ventricular internal diameter in diastole, was at the upper limit of normal, when indexed for body surface area, at 2.97 (±0.56) cm/m^2 (normal range 2.2-3.1 cm/m^2). Similar findings were found when measuring left ventricular size by different methods, such as left ventricular internal diameter in systole, left ventricular diastolic and systolic volumes, all adjusted for body surface area, Table 4-8. As described in chapter 1, in heart failure, whether there is impaired ejection fraction and increased left ventricular volume or preserved ejection fraction with reduced ventricular volume, there is usually increased left ventricular mass as a result of pathological remodelling of the ventricle with either concentric or eccentric remodelling. This was clearly shown in the patients studied with a mean left ventricular mass (adjusted for body surface area) of 118 g/m^2 (normal range 50-102 g/m^2). The two broad phenotypes of heart failure, HF-REF and HF-PEF, are clearly demonstrated in Table 4-9. Patients with HF-REF had larger ventricle sizes and volumes, when adjusted for body surface area. Mean left ventricular diastolic volume index was 84 ml/m^2 in patients with HF-REF compared to 49 ml/m^2 in patient with HF-PEF (normal range 35-75 ml/m^2). Left ventricular mass was also higher in patients with HF-REF compared to HF-PEF at 122 (±39) and 109 (±37) g/m^2 respectively.

Features of diastolic impairment were present in most patients. Mean left atrial volume, indexed for body surface area, was severely enlarged at 57 (±19) ml/m^2, with no significant difference between patients with HF-PEF and HF-REF. E/E', which, when elevated >15, is associated with increased pulmonary capillary wedge pressures and elevated left ventricular end diastolic pressures. This metric implies high filling pressure of the left ventricle. Mean E/E' was markedly elevated with a mean of 17.61 (± 7.79), with no significant difference between patients with HF-PEF or HF-REF, or between those who completed the whole study or not.

Right ventricular size was mildly enlarged, mean right ventricular internal diameter in diastole 3.54 (±0.74) cm. Other common features included dilated inferior vena cava, right atrial enlargement, and moderately elevated right ventricular systolic pressure (mean 49 ±15 mmHg). Right ventricular systolic function overall was preserved as measured by tricuspid annular plane systolic excursion (TAPSE), although those with HF-REF had lower TAPSE at 16 (±5) mm

versus 21 (±6) mm in those with HF-PEF. There were no differences in right ventricular size and function between those who participated in the whole study and those who did not.

A large proportion of participants had valve disease detected during echocardiography. 74 (24%) of participants had significant left sided valve disease, defined as ≥ moderate-severe left sided valve disease. There was no difference between those participating in the whole study and those who did not. There was a higher proportion of patients with significant left sided valve disease in the HF-PEF group.

Table 4-9 Echocardiography by ejection fraction

	All participants n = 313	EF < 50% n =209	EF ≥ 50% n = 104	p
LV structure				
LViDDi, cm/m^2	2.97 ±0.56	3.14 ±0.53	2.60 ±0.44	**< 0.001**
LViSDi, cm/m^2	2 ±1	3 ±1	2 ±0	**< 0.001**
LVDVi, ml/m^2	74 ±31	84 ±30	49 ±18	**< 0.001**
LVSVi, ml/m^2	48 ±30	61 ±28	20 ±9	**< 0.001**
LV mass index, mg/ m^2	118 ±38	122 ±39	109 ±37	**0.019**
LV systolic function				
LVEF biplane assessment	245 (78.3)	171 (81.8)	74 (71.2)	**0.032**
LVEF estimated	68 (21.7)	38 (18.2)	30 (28.8)	**0.032**
LVEF, %	39.93 ±16.55	30.12 ±9.66	59.65 ±7.29	**< 0.001**
S-Lateral, m/s	5.58 ±1.96	4.94 ±1.63	6.83 ±1.95	**< 0.001**
LV diastolic function				
E, m/s	1.05 ±0.35	0.96 ±0.29	1.22 ±0.38	**< 0.001**
a, m/s	0.75 ±0.35	0.69 ±0.32	0.87 ±0.37	**0.007**
E/a ratio	1.65 ±1.11	1.67 ±1.20	1.62 ±0.92	0.811
E'-Lateral, m/s	0.08 ±0.05	0.08 ±0.06	0.09 ±0.03	0.061
E'-Septal, m/s	0.05 ±0.05	0.05 ±0.05	0.06 ±0.02	**0.020**
E'-Average, m/s	0.07 ±0.07	0.07 ±0.09	0.08 ±0.02	0.351
E/E', cm/s	17.61 ±7.79	17.70 ±7.58	17.45 ±8.22	0.793
DT, ms	196.6 ±77.38	184.2 ±66.75	220.0 ±90.08	**< 0.001**
LAVi, ml/m^2	57 ±19	56 ±18	60 ±20	0.149
RV structure/ function				
RViDD, cm	3.54 ±0.74	3.56 ±0.72	3.49 ±0.77	0.430
TV Peak Gradient, ms	2.86 ±0.57	2.79 ±0.53	3.02 ±0.62	**0.002**
RV Systolic Pressure, mmHg	48.47 ±14.73	46.65 ±13.34	52.26 ±16.73	**0.005**
IVC Diameter, mm	2.22 ±0.57	2.24 ±0.58	2.18 ±0.55	0.475
TAPSE, mm	18 ±6	16 ±5	21 ±6	**< 0.001**
RA Volume, ml	23 ±8	23 ±8	24 ±7	0.157
Valvular disease				
Valve disease	266 (85.0)	175 (83.7)	91 (87.5)	0.381
Significant Valve Disease*	74 (23.6)	41 (19.6)	33 (31.7)	**0.018**
Significant TR[§]	23 (7.3)	13 (6.2)	10 (9.6)	0.282

Continuous variables are expressed as mean ± standard deviation unless specified, categorical variables are expressed as n (%).
DT = deceleration time; IVC = inferior vena cava; LAV ; left atrial volume index; LV = left ventricle; LVEF ; left ventricular ejection fraction; LViDDi= left ventricular internal diastolic dimension indexed; LVDVi = left ventricular diastolic volume indexed; LVISDi= left ventricular internal systolic dimension indexed; LVSVi = left ventricular systolic volume indexed; RV = right ventricle; RViDD= right ventricular internal diameter diastole; TAPSE = tricuspid annular plane systolic excursion; TV= tricuspid valve;
* Defined as ≥ moderate-severe left sided valve disease.
[§] defined as ≥ moderate-severe left tricuspid regurgitation.

4.2.6 Summary

I believe the cohort studied has a number of strengths. Firstly, and most importantly, it is a generalisable cohort. I believe this is a generalisable cohort as I tried to eliminate selection bias wherever possible. I recruited prospectively, and approached consecutive admissions of suspected heart failure. A further strength of this study is the robustness of the diagnosis of heart failure. I adhered to the most current guidelines available when deciding whether a patient met the inclusion criteria for the study. I used natriuretic peptide to screen and excluded patients with low natriuretic peptides. I also used detailed echocardiography, in accordance with the most up to date guidelines to confirm the presence of a structural or functional abnormality in keeping with the diagnosis of heart failure. I also had access to ECG and CXRs for almost every potential patient, further aiding the diagnosis. Although, as anticipated, some patients declined to participate in the full study and complete PROMs and attend follow-up visits, the proportion of such patients was relatively small (13.1%). The main differences between those who participated in the whole study and those who did not were in age and body mass index. Those who declined to participate in the PROMs and follow-up part of the study were older, median age 84.2 versus 76.0 ($p < 0.001$), and had a lower body mass index, 24.0 versus 27.0 kg/m. This would perhaps suggest that those patients who did not participate in the whole study were more elderly and frail. There were very few statistically significant differences between those who did and did not participate in the full study and completed the PROMs, in terms of echocardiographic, ECG, CXR, clinical examination findings, past medical history, or drug history. This suggests that the cohort completing PROMs is representative of patients admitted to hospital with heart failure.

An important test of generalisability would be to make comparisons between this cohort and other cohorts of patients hospitalised with a primary diagnosis of heart failure. When comparing to one of the largest heart failure cohorts, the American Get With The Guidelines (GWTG) cohort, which reported on the characteristics of over 110 000 consecutive patients admitted to hospitals across the United States of America between 2005 and 2010.[251] The cohort recruited in my study was very similar to the GWTG cohort in terms of age (median age 77

and 74, respectively) and sex (49 and 47% female sex respectively). Similarly high proportions of co-morbidities were seen in both cohorts, particularly hypertension, coronary artery disease, cerebrovascular disease, and diabetes. One notable difference was the ethnicity of patients, with the 97% being of white ethnicity in my cohort compared to 66% in the GWTG cohort. However, this reflects the demographics of the local population which the Western Infirmary, Glasgow, served. There were similarities in key objective, markers of disease severity, namely natriuretic peptides and ejection fraction. Median (IQR) BNP levels were similar between the GWTG and my cohort at 749 (424-1424) and 821 (386-1690) pg/ml, respectively. Regarding the two broad phenotypes found in heart failure based on ejection fraction, HF-REF and HF-PEF, key similarities were again seen between these cohorts. The median (IQR) ejection fraction in the GWTG cohort was 40 (25-55) %, compared to 38 (26-54)%. A very similar proportion of patients were classified as HF-PEF in both the GWTG and my cohort, at 36 and 33%, respectively. Another important cohort to make comparisons with comprised 1003 near-consecutive patients admitted to hospital with a primary diagnosis of heart failure, from three local hospitals (Glasgow Royal Infirmary, Glasgow Western Infirmary, and Royal Alexandria Hospital).[250] This study prospectively enrolled patients admitted to hospital between 2006 and 2009, and utilised natriuretic peptides to screen for eligibility. Of these 1003 patients, a further 648 went on to have microvolt T-wave alternans testing and were described in detail. My cohort and this cohort showed very similar prevalence of co-morbidities. Mean ejection fraction (± SD) was similar again between this and my cohort at 40.2 (12.2) and 39.9 (16.6), respectively.

Use of disease modifying therapy is an important metric in this study, as these medications could improve life expectancy and quality of life, both of which are key components when assessing the potential PC needs of any population. High proportions of patient were started or continued on disease modifying therapies, namely ACEi/ ARB,beta-blocker or MRA. Overall, 70, 69 and 32 % of participants in this study were started on ACEi/ARB, beta-blocker and MRA, respectively. The proportion of patients with HF-REF, that is, the patients who would benefit most from these therapies, was much higher. 79, 70, and 40 % of participants were started on ACEi/ARB, beta-blocker, or MRA. These proportions compare

favourably with patients with a reduced ejection fraction (<40%) in the GWTG cohort, with 74, 87, and 26 % taking ACEI/ARB, beta-blockers, or MRA respectively. Overall, the patients in my cohort were started on high proportions of disease modifying therapy.

In summary, the cohort studied had limited selection bias as it was near-consecutive and prospective. The cohort is highly generalisable for this reason, and this is confirmed by the consistencies seen with other large cohorts of hospitalised heart failure cohorts. This cohort also benefits from a very rigorous screening process, in which the definition of heart failure was adhered to stringently, and natriuretic peptides and echocardiography were used to make the diagnosis, therefore, I can say with confidence that all patients in the study met the ESC definition of heart failure.[3] Furthermore, the cohort was treated very well, with a very high proportion of participants being started or continued on disease modifying therapies, which is crucially important when assessing if a patient has PC needs.

Chapter 5 Results- Baseline Patient reported outcome measures

In this chapter I will report the findings from the PROMs used, namely the HADS, the KCCQ, the ESAS, and the SF-12 questionnaires. I will also report the caregiver burden questionnaire, the Zarit Burden Interview. All of these PROMs were given, in the form of a pack of questionnaires (appendix 4), to each participant who agreed to take part in the whole study. Each participant was encouraged to complete the questionnaire pack without any assistance from anyone else. If a participant had visual problems such that they could not read the questionnaires, then these were read out by a study nurse, with particular attending being paid to reduce any attempt to influence the participant. This was only necessary for a minority of participants. Participants were given 24 hours to complete the questionnaire pack. Questionnaires were administered at the beginning of the admission to hospital, at the time of consent. The median [IQR] time from admission to recruitment for those completing questionnaires was 2 [2-4] days.

5.1 Hospital Anxiety and Depression Scale

The HADS is a 14 point, 7 anxiety and 7 depression, screening questionnaire designed to be completed by patients. The HADS generates two summary scores, one for depression and one for anxiety. These scores can then be used to categorise patients into potential severity of depression and anxiety (mild, moderate, and severe).

HADS- anxiety

263 participants completed all of the questions in the HADS anxiety questionnaire. The questions and distribution of responses at baseline for the anxiety component of the HADS questionnaire are shown in Figure 5-1. All of the questions in HADS have four potential answers, from which the patient picks the answer which is most appropriate for them. For the question "I get sudden feelings of panic", most participants responded either "not at all" or "not very often", with 109 (40.5%) and 87 (32.3%), respectively. 46 (20.8%) and 17 (6.3%) of participants responded that they experience sudden feelings of panic "quite

often" and "very often indeed", respectively. A similar distribution of responses were reported to the question "I feel restless as if I have to be on the move", with 71 (26.1%) and 23 (8.5%) experiencing reporting this symptom "quite a lot" and "very much indeed", respectively.

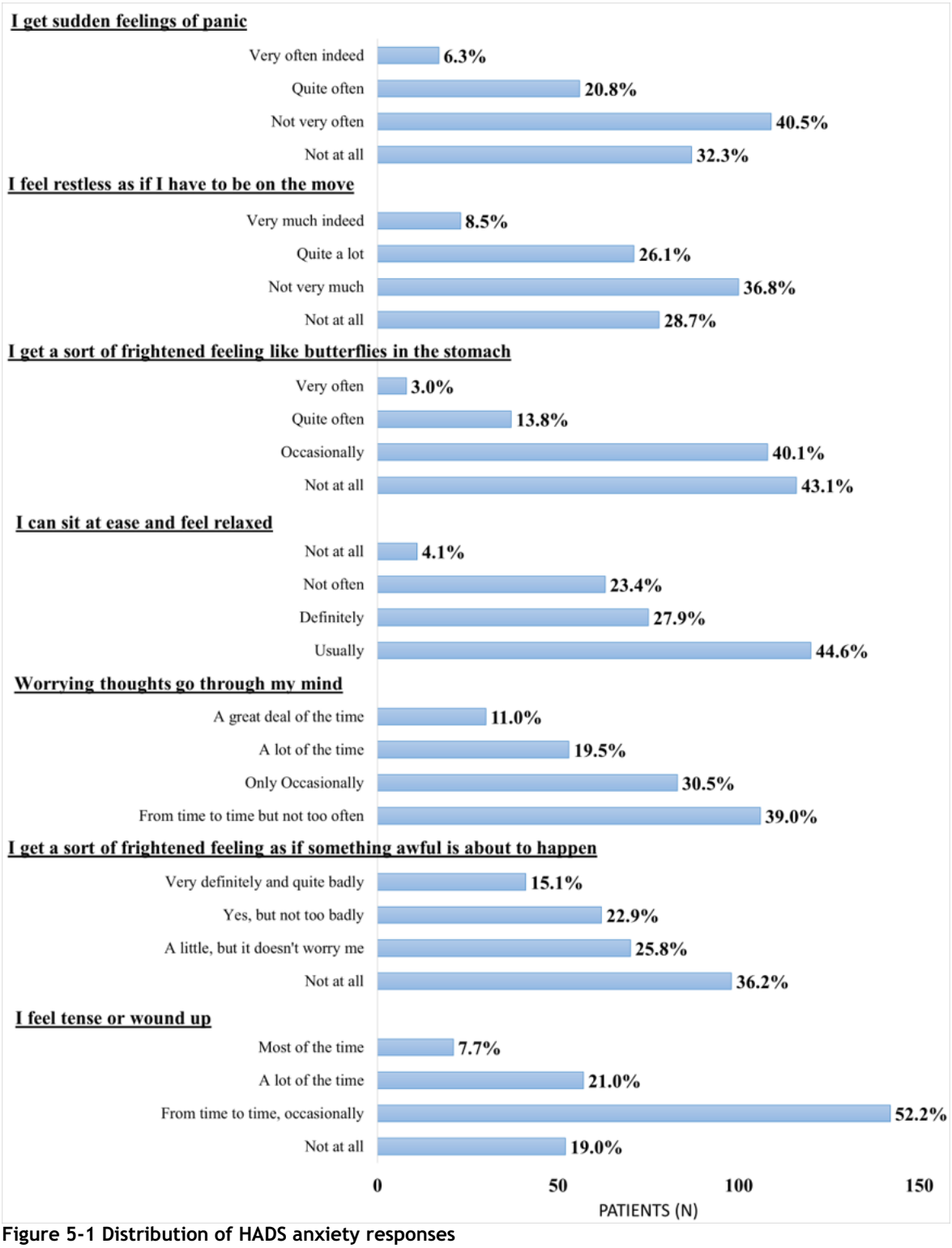


Figure 5-1 Distribution of HADS anxiety responses

A higher proportion of participants reported minimal frequency for the symptom "I get a sort of frightened feeling like butterflies in the stomach", with 83.2% reporting these symptoms either only "occasionally" or "not at all". 195 (72.5%) of participants answered "I can sit at rest and feel relaxed" "usually" or "definitely". With 74 (27.5%) reporting being able to sit at rest and feel relaxed "not often" or "not at all". A high proportion reported "worrying thoughts go through my mind" "a lot of the time" or "a great deal of the time", at 53 (19.5%) and 30 (11.0%, respectively. 103 (38.0%) reported feeling "I get a sort of frightened as if something awful is about to happen" either "yes, but not too badly" or "very definitely and quite badly". 168 (62.0%) reported experiencing this symptom either "a little, but it doesn't worry me" or "not at all". 78 (28.7%) of participants reported feeling "tense or wound up" "a lot of the time" or "most of the time", with 142 (52.2%) reporting this symptom "from time to time, occasionally", and 52 (19.1%) "not at all". Overall, most questions had a similar distribution of responses regarding proportion of participants who had moderate or severe frequency, with roughly between one quarter and one third of participants. The exception was to the symptom "I get a sort of frightened feeling like butterflies in the stomach", where only 16.8% reported moderate/severe frequency.

HADS- Depression

267 participants completed all of the questions in the HADS depression questionnaire. The questions and distribution of responses to the depression component of the HADS questionnaire are detailed in Figure 5-2. 183 (68.5%) of participants reported "I still enjoy the things I used to enjoy" "not quite so much) or "definitely as much", with 85 (31.5%) reporting "only a little" or "not at all". Most participants in the study felt they had retained their sense of humour, with 57% reporting they could "laugh and see the funny side of things" "as much as I always could", and 31.3% "not quite so much now". Most participants described feeling cheerful, with 234 (86%) reporting "I feel cheerful" "sometimes" or "most of the time". Most participants reported moderate- severe impairment in response to the statement "I feel as if I have slowed down", with 262 (96.7%) reporting having slowed down to some degree, and most feeling slowed down "nearly all the time" or "very often". Although

this question could reflect a somatisation of depression or depressive symptoms, physical symptom burden from heart failure could also contribute to the high burden reported. Just over a quarter (26.9%) of participants reported "I have lost interest in my appearance" "definitely as much now" or "I don't take as much care". A further 28.4% of participants reported mild impairment to this question. Only 99 (33.5%) of participants reported optimism for the future, reporting "I look forward with enjoyment to things" "as much as I ever did". 82 (30.1%) responded to this question with either "definitely less than I used to" or "hardly at all". However, most participants did appear to get enjoyment from common leisure activities, with most reporting "I can enjoy a good book or radio or TV program" "often" or "sometimes", with 178 (65.7%) and 60 (22.1%), respectively.

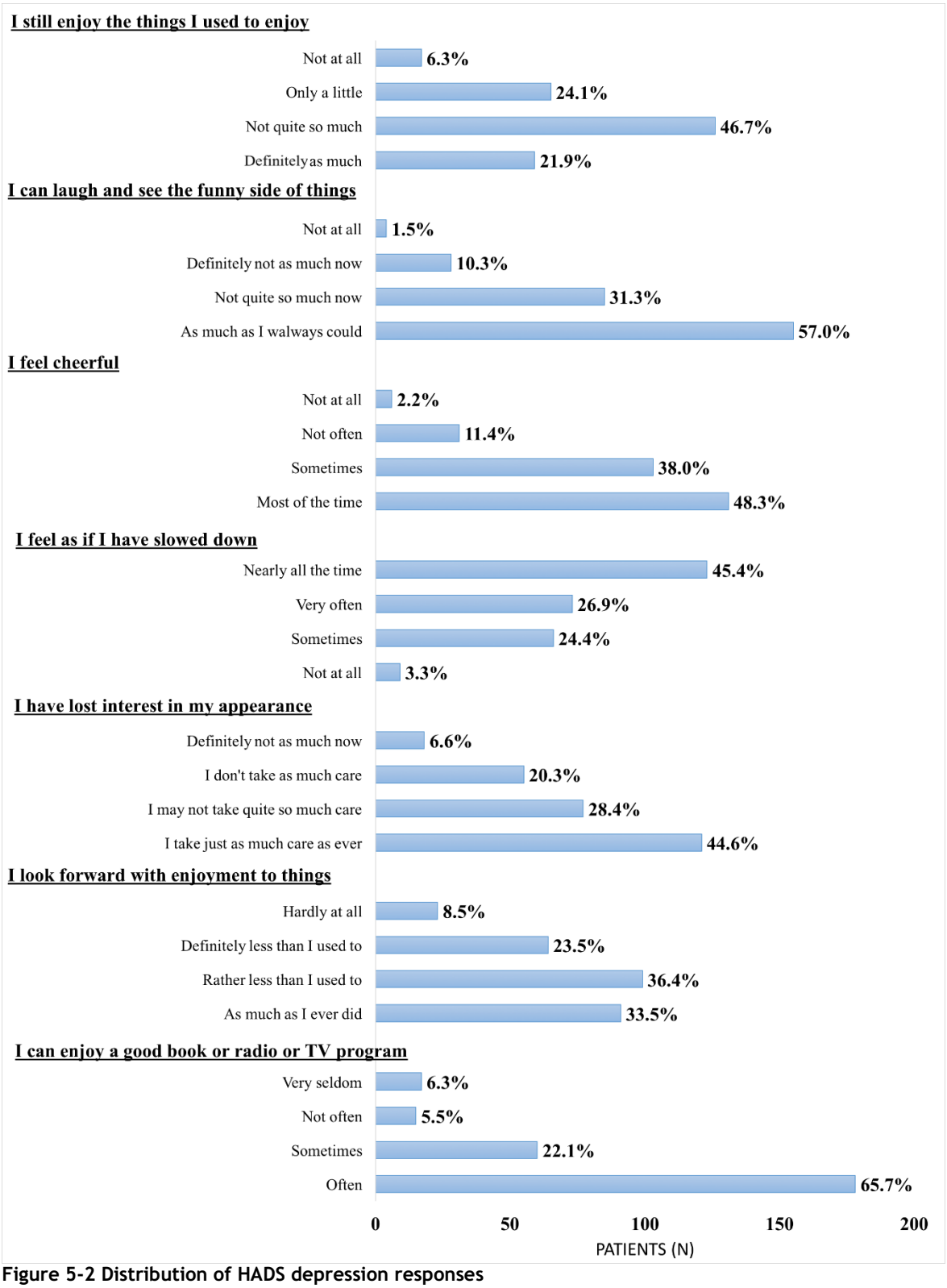


Figure 5-2 Distribution of HADS depression responses

HADS summary scores

Both HADS-Anxiety and HADS-Depression questionnaires generate a summary score, which is perhaps easier to understand and compare to other cohorts of patients. Each question has a range of responses from 0-3, with a total for both subscales being 21, with a minimum score 0. The test's authors suggest a score of 8-10 is indicative of mild cases of anxiety or depression, 11-15 moderate, and >16 suggests severe.[203] The distribution of scores for both anxiety and depression are shown in Figure 5-3 and Figure 5-4, respectively. The range for the HADS anxiety summary score was 0-21, with the mean (SD) and median [IQR] being 7.33 (4.76) and 7.00 [4-11], respectively. The range for the HADS depression summary score was 0-21 again, with the mean (SD) and median [IQR] being 7.02 (4.17) and 7.00 [4-10], respectively. As seen in Figure 5-3 and Figure 5-4, neither score was normally distributed, but positively skewed, with most participants having lower scores. The proportion of participants with none/mild, moderate and severe anxiety and depression summary scores is shown in Figure 5-15. 74.5 and 81.6% of participants scored in the none/ mild category for anxiety and depression, respectively. 19.0 and 14.6% scored in the moderate category for anxiety and depression, respectively. Only 17 (6.5%) and 10 (3.7%) participants scored in the severe mood disturbance range for anxiety and depression, respectively.

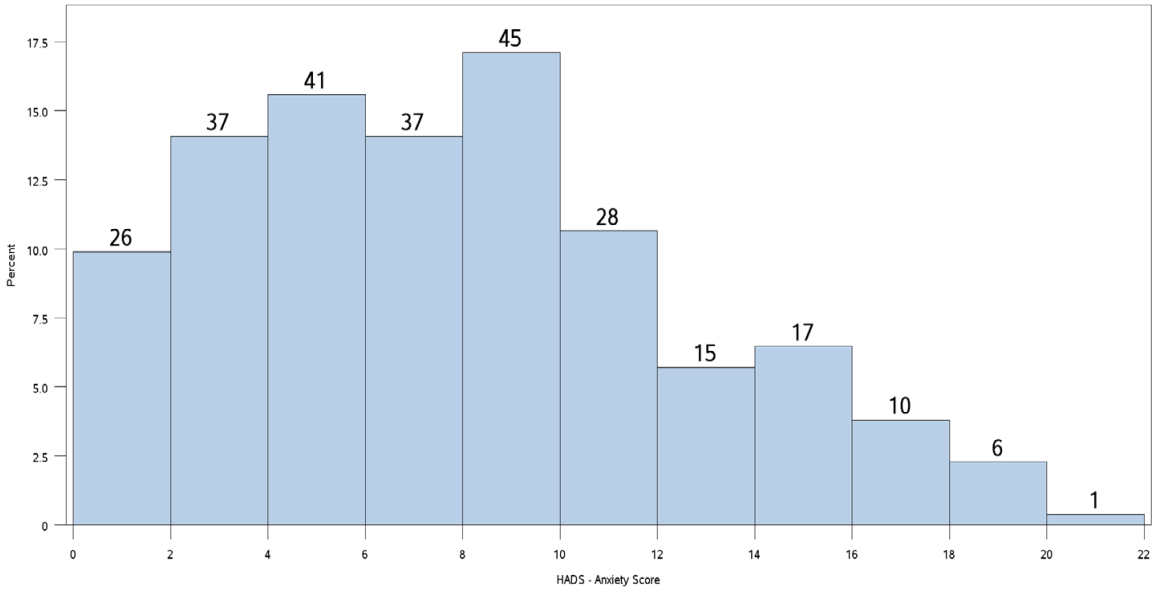


Figure 5-3 Histogram of total anxiety score

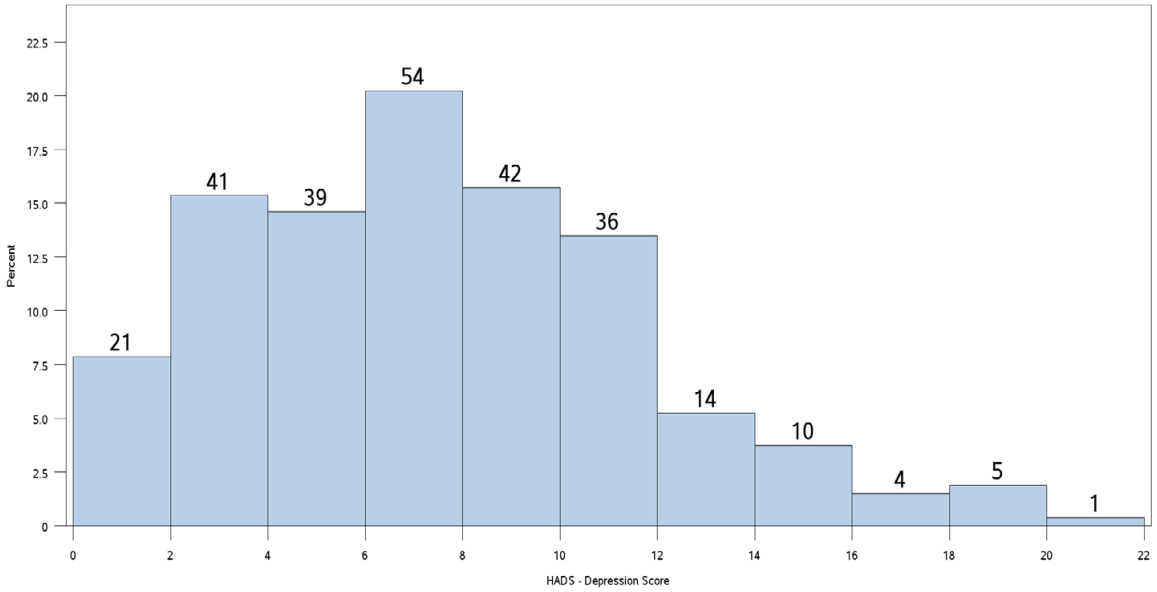


Figure 5-4 Histogram of total depression score

Comparison of selected baseline characteristics, per severity group, for both HADS Anxiety and Depression summary scores are shown in Table 5-1 and Table 5-2, respectively. Patients in the moderate or severe categories for HADS-Anxiety were more likely to be younger ($p<0.001$). A similar trend was seen regarding the HADS Depression, with patients in the moderate or severe groups being younger ($p=0.0253$). There were very few differences between the three groups of HADS Anxiety severity in terms of past medical history, examination findings, sex, echocardiographic or laboratory findings. Notable exceptions included NYHA class, with higher proportions of participants being NYHA class III/IV in the moderate or severe groups ($p=0.024$). There was a trend, albeit not

statistically significant, for patients with lower ejection fraction to have higher HADS-Anxiety scores. Patients in the severe group of HADS-Anxiety had larger ventricles, as measured by left ventricular internal diameter in diastole and adjusted for body surface area. Median scores for all of the other PROMs were worse in patients in the severe HADS-Anxiety group.

Unsurprisingly, there was a statistically significant higher proportion of participants with a past medical history of depression in the severe versus moderate, versus none/mild groups (p 0.0004). Other baseline characteristics were similar between the three groups of HADS-Depression severity. There were no differences in known markers of prognosis at baselines, such as B-type natriuretic peptide level, ejection fraction, left ventricular size, or NYHA classification. Similar to HADS-Anxiety groups, participants in higher severity groups of HADS-Depression had worse median scores for all other PROMs. The only was the mean SF12-Physical summary score, where there was no statistically significant difference between the groups of HADS-Depression severity.

Table 5-1 Baseline demographics per HADS Anxiety severity group

	None/ mild n=196	Moderate n=50	Severe n=17	p
Age- yr	76.53 ± 10.16	69.95 ± 10.16	70.86 ± 11.88	**<0.0001**
Female sex- n (%)	90 (45.9)	23 (46.0)	10 (58.8)	0.5883
Systolic blood pressure- mmHg	137.08 ± 28.95	140.22 ± 22.31	132.12 ± 23.65	0.5586
Heart rate- beats/min	86.68 ± 24.99	89.41 ± 28.19	89.35 ± 21.87	0.7559
Body-mass index- kg/m	27.67 ± 6.02	29.43 ± 7.55	27.75 ± 10.10	0.2778
Past Medical history- n(%)				
Hypertension	134 (68.4)	31 (62.0)	12 (70.6)	0.6626
Myocardial infarction	74 (37.8)	25 (50.0)	5 (29.4)	0.1941
Atrial fibrillation	111 (56.6)	21 (42.0)	7 (41.2)	0.1099
Diabetes	60 (30.6)	22 (44.0)	6 (35.3)	0.1984
CVA/TIA	41 (20.9)	8 (16.0)	3 (17.6)	0.7192
COPD	42 (21.4)	15 (30.0)	8 (47.1)	0.0398
Depression	21 (10.8)	8 (16.0)	6 (35.3)	0.0149
Symptoms- n (%)				
NYHA functional class				**0.024**
Class I	0 (0.0)	0 (0.0)	0 (0.0)	
Class II	63 (32.1)	13 (26.0)	4 (23.5)	
Class III	103 (52.6)	27 (54.0)	5 (29.4)	
Class IV	30 (15.3)	10 (20.0)	8 (47.1)	
Examination- n (%)				
Elevated JVP (> 4cm)	126 (72.8)	32 (71.1)	11 (73.3)	0.9713
Third Heart Sound	40 (20.5)	11 (22.0)	7 (41.2)	0.1441
Pulmonary crackles	152 (78.4)	39 (78.0)	15 (88.2)	0.6218
Pleural effusion	67 (34.5)	18 (36.0)	8 (50.0)	0.463
Peripheral Oedema	146 (75.3)	41 (82.0)	11 (64.7)	0.3291
Echocardiography				
Ejection fraction, %	39.99 ± 16.75	39.88 ± 16.11	34.76 ± 13.72	0.4522
LVIDD/BSA^2	2.92 ± 0.54	2.91 ± 0.53	3.44 ± 0.66	**<0.001**
LV mass/BSA^2	116.99 ± 38.05	119.20 ± 33.07	143.24 ± 40.13	0.0551
E/e'	17.15 ± 7.52	18.33 ± 8.60	18.18 ± 4.88	0.5954
Laboratory				
Sodium (mmol/l)	138.0 [134.5, 140.0]	137.0 [135.0, 139.0]	138.0 [135.0, 140.0]	0.7934
Urea (mmol/l)	8.9 [6.4, 12.5]	7.7 [6.2, 12.2]	7.8 [7.3, 11.5]	0.5625
Creatinine (umol/l)	101.5 [72.5, 141.5]	91.0 [72.0, 129.0]	92.0 [75.0, 110.0]	0.71
BNP (pg/ml)	738.5 [465.5, 1454.0]	616.5 [287.0, 1001.0]	1192.0 [378.0, 2010.0]	0.0599
Haemoglobin (g/L)	121.0 [109.0, 137.0]	124.0 [109.0, 136.0]	117.0 [102.0, 126.0]	0.5259
PROMS				
HADS-A score	5.11 ± 2.97	12.64 ± 1.52	17.35 ± 1.22	**<0.0001**
HADS-D score	5.69 ± 3.55	10.17 ± 3.06	12.94 ± 4.02	**<0.0001**
KCCQ summary score	39.00 ± 20.94	25.48 ± 16.74	10.00 ± 9.84	**<0.0001**
ESAS summary score	33.79 ± 19.06	51.98 ± 19.87	66.60 ± 20.89	**<0.0001**
SF12-physical score	30.62 ± 9.60	31.19 ± 8.41	24.24 ± 4.29	**0.028**
SF12-mental score	45.37 ± 10.84	33.63 ± 8.83	25.33 ± 8.00	**<0.0001**

Continuous variables are expressed as mean± standard deviation or median [interquartile range], categorical variables are expressed as n (%).
BNP= Brain-Type natriuretic peptide; BSA= body surface area; CVA= cerebrovascular accident; ESAS= Edmonton Symptom Assessment Scale; HADS-A= Hopsital anxiety and depression scale- anxiety; HADS-D= Hospital anxiety and depression scale- depression; JVP= jugular venous pressure; KCCQ= Kansas City Cardiomyopathy Questionnaire; LVIDD = left ventricular internal diameter diastole; NYHA = New York Heart Association; PROMs= patient reported outcome measures; SF12= Short Form 12 questionnaire; TIA = transient ischaemic attach.

Table 5-2 Baseline demographics per HADS Depression severity group

	None/ mild n=218	Moderate n=39	Severe n=10	p
Age- yr	75.83 ± 10.52	72.22 ± 9.14	69.16 ± 9.85	**0.0253**
Female sex- n (%)	106 (48.6)	12 (30.8)	7 (70.0)	**0.0392**
Systolic blood pressure- mmHg	138.22 ± 27.88	136.64 ± 28.56	127.20 ± 26.83	0.4651
Heart rate- beats/min	86.87 ± 25.13	87.03 ± 25.57	100.30 ± 38.70	0.2737
Body-mass index- kg/m	27.69 ± 6.41	29.35 ± 8.36	28.27 ± 5.69	0.3883
Past Medical history- n(%)				
Hypertension	143 (65.6)	30 (76.9)	9 (90.0)	0.1201
Myocardial infarction	84 (38.5)	24 (61.5)	2 (20.0)	**0.0103**
Atrial fibrillation	118 (54.1)	18 (46.2)	6 (60.0)	0.5949
Diabetes	67 (30.7)	18 (46.2)	3 (30.0)	0.1652
CVA/TIA	38 (17.4)	11 (28.2)	3 (30.0)	0.2037
COPD	49 (22.5)	15 (38.5)	4 (40.0)	0.0605
Depression	23 (10.6)	9 (23.1)	5 (50.0)	**0.0004**
Symptoms- n (%)				
NYHA functional class				0.1547
Class I	0 (0.0)	0 (0.0)	0 (0.0)	
Class II	70 (32.)	6 (15.4)	4 (40.0)	
Class III	112 (51.4)	25 (64.1)	3 (30.0)	
Class IV	36 (16.5)	8 (20.5)	3 (30.0)	
Examination- n (%)				
Elevated JVP (> 4cm)	139 (72.4)	26 (74.3)	7 (77.8)	0.9199
Third Heart Sound	45 (20.7)	6 (15.4)	6 (60.0)	**0.0077**
Pulmonary crackles	172 (79.3)	30 (76.9)	6 (66.7)	0.6445
Pleural effusion	79 (36.4)	9 (23.1)	5 (62.5)	0.072
Peripheral Oedema	161 (74.2)	35 (89.7)	7 (77.8)	0.1071
Echocardiography				
Ejection fraction, %	39.64 ± 16.73	39.97 ± 16.42	36.70 ± 15.15	0.8503
LVIDD/BSA^2	2.94 ± 0.54	2.97 ± 0.63	3.32 ± 0.67	0.1156
LV mass/BSA^2	116.86 ± 37.99	130.24 ± 36.66	128.57 ± 25.32	0.1951
E/e'	17.55 ± 7.76	16.99 ± 6.75	15.69 ± 6.06	0.7451
Laboratory				
Sodium (mmol/l)	138.0 [134.0, 140.0]	138.0 [135.0, 140.0]	138.0 [135.0, 139.0]	0.7338
Urea (mmol/l)	8.7 [6.4, 12.6]	8.5 [6.9, 12.2]	8.4 [6.4, 14.2]	0.9577
Creatinine (umol/l)	100.5 [73.0, 140.0]	102.0 [72.0, 133.0]	89.0 [75.0, 110.0]	0.9067
BNP (pg/ml)	735.0 [451.0, 1418.0]	749.0 [254.0, 1268.0]	780.0 [358.0, 3000.0]	0.4042
Haemoglobin (g/L)	121.0 [109.0, 136.0]	124.0 [110.0, 134.0]	120.5 [96.0, 136.0]	0.9019
PROMS				
HADS-A score	6.17 ± 4.00	12.00 ± 4.39	13.50 ± 5.46	**<0.0001**
HADS-D score	5.56 ± 2.85	12.38 ± 1.41	17.90 ± 1.37	**<0.0001**
KCCQ summary score	38.08 ± 20.30	21.91 ± 18.42	8.69 ± 8.11	**<0.0001**
ESAS summary score	35.65 ± 20.06	54.00 ± 16.73	62.61 ± 23.97	**<0.0001**
SF12-physical score	30.81 ± 9.44	29.16 ± 6.71	24.37 ± 6.07	0.0648
SF12-mental score	44.16 ± 11.02	32.87 ± 10.34	23.57 ± 10.12	**<0.0001**

Continuous variables are expressed as mean± standard deviation or median [interquartile range], categorical variables are expressed as n (%). BNP= Brain-Type natriuretic peptide; BSA= body surface area; CVA= cerebrovascular accident; ESAS= Edmonton Symptom Assessment Scale; HADS-A= Hopsital anxiety and depression scale- anxiety; HADS-D= Hospital anxiety and depression scale- depression; JVP= jugular venous pressure; KCCQ= Kansas City Cardiomyopathy Questionnaire; LVIDD = left ventricular internal diameter diastole; NYHA = New York Heart Association; PROMs= patient reported outcome measures; SF12= Short Form 12 questionnaire; TIA = transient ischaemic attach.

Normative data from the United Kingdom are available for comparison.[235] This study administered the HADS questionnaire to a sample of 1792 participants from the general population (978 males, 810 females). The mean HADS anxiety score in this population was 6.14 (±3.76), with a median of 6. The mean HADS depression score was 3.68 (±3.07), with a median of 3. Unsurprisingly, there were higher mean scores for both anxiety and depression in my cohort of patients admitted to hospital because of heart failure. The prevalence of depression has previously been described in heart failure, and the effects of depression on all-cause mortality.[252] This meta-analysis demonstrated a significant influence of depression on all-cause mortality. Although the above review analysed 26 studies with over 80 000 combined patients, the assessment tool for assessment of depression varied, with the most common depression screening tool being the Beck Depression Inventory and the Patient Health Questionnaire. However, the HADS has been used in a number of studies which allows for comparison. A particularly useful comparison is the study by Junger *et al*, of 209 patients with chronic heart failure as this not only provides mean HADS depression and anxiety scores, but also a description of potential severity based on summary scores.[253] The mean total depression score and anxiety scores were 6.4 (± 4.3) and 7.0 (± 4.0), showing similar results to the participants in my study. 30.1% of all participants in the study by Junger *et al* had a HADS depression score of ≥8, and 21.5% had a HADS anxiety score of ≥10. Although the mean total scores in my cohort were similar, a larger proportion of participants had higher scores in the depression sub-scale, with a 25% having a score of ≥10. A similar trend was seen in anxiety scores, with 25% having a score of ≥11. The larger proportion of patients with both higher anxiety and depression scores perhaps reflects my cohort being admitted to hospital rather than a community sample. Overall, prevalence of high scores of depression and anxiety were seen in my cohort when compared to both community heart failure cohorts and normative data.

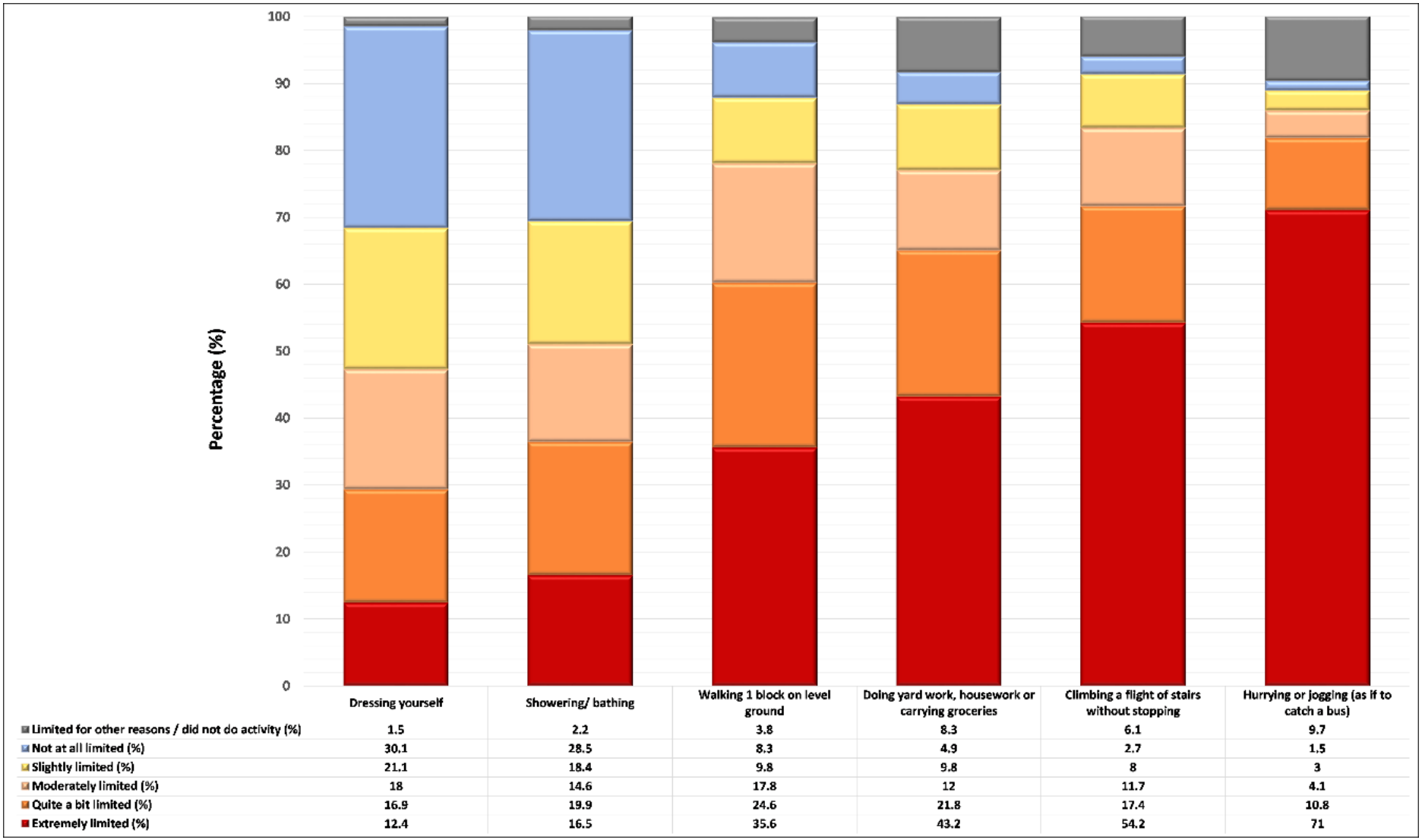
5.2 Kansas City Cardiomyopathy Questionnaire

The KCCQ is a heart failure, disease specific questionnaire which is self-administered by patients.[179] Patients are given instructions to reflect on the preceding two weeks when completing the KCCQ. The KCCQ comprised 23 questions, each of which contributes to a different sub-domains including: Physical Limitations Score; Symptom Stability Score; Symptom Frequency Score; Symptom Burden Score; Self-efficacy Score; Social Limitations Score; and Quality of Life Score. For each sub-domain a score is calculated between 0-100, with higher scores representing better quality of life and lower symptom burden. These sub-domain scores are then used to calculate additional summary scores including: Total Symptom Summary Score, Clinical Summary Score, and an Overall Summary Score. The Total Symptom Summary Score is a combination of Symptom frequency and severity. The Clinical Summary Score combines Physical Limitations Score with Total Symptom Score. The Overall Summary Score combines all domains and represents a mean of Physical Limitation Score, Total Symptom Score, Quality of Life Score, and Social Limitation Score. A detailed description of how to score the KCCQ is provided in appendix 5.

Physical Limitations

The first 6 questions in the KCCQ comprise the Physical Limitations sub-domain. The responses given at the baseline assessment are detailed in Figure 5-5. Patients are asked to reflect on how much their physical symptoms of heart failure (dyspnoea, fatigue, or oedema) have restricted them from doing physical activities. The specific physical activities remarked upon include getting dressed, showering/ bathing, walking one block on flat ground, doing yard work/ housework/ carrying groceries, climbing one flight of stairs without stopping, and hurrying or jogging. There was a higher proportion of participants who felt extremely limited by more strenuous activities. Most participants (51.2%) were not limited at all or only slightly limited when dressing. A further 93 (34.9%) participants were moderately or quite a bit limited when dressing, with 33 (12.4%) being severely limited. This compares to 12 (4.5%) reporting only to be slightly limited or not limited at all, with a further 40 (14.9%) being moderately or quite a bit limited, and 191 (71%) being extremely limited. Most

patients reported some degree of physical limitation, with most reporting marked limitation on mild- moderately strenuous activity.



	Dressing yourself	Showering/ bathing	Walking 1 block on level ground	Doing yard work, housework or carrying groceries	Climbing a flight of stairs without stopping	Hurrying or jogging (as if to catch a bus)
Limited for other reasons / did not do activity (%)	1.5	2.2	3.8	8.3	6.1	9.7
Not at all limited (%)	30.1	28.5	8.3	4.9	2.7	1.5
Slightly limited (%)	21.1	18.4	9.8	9.8	8	3
Moderately limited (%)	18	14.6	17.8	12	11.7	4.1
Quite a bit limited (%)	16.9	19.9	24.6	21.8	17.4	10.8
Extremely limited (%)	12.4	16.5	35.6	43.2	54.2	71

Figure 5-5 KCCQ summary of physical burden at baseline

Symptoms

The physical symptoms that the KCCQ asked patients about are fatigue, dyspnoea, and peripheral oedema. Patients were asked to reflect on how often, in the previous two weeks, they had been limited by these symptoms. The frequency of these symptoms are detailed in Table 5-3. The most common symptom described by participants was fatigue, with almost every participant who completed this question reporting fatigue at least once per week and only 2.3% denying any fatigue in the previous two weeks. Dyspnoea was also extremely common, limiting all participants who completed this question at least once in the previous two weeks, with only 11 (4.1%) denying any limitation due to dyspnoea. A larger proportion of participants, 62 (23.0%), did not describe any peripheral oedema. However, half of all participants reported oedema every morning (137 participants, 50.9%). A further 52 participants (19.3%) reported peripheral oedema either one to two times per week or three or more times per week. A high proportion of participants reported limitations due to either fatigue or dyspnoea (or both) on a daily basis. 41 (15.4%) participants reported fatigue at least once per day, with 38 (14.2%) reporting limitation due to dyspnoea at least once per day. A further 89 (33.5%) of participants reported fatigue limiting them several times a day, with 73 (27.4) feeling fatigue limited them all the time. 94 (35.1%) participants reported limitation due to dyspnoea several times per day, with 83 (31.0%) reporting feeling limited by dyspnoea all the time. Another specific symptom which is reported is paroxysmal nocturnal dyspnoea or orthopnoea. The KCCQ asks participants to report how often they have been "forced to sleep sitting up or propped up due to shortness of breath". 101 (37.4%) participants reported to experiencing this symptom every night, with 40 (14.8%) reporting three or more times per week, 18 (6.7%) 1-2 times per week, 22 (8.1%) less than once a week, and 89 (33.0%) never over the previous two weeks.

Table 5-3 KCCQ symptom frequency

	Oedema n (%)	Fatigue n (%)	Dyspnoea n (%)
n	269	266	268
Every morning	137 (50.9)	-	-
All the time	-	73 (27.4)	83 (31.0)
Several times per day	-	89 (33.5)	94 (35.1)
At least once per day	-	41 (15.4)	38 (14.2)
Three or more times a week	28 (10.4)	29 (10.9)	14 (5.2)
One to two times a week	24 (8.9)	11 (4.1)	14 (5.2)
Less than once a week	18 (6.7)	17 (6.4)	14 (5.2)
Never over the past two weeks	62 (23.0)	6 (2.3)	11 (4.1)

The KCCQ also asks patients to reflect on the burden each of these three symptoms (oedema, fatigue, and dyspnoea) creates. The distribution of responses is displayed in Figure 5-6.

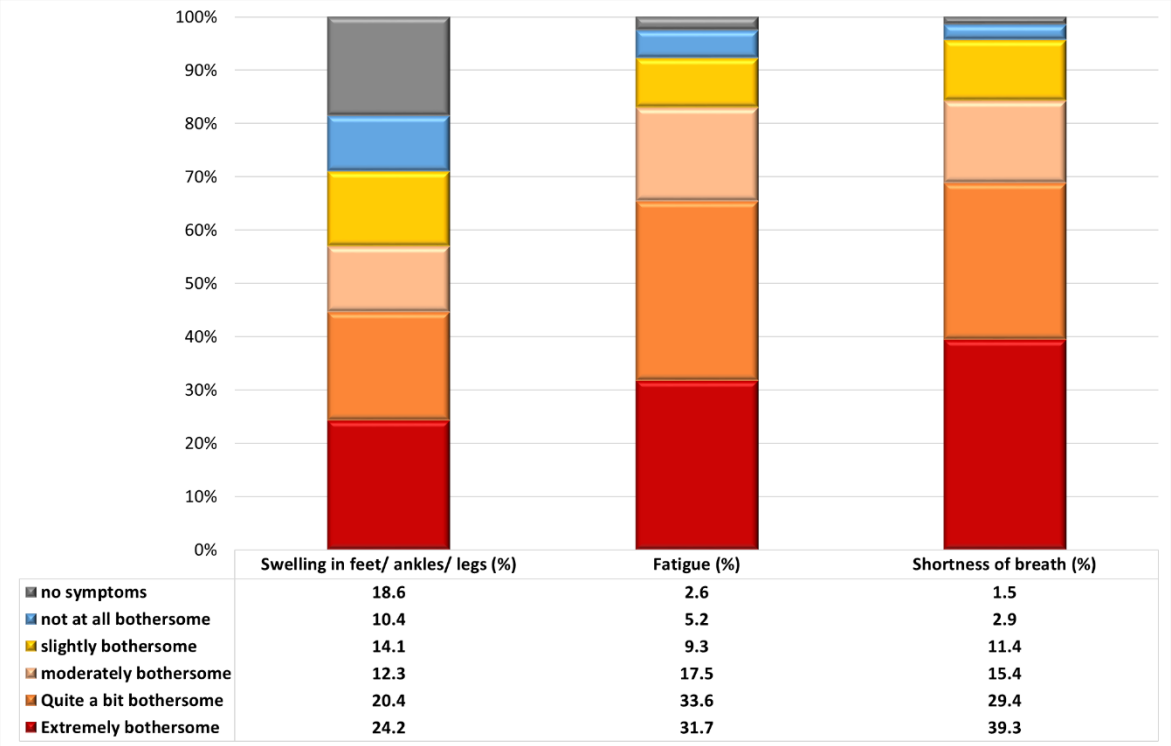


Figure 5-6 KCCQ symptom burden at baseline

Most participants felt at least some burden from all of the three physical symptom categories. Oedema represented the lowest overall burden for participants, with almost 30% either not having any symptoms, or rating the burden of oedema as "not bothersome at all". This contrasts to both fatigue and dyspnoea, with only 7.8% and 4.4% respectively, reporting no burden. 12.3% of participants felt moderately bothered by oedema, with 20.4% and 24.4%

reporting oedema to be “quite a bit” and “extremely bothersome”, respectively. A higher proportion of participants found fatigue to be “quite a bit” and “extremely bothersome” at 33.6 and 31.7%, respectively. An even higher proportion of burden was reported due to dyspnoea, with “quite a bit” and “extremely bothersome” reported by 29.4 and 39.3%, respectively.

Self-efficacy

The KCCQ asks patients to reflect on how their understanding of heart failure. Specifically, they are asked who they should contact if their symptoms were to deteriorate and their understanding of what action they can take themselves to prevent deterioration in symptoms. Although this is only applicable to patients with a known diagnosis of heart failure, these questions are useful to gain a baseline assessment of a patients understanding of a heart failure treatment. There were a wide variety of responses to “How sure are you that you know what to do, or whom to call, if your heart failure gets worse”. Just over one third of participants, 99 (36.5%), answered “not at all” or “not very sure” to this question. A further 30 (11.1%) were “somewhat sure”. 142 (52.2%) felt either “mostly” or “completely sure”. This is somewhat surprising, as only 120 (44.1%) of participants had a known previous diagnosis of heart failure. I suspect that some participants answered this question thinking they would contact their own general practitioner, rather than a heart failure nurse, in the event of a deterioration in their symptoms. In response to the question “How well do you understand what things you are able to do to keep your heart failure symptoms from getting worse?”, over half (137 participants) again answered that they “mostly” or “completely understand”. These answers would be expected from patients who have previously been through the heart failure liaison service, as education on this subject is an integral part of the liaison service. Again, it is somewhat surprising that such a high proportion answered this question with positive answers.

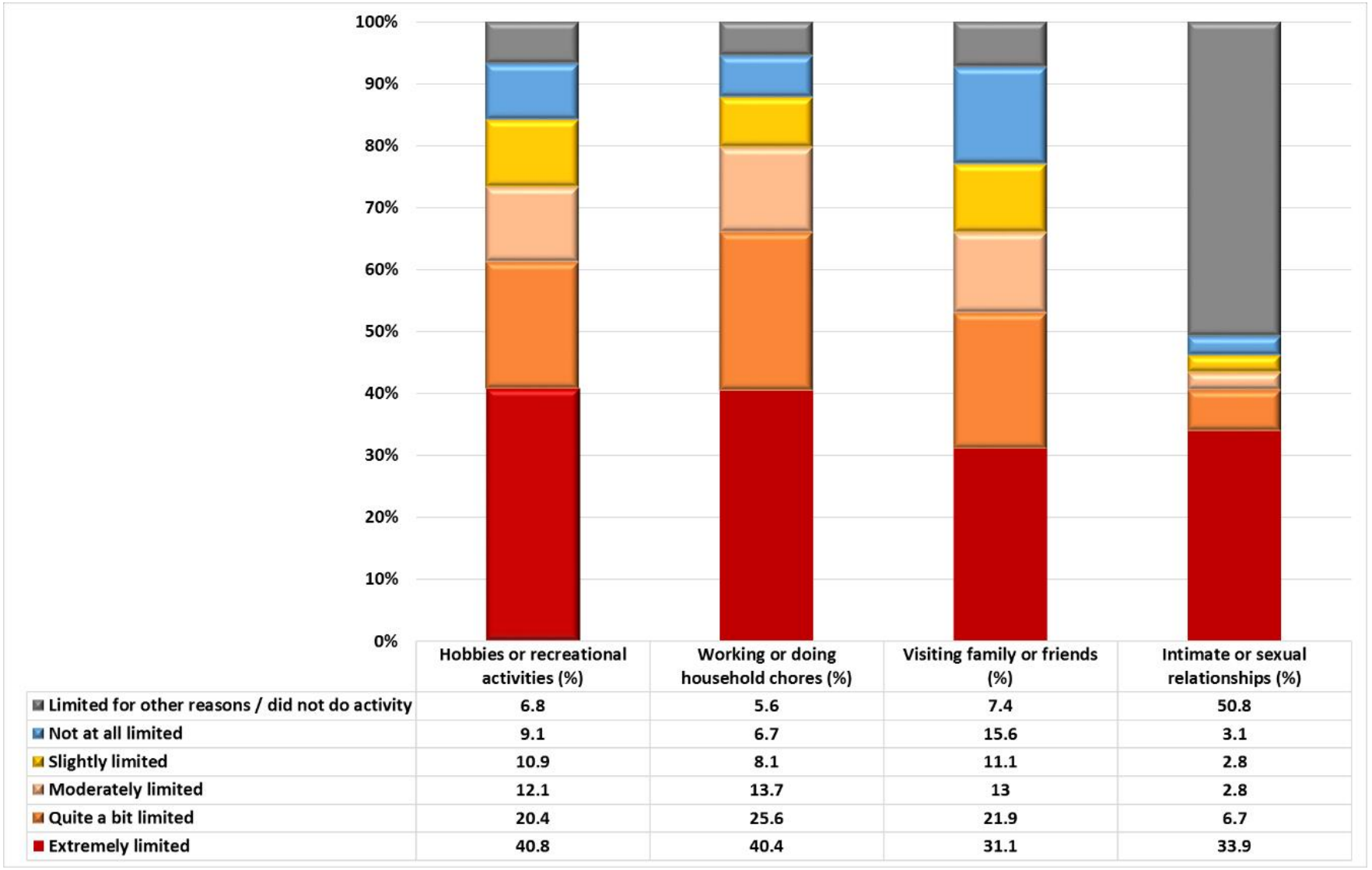
Quality of life

There are three questions pertaining to general quality of life assessment in the KCCQ. These include “How much has heart failure limited your enjoyment of life?”, “If you had to spend the rest of your life with your heart failure the way

it is right now, how would you feel about this?", and "How often have you felt down in the dumps because of your heart failure?". 77 (28.6%) participants felt that heart failure had extremely limited their enjoyment of life. A further 130 (48.4%) felt that heart failure had limited their enjoyment of life "moderately" or "quite a bit". Most participants would have been dissatisfied if they had to spend the rest of their lives with heart failure as it was at the time of the questionnaire, with 62 (23%) somewhat, 54 (20.0%) mostly, and 110 (40.7%) extremely dissatisfied. Most participants felt discouraged as a result of their heart failure symptoms, with 93 (34.2%) occasionally, 70 (25.7%) most, and 45 (16.5%) all of the time.

Social limitation

The KCCQ asks patients to rate how limited they are in getting to or performing a variety of social activities. The distribution of responses to these questions are represented in Figure 5-7. The social activities reported include hobbies or recreational activities, working or doing household chores, visiting family or friends, and intimate or sexual relationships. There was a high proportion of participants reporting extreme limitation in all of these activities. 20.4 and 40.8% of participants felt "quite a bit" and "extremely limited", respectively, when participating in hobbies or recreational activities. 21.9 and 31.1% of participants felt "quite a bit" and "extremely limited", respectively, when visiting family or friends. 25.6 and 40.4% of participants felt "quite a bit" and "extremely limited", respectively, when working or doing household chores. 6.7 and 33.9% of participants felt "quite a bit" and "extremely limited", respectively, when participating in intimate or sexual relationships, although 50.8% of participants were limited for other reasons or did not do this activity.



	Hobbies or recreational activities (%)	Working or doing household chores (%)	Visiting family or friends (%)	Intimate or sexual relationships (%)
Limited for other reasons / did not do activity	6.8	5.6	7.4	50.8
Not at all limited	9.1	6.7	15.6	3.1
Slightly limited	10.9	8.1	11.1	2.8
Moderately limited	12.1	13.7	13	2.8
Quite a bit limited	20.4	25.6	21.9	6.7
Extremely limited	40.8	40.4	31.1	33.9

Figure 5-7 KCCQ Social Limitation at baseline

Summary scores

As detailed above, summary scores are available for the various sub-domains and also overall. The overall summary score is often used in clinical trials to track changes in heart failure specific quality of life. The sub-domain summary scores and overall scores are detailed in Table 5-4. Also detailed in Table 5-4 are the summary scores reported in the original results paper describing and validating the KCCQ.[179]

Table 5-4 KCCQ sub-domain scores

	PCHF cohort	KCCQ responsiveness cohort	KCCQ reliability cohort
Setting/ patient group	Inpatient/ ADHF	Inpatient/ ADHF	Outpatient/ CHF
n	272	39	39
Score			
Physical limitation	34.8 (25.1)	34.7	64.4
Total symptoms	35.1 (22.8)	31.3	76.6
Social limitation	31.6 (29.4)	31.1	59.2
Self-efficacy	56.0 (31.6)	67.6	83.3
Quality of life	36.4 (25.2)	30.5	64.5
Clinical summary score	34.9 (21.4)	33.0	70.5
Overall summary score	34.5 (21.1)	31.8	66.2

Values are expressed as mean (±SD), or mean.
ADHF= acute decompensated heart failure; CHF= chronic heart failure; KCCQ= Kansas City Cardiomyopathy Questionnaire; PCHF= Palliative Care in Heart Failure.

The summary scores from my cohort (labelled PCHF) are very consistent with the cohort of patients hospitalised due to heart failure that were used to assess the responsiveness of the KCCQ. There are particularly similar mean results for the Physical and Social Limitation sub-domain scores. The mean Physical Limitation scores in my cohort and the KCCQ responsiveness cohort were 34.8 and 34.7, respectively. The mean Social Limitation scores in my cohort and the KCCQ cohort were 31.6 and 31.1, respectively. The mean Clinical Summary Score also showed good concordance with the KCCQ cohort, at 34.9 and 33.0 respectively. The two main discrepancies, were between the Quality of Life and Self-efficacy scores. In the PCHF cohort, the QOL summary score mean was 36.4, and was lower in the KCCQ cohort at 30.5. The reverse was true when comparing the Self-efficacy scores between the two cohorts, with the mean Self-efficacy score being much lower in my cohort at 56.0 versus 67.6 in the KCCQ cohort. All of

the sub-domain and summary scores were lower in my cohort and the KCCQ in-patient cohort compared to the outpatient, chronic heart failure cohort.

The distribution of the KCCQ Overall Summary Scores is shown in Figure 5-8. The Overall Summary score was also similar in my cohort to the KCCQ cohort, at 34.5 and 31.8, respectively. The Overall Summary Score is important, as this allows for comparison between different cohorts, and change in clinical condition over time. The KCCQ Overall Summary Score is one of the most responsive markers to change in clinical status in heart failure when measured over time.

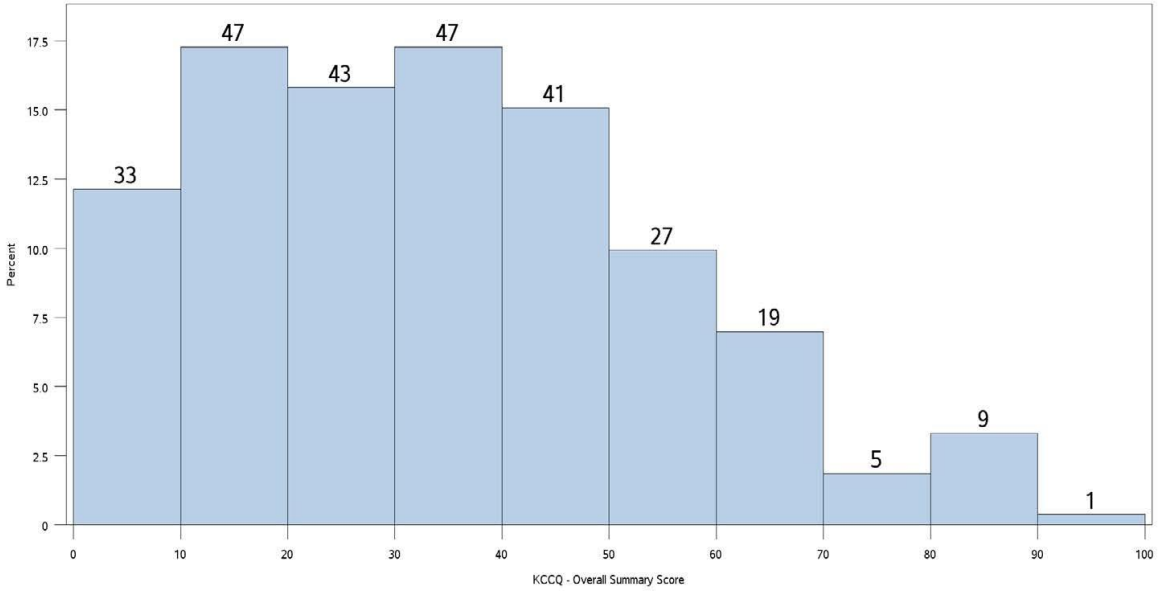


Figure 5-8 Distribution of KCCQ Overall Summary Scores at Baseline

Comparison of KCCQ Overall Summary Score with other cohorts can be seen in Figure 5-9. The difference in KCCQ Overall Summary Score between patients hospitalised due to heart failure, represented in orange, and chronic heart failure patients in the community is clear. The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) provides a useful comparison.[112] This was a multi-centre randomised controlled clinical trial of which 1458 participants had a KCCQ performed at baseline. As this study was a pharmacotherapy trial of patients with HF-REF, there are some differences between this and my cohort. Namely, lower age and ejection fraction, and a higher incidence of previous hospitalisation for heart failure in the EVEREST study versus my cohort. However, despite these differences in baseline

characteristics, there was a very similar mean KCCQ Overall Summary Score between EVEREST and PCHF at 31.6 and 34.5. The clear difference in KCCQ Overall Summary Score between patients admitted to hospital with heart failure and chronic heart failure can be seen. This highlights both the potential responsiveness to change of the KCCQ Overall Summary Score, and the similarity between my cohort and other acute heart failure cohorts.

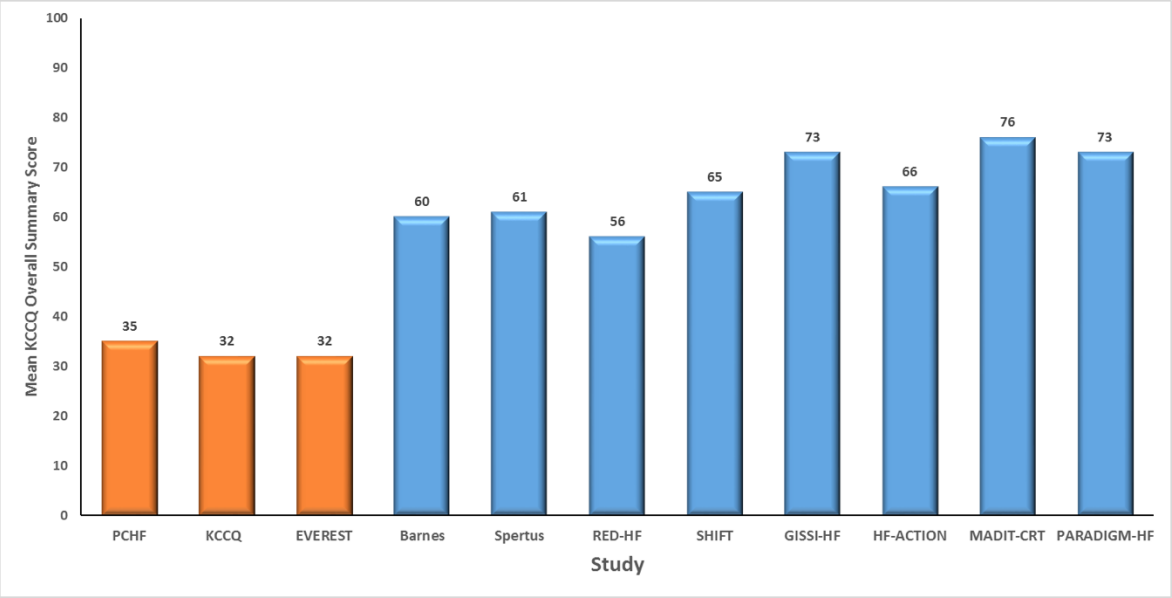


Figure 5-9 Comparison mean KCCQ Overall Summary Score selected cohorts
Orange columns = hospitalised heart failure cohorts, blue columns = community heart failure cohorts. PCHF= Palliative care in heart failure; KCCQ[179]= Kansas City Cardiomyopathy Questionnaire; EVEREST[112] = Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan ; Barnes *et al*[183] ; Spertus *et al*[254]; RED-HF[255] = Reduction of Events With Darbepoetin Alfa in Heart Failure Trial; SHIFT[71] = Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial; GISSI-HF[256]=Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-heart failure; HF-ACTION[257] = Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training ; MADIT-CRT[79]=Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy ; PARADIGM-HF[258]=Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial.

Selected baseline characteristics for participants in different severity categories of KCCQ Overall Summary Score are shown in Table 5-5. The KCCQ severity categories appeared to divide the cohort more evenly with 43% and 35% being in either moderate or severe categories. This is a higher proportion than reported in the EVEREST study, which only had 9% in the severe group and 32% in moderate. This perhaps reflects when the KCCQ was completed, at baseline in my study and after one week in EVEREST. The other main difference is that EVEREST was a randomised controlled clinical trial and my cohort was unselected. There were no differences between severity groups in my study in terms of age, sex, blood pressure, heart rate, or body mass index. Past medical

history was similar between the three groups, with the exception of higher prevalence of diabetes with increasing severity of KCCQ Overall Severity group (p=0.0101). There were clear differences in NYHA class between the different KCCQ groups, with more severe KCCQ having a higher proportion of NYHA III/IV than moderate and none/mild groups (p<0.0001). This finding is in keeping with previous studies comparing KCCQ summary score to NYHA class.[179, 234] There were no significant differences between groups regarding echocardiographic or laboratory findings. The EVEREST study reported similar ejection fraction between groups of KCCQ severity, in keeping with my study, but higher levels of BNP with lower scores in KCCQ. Again, this difference perhaps reflects the difference in timing of sampling of blood and the KCCQ in both studies, with higher BNP levels expected across all groups of participants expected the closer to admission a sample is taken, such as in my study. Participants with higher KCCQ Overall Summary score category had higher proportion of oedema on physical examination. This is to be expected as the presence of oedema results in a higher KCCQ Symptom Score, and therefore a higher KCCQ Overall Summary score. The KCCQ Summary Score severity categories appeared to discriminate well the severity of other PROMs. There were worse mean scores across all PROMs, with a stepwise deterioration in mean score from none/mild to moderate to severe KCCQ Overall Summary severity categories (p<0.0001 for all PROMs).

Table 5-5 Baseline characteristics per KCCQ severity group

	None/ mild n=60	Moderate n=117	Severe n=95	p
Age- yr	75.78 ± 10.10	76.12 ± 9.84	72.98 ± 11.27	0.0749
Female sex- n (%)	29 (48.3)	51 (43.6)	48 (50.5)	0.5878
Systolic blood pressure- mmHg	140.92 ± 27.07	141.48 ± 28.81	131.62 ± 26.23	**0.0241**
Heart rate- beats/min	87.86 ± 23.62	84.81 ± 24.47	89.93 ± 28.10	0.3496
Body-mass index- kg/m	27.92 ± 7.19	27.30 ± 6.01	28.77 ± 7.08	0.2913
Past Medical history- n(%)				
Hypertension	43 (71.7)	75 (64.1)	66 (69.5)	0.5327
Myocardial infarction	20 (33.3)	50 (42.7)	41 (43.2)	0.4097
Atrial fibrillation	31 (51.7)	64 (54.7)	49 (51.6)	0.8802
Diabetes	14 (23.3)	33 (28.2)	42 (44.2)	**0.0101**
CVA/TIA	11 (18.3)	22 (18.8)	19 (20.0)	0.9612
COPD	11 (18.3)	28 (23.9)	30 (31.6)	0.1627
Depression	6 (10.2)	12 (10.3)	19 (20.2)	0.0755
Symptoms- n (%)				
NYHA functional class				**<0.0001**
Class I	0 (0.0)	0 (0.0)	0 (0.0)	
Class II	34 (56.7)	33 (28.2)	15 (15.8)	
Class III	22 (36.7)	67 (57.3)	52 (54.7)	
Class IV	4 (6.7)	17 (14.3)	28 (29.5)	
Examination- n (%)				
Elevated JVP (> 4cm)	38 (70.4)	71 (68.9)	67 (79.8)	0.2226
Third Heart Sound	14 (23.7)	23 (19.7)	22 (23.2)	0.7608
Pulmonary crackles	48 (81.4)	92 (78.6)	72 (76.6)	0.7833
Pleural effusion	18 (30.5)	40 (34.2)	37 (39.8)	0.4783
Peripheral Oedema	46 (78.0)	81 (69.2)	79 (84.0)	**0.04**
Echocardiography				
Ejection fraction, %	39.32 ± 17.28	40.34 ± 17.41	38.94 ± 15.07	0.8182
LVIDD/BSA^2	2.97 ± 0.59	2.96 ± 0.56	2.96 ± 0.56	0.998
LV mass/BSA^2	115.89 ± 31.98	122.89 ± 41.52	115.97 ± 34.23	0.4312
E/e'	17.17 ± 7.64	17.95 ± 7.56	17.03 ± 7.59	0.6649
Laboratory				
Sodium (mmol/l)	137.0 [134.0, 139.0]	138.0 [135.0, 140.0]	138.0 [135.0, 140.0]	0.5852
Urea (mmol/l)	8.1 [5.6, 11.2]	8.8 [6.6, 12.1]	8.5 [6.3, 14.2]	0.3013
Creatinine (umol/l)	92.5 [70.0, 124.0]	103.0 [75.0, 141.0]	97.0 [71.0, 136.0]	0.2631
BNP (pg/ml)	642.0 [448.0, 1288.5]	733.0 [451.0, 1192.0]	749.0 [378.0, 1619.0]	0.9267
Haemoglobin (g/L)	125.5 [111.5, 137.0]	122.0 [107.0, 138.0]	120.0 [107.0, 134.0]	0.5473
PROMS				
HADS-A score	5.07 ± 3.64	6.54 ± 4.23	9.74 ± 4.99	**<0.0001**
HADS-D score	3.69 ± 3.01	6.71 ± 3.11	9.52 ± 4.37	**<0.0001**
KCCQ summary score	64.87 ± 12.04	36.72 ± 7.21	12.64 ± 6.89	**<0.0001**
ESAS summary score	25.28 ± 19.45	34.90 ± 17.55	53.19 ± 19.72	**<0.0001**
SF12-physical score	38.90 ± 8.42	30.02 ± 7.63	25.40 ± 7.46	**<0.0001**
SF12-mental score	51.52 ± 9.42	43.62 ± 9.77	33.60 ± 10.66	**<0.0001**

Continuous variables are expressed as mean± standard deviation or median [interquartile range], categorical variables are expressed as n (%). BNP= Brain-Type natriuretic peptide; BSA= body surface area; CVA= cerebrovascular accident; ESAS= Edmonton Symptom Assessment Scale; HADS-A= Hopsital anxiety and depression scale- anxiety; HADS-D= Hospital anxiety and depression scale- depression; JVP= jugular venous pressure; KCCQ= Kansas City Cardiomyopathy Questionnaire; LVIDD = left ventricular internal diameter diastole; NYHA = New York Heart Association; PROMs= patient reported outcome measures; SF12= Short Form 12 questionnaire; TIA = transient ischaemic attach.

5.3 Edmonton symptom assessment scale

The ESAS is a PROM often used in PC to monitor the symptom burden of patients with cancer.[227] The ESAS is often used clinically as a trigger tool to prompt a further detailed assessment of symptom burden. The ESAS consists of ten Likert scales from 0-10 inclusive, with each scale representing a different symptom. The symptoms included in this PROM include shortness of breath, tiredness, drowsiness, lack of appetite, anxiety, depression, pain, nausea, and the patients' overall assessment of their own wellbeing. There is also an additional space for respondents to fill in any other symptoms they may have as the tenth symptom. An overall summary score is then created by totalling the sum of the individual scores. Although a number of studies have used differing cut-offs to categorise each symptom as mild/ moderate/ severe, there is no consensus regarding this.[259] I have chosen to use a pragmatic and intuitive approach to categorise each individual symptom as follows: 0-4 = none/mild; 5-7 = moderate; 8-10 = severe. This principle has previously been applied to patients with heart failure and allows for comparison.[129] A similar principle was applied to the ESAS overall summary score, with 0-33 being classified as none-mild, 34-66 as moderate, and 67-100 as severe burden.

Symptom distribution

A breakdown of the different symptom scores are expressed in Table 5-6. The range of responses for every symptom was 0-10. The symptom with the highest median score was dyspnoea, with a median (IQR) of 7 [4-9]. This is not surprising given most patients completed this questionnaire on the first few days of a hospital admission for decompensated heart failure. The next highest median [IQR] score was bother tiredness and the patients' assessment of their general wellbeing, at 5 [4-8] and 5 [3-7]. Anxiety, pain, depression, and drowsiness all had lower median scores, between 2-3. Nausea appeared to be the least common/ problematic symptom of the 9 assessed, with a median [IQR] of 0 [0-3].

Table 5-6 ESAS symptom distribution

Symptom	Median [IQR]
Pain	2 [0-5]
Tiredness	5 [4-8]
Drowsiness	2 [2-7]
Nausea	0 [0-3]
Lack of appetite	3 [0-6]
Dyspnoea	7 [4-9]
Depression	2 [0-5]
Anxiety	3 [0-6]
General wellbeing	5 [3-7]

The distribution, expressed as a percentage, of the different severity categories for each symptom is shown in Figure 5-10. Again, it is quite clear that shortness of breath or dyspnoea is the most problematic symptom, with 54% falling into the severe category, 21.9% in moderate, and only 24.2% in the none/ mild category. A similar proportion of symptom burden/ severity was seen regarding tiredness, with 48.5% falling into the severe category, 29.2% moderate, and only 22.4% with only none/mild burden. The patients' own assessment of their overall wellbeing and drowsiness had similar distribution of patients in terms of severity of symptom burden. Overall wellbeing was reported in the severe range for 30.1%, moderate for 33.8% and none/mild in 36.1%. Lack of appetite, anxiety, depression, and pain all had higher proportions of patients in the none/mild range, with 50.4, 54.9, 59.9, and 63.9%, respectively. The lowest burden from any of the symptoms assessed was nausea, with only 22% in the moderate or severe range.

Although ESAS has primarily been used in cancer patients, there are some studies starting to use this symptom assessment scale in heart failure. One such study, which allows interesting comparison, is by Evangelista *et al*, who performed the ESAS in 36 patients who had been admitted to hospital with heart failure.[129] Interestingly, they found that the symptom with the highest median score was pain, with a median [IQR] of 6 [0-7]. This compares to a median [IQR] of 2 [0-5] in my cohort at baseline. Most other symptoms had median scores of 4, with the exception of Loss of Appetite and Nausea, both with median scores of 3.

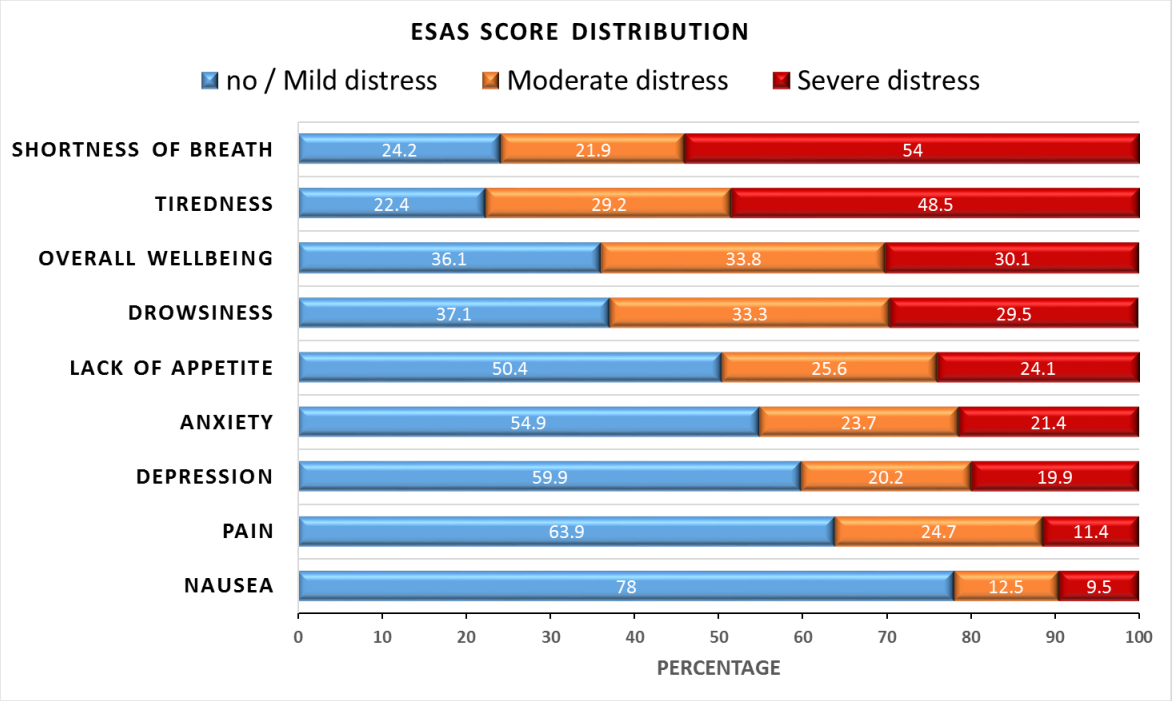


Figure 5-10 ESAS symptom severity distribution at baseline

An ESAS summary score can be generated by totalling all of the individual symptom scores. The ESAS summary score has a potential range of 0-100. The distribution of ESAS summary scores is shown in Figure 5-11. The mean (±SD) and median [IQR] total summary scores at baseline were 39.18 (±21.64) and 38.89 [22-56.67]. This was higher than the median [IQR] reported by Evangelista *et al* at 34.00 [29.00-40.75]. This higher symptom burden in my cohort perhaps reflects the larger sample size. Another difference between the cohorts was there was a much higher proportion of patients who were NYHA class III in my cohort versus the cohort reported by Evangelista *et al*, at 52 versus 31 %. There was also a much higher proportion of NYHA class IV patients in my study at 18% versus 0%. The distribution of ESAS summary score severity categories is detailed in Figure 5-15. Using the cut offs described previously, 40.1% of patients had ESAS summary scores in the none/mild category, 50.2% in the moderate, and 9.7% in the severe.

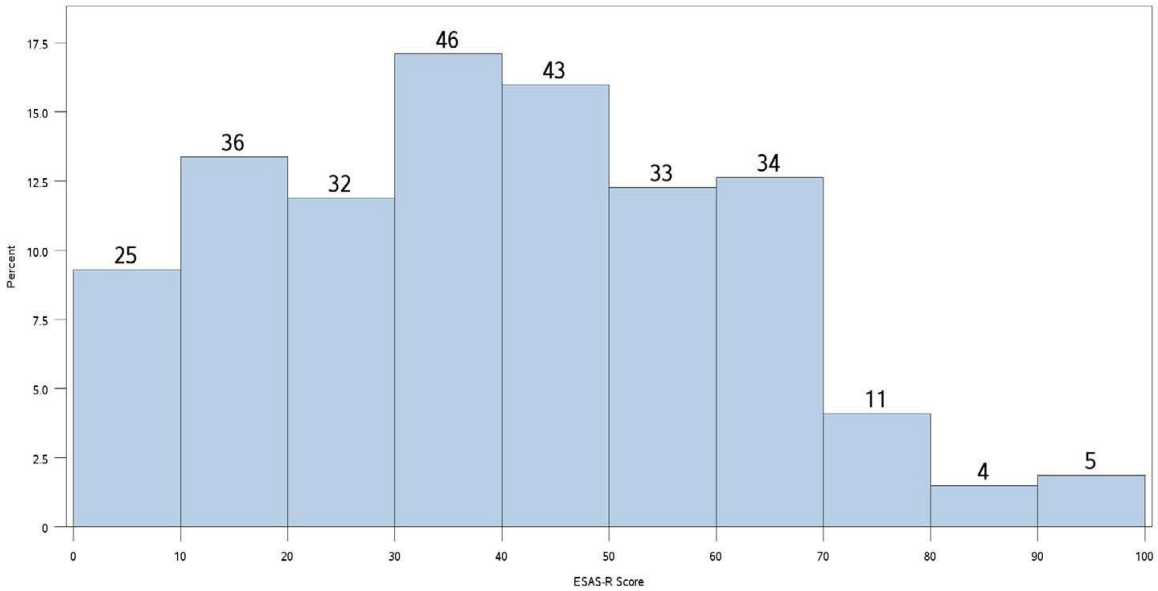


Figure 5-11 Distribution of ESAS summary scores at baseline

Comparison of selected baseline characteristics by ESAS severity group is provided in Table 5-7. ESAS severity groups had similar baseline characteristics with a few notable exceptions including age, history of myocardial infarction, depression, NYHA class, and PROMs summary scores. Patients who scored in the severe ESAS summary category were younger than those in non/mild or moderate (p=0.0034). Patients in moderate or severe categories were more likely to have had a previous myocardial infarction or a diagnosis of depression. ESAS severity category did not discriminate NYHA class as clearly as KCCQ Overall Summary severity categories, with similar proportions of NYHA III/IV between ESAS severity categories moderate and severe. However, there was a lower proportion of participants in NYHA class IV who scored in the none/mild severity for ESAS. Participants in severe severity category for ESAS had worse scores on all other PROM mean scores, with a stepwise worsening of mean score going from none/mild to moderate to severe. The exception to this was the SF12-Physical summary score, where moderate and severe ESAS categories had similar mean scores.

Table 5-7 Baseline characteristics per ESAS severity group

	None/ mild n=108	Moderate n=135	Severe n=26	p
Age- yr	74.99 ± 10.23	76.13 ± 10.05	68.58 ± 12.19	**0.0034**
Female sex- n (%)	49 (45.4%)	63 (46.7%)	14 (53.8%)	0.7379
Systolic blood pressure- mmHg	141.64 ± 27.59	136.40 ± 28.25	132.85 ± 26.24	0.2088
Heart rate- beats/min	86.91 ± 26.85	86.08 ± 24.31	94.58 ± 27.38	0.3
Body-mass index- kg/m	28.12 ± 6.68	27.75 ± 6.61	29.00 ± 7.18	0.6814
Past Medical history- n(%)				
Hypertension	67 (62.0%)	99 (73.3%)	17 (65.4%)	0.1642
Myocardial infarction	31 (28.7%)	66 (48.9%)	12 (46.2%)	**0.0052**
Atrial fibrillation	58 (53.7%)	70 (51.9%)	15 (57.7%)	0.8521
Diabetes	31 (28.7%)	45 (33.3%)	13 (50.0%)	0.1165
CVA/TIA	15 (13.9%)	32 (23.7%)	5 (19.2%)	0.1567
COPD	21 (19.4%)	37 (27.4%)	10 (38.5%)	0.0972
Depression	6 (5.7%)	24 (17.8%)	6 (23.1%)	**0.0076**
Symptoms- n (%)				
NYHA functional class				**0.0005**
Class I	0 (0.0)	0 (0.0)	0 (0.0)	
Class II	45 (41.7)	29 (21.5)	7 (26.9)	
Class III	55 (50.9)	71 (52.6)	13 (50.0)	
Class IV	8 (7.4)	35 (25.9)	6 (23.1)	
Examination- n (%)				
Elevated JVP (> 4cm)	67 (69.1%)	92 (78.6%)	15 (62.5%)	0.1358
Third Heart Sound	23 (21.5%)	28 (20.7%)	7 (26.9%)	0.7813
Pulmonary crackles	82 (76.6%)	107 (79.9%)	20 (76.9%)	0.8217
Pleural effusion	33 (30.8%)	51 (38.3%)	11 (42.3%)	0.3678
Peripheral Oedema	80 (74.8%)	104 (77.6%)	19 (73.1%)	0.8178
Echocardiography				
Ejection fraction, %	40.32 ± 16.43	39.16 ± 16.80	40.19 ± 16.71	0.856
LVIDD/BSA^2	2.96 ± 0.52	2.96 ± 0.60	2.94 ± 0.52	0.9936
LV mass/BSA^2	114.64 ± 29.37	121.93 ± 41.30	117.70 ± 41.83	0.4312
E/e'	17.81 ± 8.35	17.00 ± 6.96	18.30 ± 7.82	0.621
Laboratory				
Sodium (mmol/l)	138.0 [136.0, 140.0]	138.0 [134.0, 140.0]	137.5 [135.0, 140.0]	0.2201
Urea (mmol/l)	8.2 [6.1, 11.8]	8.8 [6.5, 12.2]	10.9 [7.5, 14.2]	0.2643
Creatinine (umol/l)	95.5 [72.0, 133.5]	98.0 [71.0, 135.0]	109.5 [87.0, 151.0]	0.1446
BNP (pg/ml)	612.0 [394.5, 1207.5]	798.0 [451.0, 1478.0]	754.5 [424.0, 1866.0]	0.1658
Haemoglobin (g/L)	122.0 [107.0, 139.0]	122.0 [109.0, 134.0]	119.0 [96.0, 128.0]	0.4221
PROMS				
HADS-A score	5.00 ± 3.72	8.07 ± 4.44	12.73 ± 4.48	**<0.0001**
HADS-D score	4.77 ± 3.40	8.15 ± 3.79	10.44 ± 4.52	**<0.0001**
KCCQ summary score	45.51 ± 20.59	28.54 ± 17.38	18.98 ± 18.81	**<0.0001**
ESAS summary score	17.78 ± 9.66	48.99 ± 9.94	77.13 ± 9.65	**<0.0001**
SF12-physical score	33.46 ± 9.88	28.30 ± 8.08	28.18 ± 7.85	**<0.0001**
SF12-mental score	48.46 ± 10.69	39.10 ± 10.73	29.61 ± 9.05	**<0.0001**

Continuous variables are expressed as mean± standard deviation or median [interquartile range], categorical variables are expressed as n (%). BNP= Brain-Type natriuretic peptide; BSA= body surface area; CVA= cerebrovascular accident; ESAS= Edmonton Symptom Assessment Scale; HADS-A= Hopsital anxiety and depression scale- anxiety; HADS-D= Hospital anxiety and depression scale- depression; JVP= jugular venous pressure; KCCQ= Kansas City Cardiomyopathy Questionnaire; LVIDD = left ventricular internal diameter diastole; NYHA = New York Heart Association; PROMs= patient reported outcome measures; SF12= Short Form 12 questionnaire; TIA = transient ischaemic attach.

5.4 Short form 12

The SF12 questionnaire, is a general quality of life questionnaire, based upon the longer Short Form 36 questionnaire. Both the SF12 and 36 questionnaires are designed to provide eight separate domains of different aspects of general health, and also provide two summary scores. These summary scores, the SF12-Physical Function and SF12-Mental well-being aggregate scores are useful for comparison between populations. Higher scores indicate better physical and mental health. The SF12 is a validated and shorter version of the SF36. The SF12 is able to reliably reproduce the overall summary scores generated from the SF36 but has the advantage of reduced participant burden due to a shorter form.[193] The eight domains that make up the SF12 include: physical functioning; physical role; bodily pain; general health; vitality; social functioning; emotional role; and mental health. An example of the SF12 questionnaire is provided in appendix 4.

Although the SF12 produces a score for each of the above sub-domains, the SF36 provides more reliable sub-domain scores, and it is recommended by the developers of the SF12 and those who have validated the SF12 that the two summary scores are used for comparison purposes. The mean (SD) and median [IQR] scores for SF12-Physical Function aggregate score at baseline were 30.31 (9.18) and 30.33 [23.98-36.16], respectively. The distribution of scores for the Physical Function summary score at baseline are shown in Figure 5-12. The mean (SD) and median [IQR] scores for the SF12-Mental wellbeing aggregate score at baseline were 41.79 (12.06) and 42.22 [32.82-50.36]. The distribution of scores for the Mental Wellbeing summary score at baseline are shown in Figure 5-13.

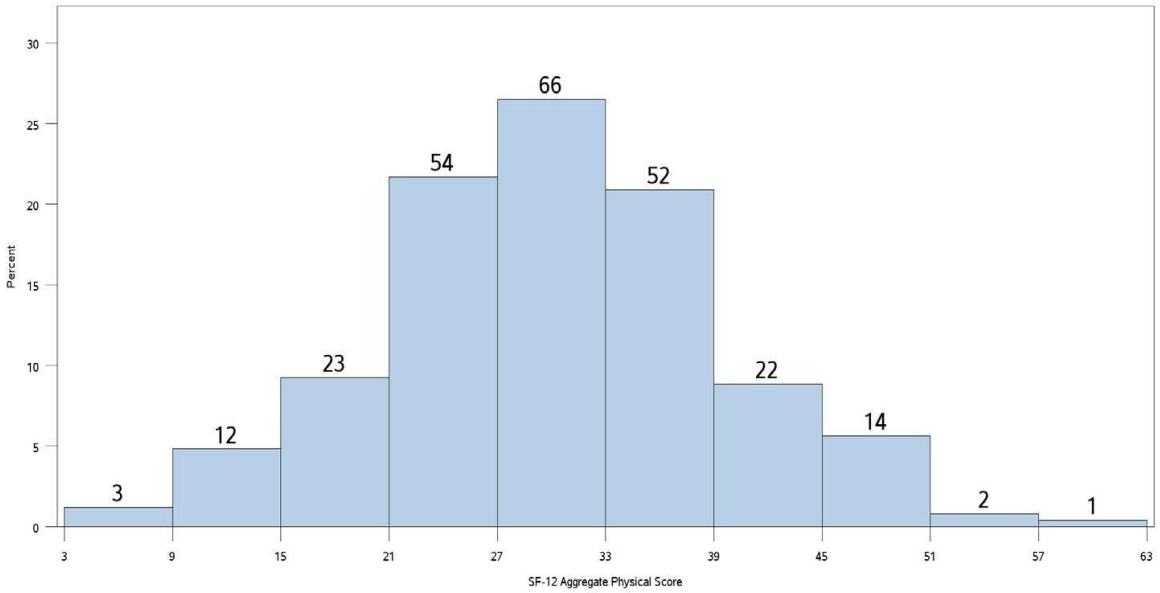


Figure 5-12 Distribution of SF-12 Aggregate Physical function scores at baseline

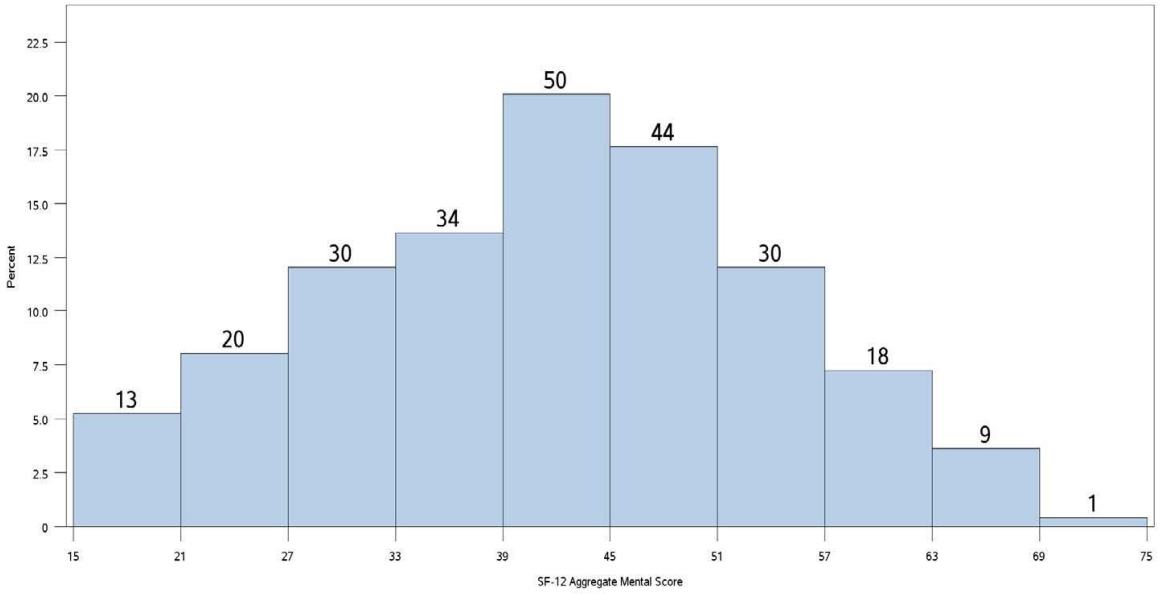


Figure 5-13 Distribution of SF-12 Mental Wellbeing summary scores at baseline

SF12 has been validated in a large population sample in the United Kingdom, which included both participants with no known disease and patients with chronic disease including heart failure.[193] This sample included a community sample of over 9000 participants. The mean (SD) values for both SF12-Physical Function and SF12-Mental well-being aggregate scores were both 50.00 (9.72). In this sample there were 68 participants with a diagnosis of heart failure. These participants had much lower scores of 31.47 (12.19) and 38.36 (12.46) for SF12-Physical Function and SF12-Mental well-being aggregate scores, respectively. The SF12 has also been administered to a large sample of 476 chronic heart failure patients in the United States of America.[254] This study reported mean (SD) scores of 35 (11) and 49 (12) for SF12-Physical Function and

SF12-Mental well-being aggregate scores, respectively. The results of the SF12 in my cohort are similar to those seen in previous cohorts of patients with heart failure, and are much lower than what is seen in the general population.

Using the cut-offs previously described, 123 (49.4%), 91 (36.5%), and 35 (14.1%) participants would be classified in none/mild, moderate and severe categories of the SF12-Physical Function aggregate score, respectively. 199 (79.9%), 37 (14.9%), and 13 (5.2%) would be classified in none/mild, moderate and severe categories of the SF12-Mental wellbeing aggregate score, respectively. Selected baseline characteristics are provided per severity category for both SF12-Physical Function and SF12-Mental well-being aggregate scores in Table 5-8 and Table 5-9, respectively. Baseline characteristics were similar between the three groups of severity for both the SF12-Physical Function and SF12-Mental well-being aggregate scores. A higher proportion of participants in the none/mild category of the SF12-Physical function were female compared to the moderate or severe groups. There was also a higher proportion of participants with a third heart sound in the severe category for SF12-Mental wellbeing compared to moderate or mild/none. The main differences between the groups for both summary scores, were in the other mean PROMs scores, with the exception of mean SF12-Physcial and mental aggregate scores.

Table 5-8 Baseline characteristics per SF12-physical severity group

	None/ mild n=123	Moderate n=91	Severe n=35	p
Age- yr	75.16 ± 10.40	73.47 ± 10.99	75.22 ± 9.28	0.4668
Female sex- n (%)	67 (54.5)	32 (35.2)	14 (40.0)	**0.0154**
Systolic blood pressure- mmHg	140.38 ± 24.42	137.08 ± 32.22	129.46 ± 27.25	0.1249
Heart rate- beats/min	88.12 ± 25.02	86.14 ± 26.11	85.43 ± 25.34	0.792
Body-mass index- kg/m	28.05 ± 7.85	28.20 ± 5.39	28.52 ± 5.62	0.9338
Past Medical history- n(%)				
Hypertension	83 (67.5)	61 (67.0)	27 (77.1)	0.506
Myocardial infarction	41 (33.3)	41 (45.1)	18 (51.4)	0.0765
Atrial fibrillation	64 (52.0)	48 (52.7)	19 (54.3)	0.9721
Diabetes	34 (27.6)	34 (37.4)	18 (51.4)	0.0257
CVA/TIA	23 (18.7)	18 (19.8)	6 (17.1)	0.9419
COPD	27 (22.0)	28 (30.8)	8 (22.9)	0.3197
Depression	15 (12.3)	12 (13.2)	7 (20.6)	0.4536
Symptoms- n (%)				
NYHA functional class				0.074
Class I	0 (0.0)	0 (0.0)	0 (0.0)	
Class II	42 (34.1)	26 (28.6)	9 (25.7)	
Class III	63 (51.2)	51 (56.0)	14 (40.0)	
Class IV	18 (14.6)	14 (15.4)	12 (34.3)	
Examination- n (%)				
Elevated JVP (> 4cm)	77 (72.0)	58 (70.7)	25 (86.2)	0.2407
Third Heart Sound	26 (21.3)	19 (20.9)	8 (22.9)	0.9708
Pulmonary crackles	92 (75.4)	72 (80.0)	29 (82.9)	0.557
Pleural effusion	42 (34.4)	29 (32.6)	15 (42.9)	0.5499
Peripheral Oedema	92 (75.4)	71 (78.9)	29 (82.9)	0.6124
Echocardiography				
Ejection fraction, %	39.25 ± 16.56	42.29 ± 16.91	33.54 ± 14.44	0.0279
LVIDD/BSA^2	3.00 ± 0.56	2.86 ± 0.55	3.05 ± 0.60	0.1116
LV mass/BSA^2	113.52 ± 28.64	126.04 ± 47.61	117.58 ± 31.67	0.1183
E/e'	16.66 ± 6.64	17.52 ± 7.87	18.70 ± 9.86	0.3748
Laboratory				
Sodium (mmol/l)	138.0 [135.0, 140.0]	137.0 [134.0, 139.0]	138.0 [136.0, 140.0]	0.2392
Urea (mmol/l)	8.0 [6.0, 11.7]	8.7 [6.4, 14.3]	9.2 [7.3, 14.8]	0.0972
Creatinine (umol/l)	91.0 [70.0, 130.0]	104.0 [74.0, 148.0]	107.0 [77.0, 140.0]	0.0651
BNP (pg/ml)	598.0 [418.0, 1192.0]	733.0 [388.0, 1403.0]	911.0 [525.0, 1697.0]	0.2497
Haemoglobin (g/L)	125.0 [113.0, 139.0]	115.0 [103.0, 135.0]	117.0 [107.0, 133.0]	0.0575
PROMS				
HADS-A score	6.84 ± 4.29	8.27 ± 5.19	7.11 ± 4.83	0.091
HADS-D score	6.02 ± 3.95	8.18 ± 4.41	7.65 ± 3.52	**0.0006**
KCCQ summary score	43.91 ± 22.05	26.54 ± 16.32	20.95 ± 14.30	**<0.0001**
ESAS summary score	34.68 ± 21.72	45.12 ± 20.56	44.32 ± 19.78	**0.0009**
SF12-physical score	37.68 ± 5.84	25.79 ± 2.79	16.18 ± 3.79	**<0.0001**
SF12-mental score	42.46 ± 11.91	39.63 ± 13.14	45.05 ± 8.39	0.0528

Continuous variables are expressed as mean± standard deviation or median [interquartile range], categorical variables are expressed as n (%). BNP= Brain-Type natriuretic peptide; BSA= body surface area; CVA= cerebrovascular accident; ESAS= Edmonton Symptom Assessment Scale; HADS-A= Hopsital anxiety and depression scale- anxiety; HADS-D= Hospital anxiety and depression scale- depression; JVP= jugular venous pressure; KCCQ= Kansas City Cardiomyopathy Questionnaire; LVIDD = left ventricular internal diameter diastole; NYHA = New York Heart Association; PROMs= patient reported outcome measures; SF12= Short Form 12 questionnaire; TIA = transient ischaemic attach.

Table 5-9 Baseline characteristics per SF12-mental severity group

	None/ mild n=199	Moderate n=37	Severe n=13	p
Age- yr	75.30 ± 10.23	72.27 ± 11.97	69.53 ± 7.41	0.0552
Female sex- n (%)	90 (45.2)	17 (45.9)	6 (46.2)	0.9951
Systolic blood pressure- mmHg	137.58 ± 28.83	139.58 ± 24.43	132.54 ± 26.83	0.7413
Heart rate- beats/min	86.52 ± 24.52	84.31 ± 24.32	101.85 ± 36.74	0.085
Body-mass index- kg/m	27.96 ± 6.52	28.44 ± 6.40	30.63 ± 9.74	0.3731
Past Medical history- n(%)				
Hypertension	136 (68.3)	24 (64.9)	11 (84.6)	0.4075
Myocardial infarction	77 (38.7)	19 (51.4)	4 (30.8)	0.2748
Atrial fibrillation	107 (53.8)	19 (51.4)	5 (38.5)	0.5559
Diabetes	64 (32.2)	17 (45.9)	5 (38.5)	0.2572
CVA/TIA	38 (19.1)	6 (16.2)	3 (23.1)	0.8492
COPD	47 (23.6)	10 (27.0)	6 (46.2)	0.1875
Depression	22 (11.2)	9 (24.3)	3 (23.1)	0.0625
Symptoms- n (%)				
NYHA functional class				0.2087
Class I	0 (0.0)	0 (0.0)	0 (0.0)	
Class II	68 (34.2)	7 (18.9)	2 (15.4)	
Class III	98 (49.2)	23 (62.2)	7 (53.8)	
Class IV	33 (16.6)	7 (18.9)	4 (30.8)	
Examination- n (%)				
Elevated JVP (> 4cm)	124 (72.1)	27 (75.0)	9 (90.0)	0.4473
Third Heart Sound	39 (19.7)	5 (13.5)	9 (69.2)	**<0.0001**
Pulmonary crackles	155 (78.3)	27 (75.0)	11 (84.6)	0.7675
Pleural effusion	69 (34.8)	11 (30.6)	6 (50.0)	0.4719
Peripheral Oedema	150 (75.8)	30 (83.3)	12 (92.3)	0.26
Echocardiography				
Ejection fraction, %	39.41 ± 17.01	42.86 ± 13.82	32.46 ± 15.92	0.1448
LVIDD/BSA^2	2.93 ± 0.56	3.01 ± 0.57	3.10 ± 0.71	0.49
LV mass/BSA^2	118.81 ± 38.01	119.53 ± 42.50	122.43 ± 29.06	0.9575
E/e'	17.48 ± 7.84	15.98 ± 6.93	17.18 ± 5.67	0.5881
Laboratory				
Sodium (mmol/l)	138.0 [135.0, 140.0]	138.0 [135.0, 140.0]	138.0 [135.0, 139.0]	0.8865
Urea (mmol/l)	8.7 [6.3, 12.2]	8.5 [6.2, 13.9]	10.5 [6.4, 15.8]	0.59
Creatinine (umol/l)	97.0 [72.0, 140.0]	102.0 [77.0, 132.0]	110.0 [71.0, 136.0]	0.819
BNP (pg/ml)	710.0 [444.0, 1329.0]	521.0 [388.0, 1044.0]	1619.0 [646.0, 2010.0]	0.0957
Haemoglobin (g/L)	122.0 [109.0, 137.0]	122.0 [97.0, 133.0]	126.0 [107.0, 130.0]	0.5969
PROMS				
HADS-A score	6.21 ± 4.07	11.60 ± 4.10	13.92 ± 4.15	**<0.0001**
HADS-D score	5.98 ± 3.40	10.00 ± 3.89	14.69 ± 3.84	**<0.0001**
KCCQ summary score	38.87 ± 20.65	20.02 ± 13.10	5.58 ± 4.56	**<0.0001**
ESAS summary score	34.61 ± 18.97	59.75 ± 19.18	62.64 ± 17.73	**<0.0001**
SF12-physical score	30.57 ± 9.91	29.83 ± 5.38	27.79 ± 5.04	0.5382
SF12-mental score	46.21 ± 8.94	26.34 ± 2.53	18.10 ± 1.78	**<0.0001**

Continuous variables are expressed as mean± standard deviation or median [interquartile range], categorical variables are expressed as n (%). BNP= Brain-Type natriuretic peptide; BSA= body surface area; CVA= cerebrovascular accident; ESAS= Edmonton Symptom Assessment Scale; HADS-A= Hopsital anxiety and depression scale- anxiety; HADS-D= Hospital anxiety and depression scale- depression; JVP= jugular venous pressure; KCCQ= Kansas City Cardiomyopathy Questionnaire; LVIDD = left ventricular internal diameter diastole; NYHA = New York Heart Association; PROMs= patient reported outcome measures; SF12= Short Form 12 questionnaire; TIA = transient ischaemic attach.

5.5 Zarit Burden Interview

The Zarit Burden Interview consists of 22 questions, which are self-administered by the caregiver, with possible answers provided, with a possible score of 0-4 for each question.[195] A total score is generated with a potential range of 0-88. Higher summary scores for the ZBI indicate higher burden. Cut-offs have been suggested by the developers of the ZBI with 0-21 indicating little or no burden, 21-40 mild-moderate burden, 41-60 moderate-severe, and 61-88 severe burden. 93 (34.2%) caregivers were available and/or willing to complete the ZBI. The mean (SD) and median [IQR] scores for the ZBI at baseline were 19.32 (14.05) and 16.00 [09.00-28.00], with a range of 0-58. The distribution of scores at baseline is shown in Figure 5-14. Using the above cut-offs, 57 (61.3%) reported little or no burden, 25 (26.9%) reported mild-moderate burden, 11 (11.8%) reported moderate-severe burden, and no caregivers reported severe burden. The ZBI has been used in numerous other conditions and is one of the most commonly used caregiver strain assessments.[195] The ZBI has also been used in heart failure, with one study of 50 patients with heart failure and their primary caregivers reporting a similar mean (SD) ZBI score of 16.0 (14.4).[260] Although the ZBI mean scores are similar between this and my study, the low proportion of caregivers with high levels of burden is surprising given the high symptom and quality of life burden reported by participants themselves. This could reflect the smaller sample size of the ZBI.

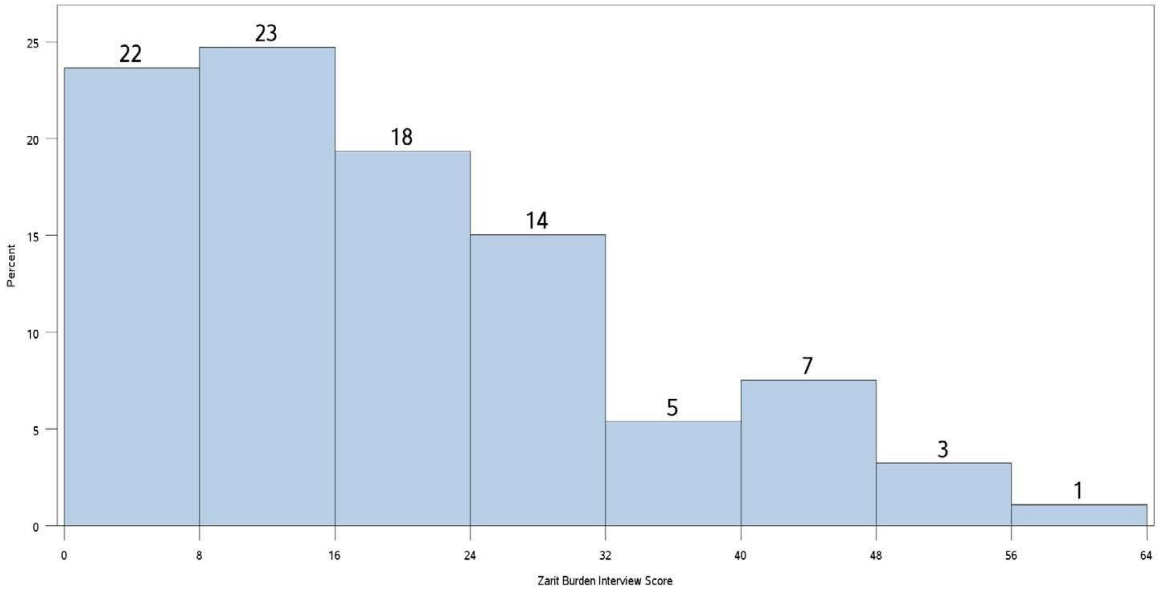


Figure 5-14 Distribution of Zarit Burden Interview summary scores at baseline

5.6 Summary scores

The distribution of severity score categories is provided in Figure 5-15. The KCCQ severity categories used classified the highest proportion of participants as either moderate or severe (77.9%). This was followed by the ESAS, which using the cut-offs previously described, categorised 59.9% of participants as moderate or severe. The ESAS cut-offs used classified fewer participants as severe compared to the KCCQ, with 9.7 and 34.9%, respectively. The SF-12 Physical summary score categories classified a similar proportion of participants as none/mild, moderate or severe, as the ESAS. The three PROMs which predominantly assess mood (SF-12 Mental wellbeing, HADS-Depression, and HADS-Anxiety) had similar distributions of severity scores, with most participants being classed as none/mild (74.5-81.6%). A similar proportion of participants were classified as moderate or severe (18.3-25.5%) on the mood assessment PROMs. That there was such similarity between the SF-12 Mental wellbeing and both HADS assessments is suggestive that the cut-offs used in SF-12 Mental Wellbeing are appropriate. Although the KCCQ classified a high proportion of participants as severe, or moderate, the cut-offs used are justifiable as they have been used in large cohorts of both patients admitted to hospital with heart failure and chronic heart failure patients.[184, 234] In both cohorts, a KCCQ Overall Summary score of less than 25 was associated with poor outcomes including increased mortality and increased readmissions. In an analysis of the EVEREST study, KCCQ score of less than 25 was the strongest predictor of persistently impaired QOL (assessed as KCCQ less than 45) or death at 6 months follow-up.[112] Overall, 114 (41.9%) of participants scored severe in any of the PROMs at baseline assessment. Of these, most scored severe in one PROM (n = 59, 51.8%). A further 38 (33.3%) participants scored severe in two PROMs. 10 (8.8%) of those in the severe overall category scored severe in three PROMs, with 4 and 3 participants scoring severe in 4 and 5 PROMs respectively.

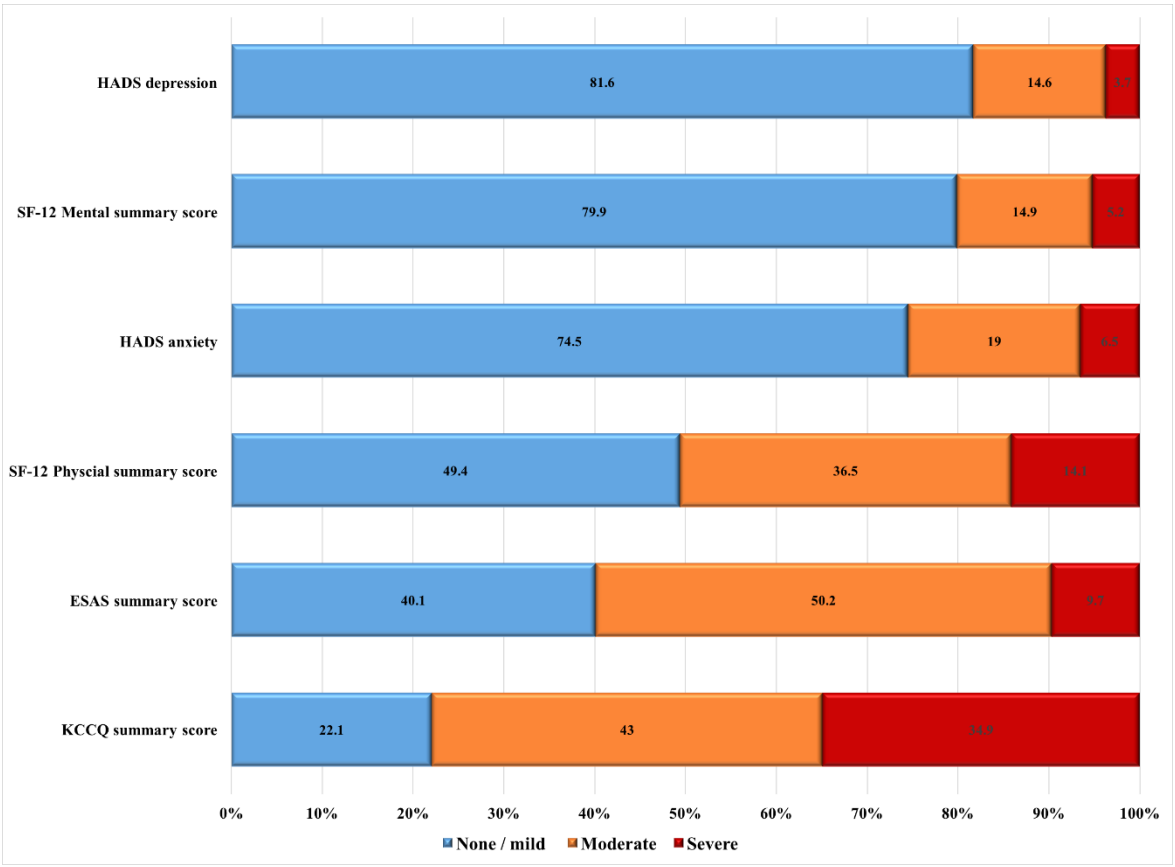


Figure 5-15 Baseline PROM severity categories

5.7 Summary

In this chapter, I have shown that patients admitted to hospital because of heart failure suffer from a number of physical and psychological symptoms, as reported using reproducible and objective PROMs. The most common physical symptoms were shortness of breath and fatigue, followed by drowsiness and lack of appetite. Although less frequent, pain and nausea were not uncommon. Patients with higher symptom burden and lower mood or worse anxiety were more likely to have worse quality of life, as anticipated. Higher scores for depression and anxiety were present compared to the general population.

Interestingly, very few of the known predictors of prognosis were statistically significantly different between the groups of severity for any of the PROMs. Notable exceptions were age in the HADS Depression and Anxiety, and ESAS, with worse severity category being associated with lower age. Worse NYHA class was associated with worse KCCQ, ESAS and HADS-Anxiety severity category. Measures of heart structure and function, such as left ventricular size, reduced ejection fraction, or elevated BNP, were not associated with worsening severity category of any PROM. The only exception to this being HADS-Anxiety severe category having higher left ventricular indexed size, higher BNP and lower ejection fraction (although the differences in BNP and ejection fraction did not reach statistical significance). This suggests that severity of physiological dysfunction does not necessarily correlate with severity of symptom burden or QOL impairment.

Of all of the PROMs used, the KCCQ appeared to be the most sensitive at identifying patients with severe impairment, as defined as a KCCQ summary score less than 25. Perhaps the KCCQ is not specific for severe impairment, and is over-classifying patients into this group? The results of the KCCQ in the current study are comparable with other hospitalised cohorts, as demonstrated earlier, and the cut-off value of 25 has been shown to identify patients with heart failure at risk of reduced life expectancy and unfavourable future QOL. The KCCQ cut-offs used also correlated well with NYHA classification, as previously shown, indicating that the results of the KCCQ are in keeping with other published cohorts. Patients with severe KCCQ were also more likely to have worse scores in all of the other PROMs, with statistically significant

separation of scores for each PROM between all of the categories of KCCQ severity. The ESAS also identified a group of patients with worse scores in all other PROMs measured.

This chapter has also highlighted the importance of using multiple different types of PROMs to describe the multi-faceted influence heart failure has on patients' lives, and therefore, potential palliative care needs. Although the KCCQ did appear to have the highest sensitivity for identifying patients with heart failure with severe impairment of quality of life, it did not identify all patients who scored severely at baseline. Of the 114 (41.9%) of patients who scored severely in any domain at baseline, 95 (83%) of these scored severely in KCCQ.

The change over time in symptom burden, mood disturbance, and QOL will be explored further in the following chapter.

Chapter 6 Follow up- the patient journey

6.1 Introduction

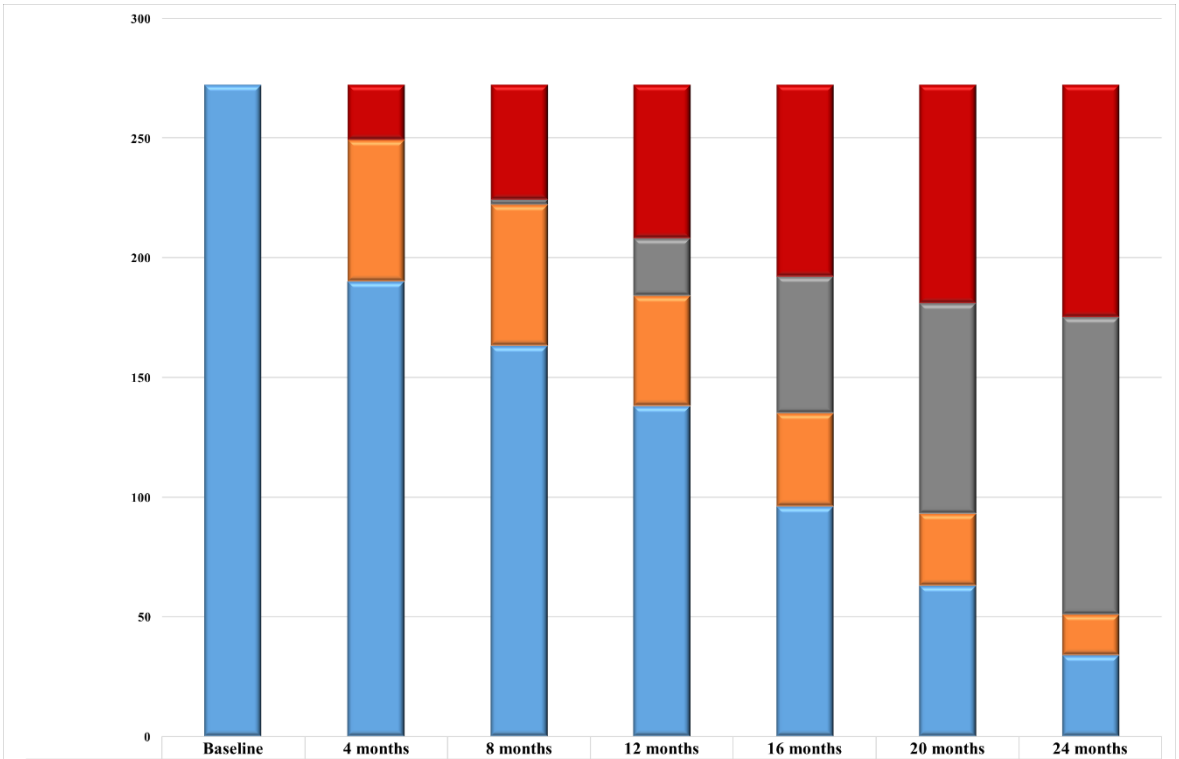
This chapter describes the follow-up of participants. Participants had two types of follow-up, actively through study visits, and passively through linkage with medical records and the Greater Glasgow and Clyde SafeHaven. The Greater Glasgow and Clyde SafeHaven has details of every hospital admission and death within the Greater Glasgow and Clyde health board, in which the study was performed. Details of cause and location of both hospitalisation and deaths are available through coding using the Scottish Morbidity Record. This chapter will describe the proportion of participants who met the definition of PC needs and compare baseline demographics with those who did not.

6.2 Follow up-study visits

All participants agreeing to take part in the PROM aspect of the study were invited to attend for study visits every 4 months for the duration of the study. The minimum number of potential study visits was two for the last participant recruited, and the maximum number of potential study visits was 7 for the first participant recruited. The first study visit took place on the 14th of May 2013 and the last on the 25th of June 2015. There were a total of 691 study visits carried out during this time period. Flexible appointments were offered at 4 months +/- one week in attempt to achieve maximum retention of participants. Given the nature of the study and the participants involved, participants were offered home visits or to attend the research facility at the British Heart Foundation Glasgow Cardiovascular Research Centre. 37.0% of all study visits were carried out in the participants' home. Prior to each study visit, participants were posted the same questionnaire pack containing the PROMs, as described earlier. A detailed medical history, physical examination, and laboratory tests were taken, as detailed in study visit case report form. Where available, caregivers were invited to complete the Zarit Burden Interview caregiver strain questionnaire.

Retention in the study was good, with the proportion of participants attending demonstrated in Figure 6-1. 190 (69.9%) participants attended the 4 month

study visit. Of the 82 who did not attend, 23 were due to death, 4 due to deteriorating health, 11 did not want to attend, and 44 failed to attend or provide a reason. As the time from recruitment increased, unsurprisingly, the proportion of participants not attending due to death increased. The proportion of participants not attending due to death steadily increased from 8.5% at the 4-month study visit, to 35.6% at the 24-month visit. As there was a variable follow-up period for study assessments for participants, from minimum 8 months to maximum 28 months, the proportion of participants who were unable to attend a visit for this reason increased over time. The proportion of participants where a study visit was not possible due to the time they entered the study rose steadily from 24 (8.8%) at the 12-month visit, to 124 (45.6%) at the 24-month visit. Participants did not attend for a variety of other reasons, including fatigue with assessments, a feeling of having too many appointments, or due to deteriorating health. However, most commonly there was no reason available or given for no attendance. The proportion of participants who failed to attend for reasons other than death or visit not possible increased as the study progressed. 59 (23.7%) participants who could potentially have attended (excluding those who died) the 4-month study visit did not attend. This proportion increased over time, and 17 (33.3%) of participants who could potentially have attended (excluding participants who died or could not have had a study visit due to time of entry to the study) at the 24-month visit. Overall, of the number of possible study visits (excluding missed visits due to death or late entry into the study), 78% of study visits were completed. In total, including the inpatient assessment, there were 963 patient assessments.



	Baseline	4 months	8 months	12 months	16 months	20 months	24 months
Deceased (n)	0	23	48	64	80	91	97
Not possible (n)	0	0	2	24	57	88	124
Missed visit (n)	0	59	59	46	39	30	17
Attended (n)	272	190	163	138	96	63	34

Figure 6-1 Attendance at study visits

6.3 Passive follow-up

Participants provided consent to be passively followed up through medical record linkage, which is available through the Greater Glasgow and Clyde SafeHaven service. Both services utilise the Scottish Morbidity Record linked to each patient, which records details of hospitalisations and deaths, amongst other data.

The minimum follow-up through data linkage was 368 days, and the maximum was 1056 days. The median [IQR] and mean (±SD) follow up in days for the 272 participants who completed the questionnaire aspect of the study were 774.5 [608.0-912.5] and 754.3 (±190.8), respectively.

6.3.1 Hospitalisations

Details of hospitalisations, including cause and length of stay were available through analysis of the Scottish Morbidity Record via the Greater Glasgow SafeHaven records. During the follow-up period, 217 (79.8%) participants were readmitted to hospital. Of those hospitalised, the range of number of hospitalisations was 1 to 32. The median number of readmissions was 3 [2-5]. The total number of unscheduled or emergency hospitalisations during the follow-up period was 503. Of these, 183 (36.4%) were for cardiovascular causes (heart failure, myocardial infarction, arrhythmia, stroke or other cardiovascular causes). The most common cardiovascular reason for hospitalisation was heart failure (56.8%), followed by arrhythmia (16.9%). 4.9% of cardiovascular readmissions were due to myocardial infarction. The majority of repeat hospitalisations were not due to cardiovascular causes, with 320 (63.6%) due to non-cardiovascular causes.

6.3.2 Mortality

During the follow-up period from 9th January 2013 – 1st December 2015, there were 103 deaths, or 37.9% of participants. The survival of the 272 participants in the cohort who completed the questionnaire aspect of the study is demonstrated in Figure 6-2. The mortality was similar in this cohort to other cohorts of patients hospitalised because of heart failure locally and nationally.[26, 261] Figure 6-2 highlights the high mortality associated with heart failure

following a hospitalisation due to decompensation. 23.1 and 35.7% of participants had died by one and two years following recruitment, respectively. Cause and location of death will be explored in more detail in following chapter.

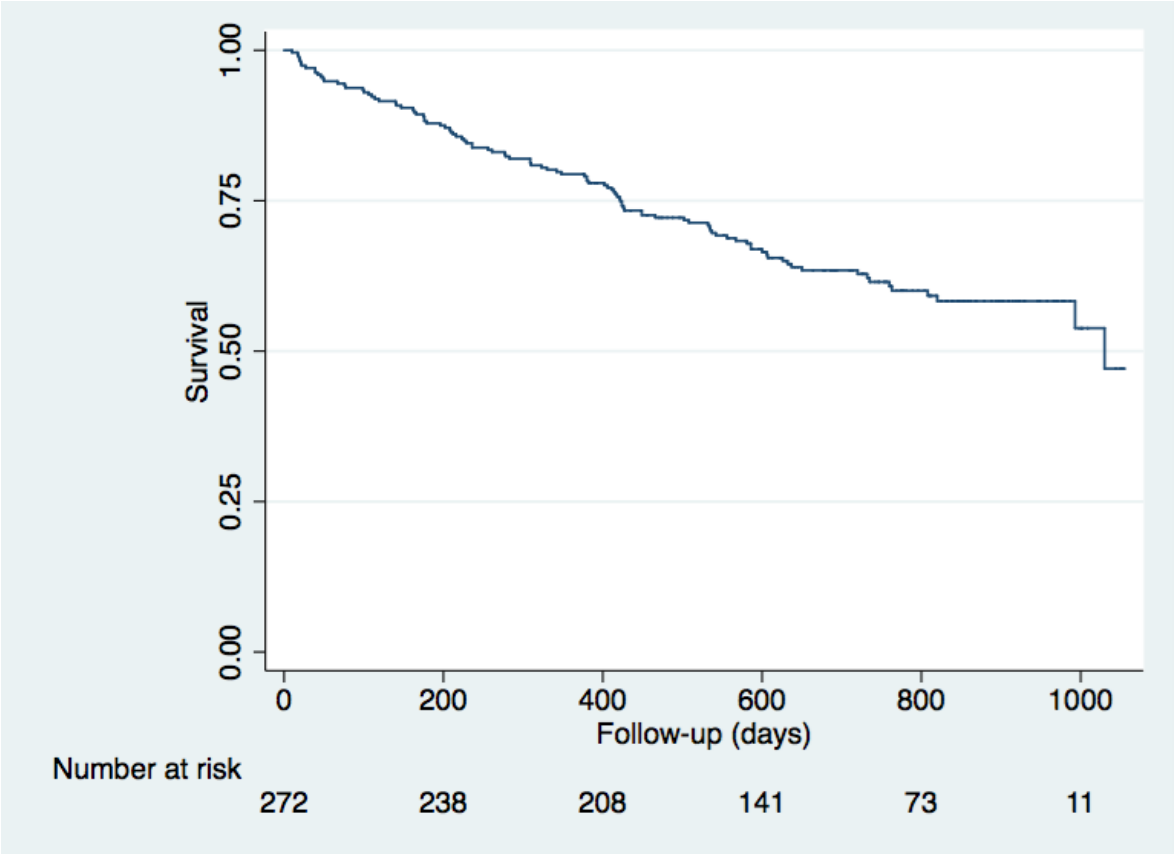


Figure 6-2 Kaplan-Meier mortality

6.4 Patient journey- patients with palliative care needs

Details of the proportion of participants who scored severe in each of the PROMs are shown in Table 6-1. At baseline, a high proportion of participants were graded as overall severe, defined as scoring severe in any PROM, with 41.9%. Most of these participants were severe as evaluated by the KCCQ (34.9%). The next most common contributing PROM was the SF-12 Physical PROM with 35 (14.1%) participants, followed by the ESAS summary score with 26 (9.7%) participants. The three mood assessments, SF-12 Mental, HADS Anxiety and Depression, scored similar proportions of participants as severe at baseline, with 5.2%, 6.5%, and 3.7%, respectively. The proportion of participants who attended study visits that were categorised as severe overall fell from baseline to the 4-month assessment at 27.8%. This proportion remained fairly constant for the remainder of the study, for the patients who attended study visits, at between 24 and 34%. Throughout the study, the KCCQ and SF-12 Physical PROMs

contributed most to the classification of overall severity. Between 15 and 23% of participants who attended study visits were scored as severe on KCCQ. Between 12 and 20% of participants who attended study visits were scored as severe on SF-12 Physical.

Table 6-1 PROM severity per study visit

	Baseline n=272	4 month n= 187	8 month n=159	12 month n= 136	16 month n=94	20 month n= 61	24 month n= 35
Severe PROM							
HADS-Anxiety	17 (6.5)	4 (2.3)	4 (2.6)	3 (2.3)	1 (1.2)	1 (1.7)	2 (6.2)
HADS-Depression	10 (3.7)	4 (2.2)	7 (4.5%)	2 (1.6)	3 (3.3)	5 (8.2)	2 (5.9)
KCCQ overall	95 (34.9)	28 (15.0)	27 (17.0)	24 (17.6)	14 (15.1)	14 (23.0)	6 (17.6)
ESAS overall	26 (9.7)	13 (7.1)	13 (8.2)	13 (9.6)	7 (7.5)	5 (8.2)	5 (14.7)
SF-12 Physical	35 (14.1)	28 (15.9)	30 (20.4)	17 (13.3)	10 (11.8)	10 (17.5)	6 (18.8)
SF-12 Mental	13 (5.2)	5 (2.8)	5 (3.4)	5 (3.9)	0 (0.0)	3 (5.3)	1 (3.1)
Overall Severe	114 (41.9)	52 (27.8)	55 (34.6)	41 (30.1)	23 (24.4)	22 (36.0)	12 (34.3)

Values expressed as n (%)
ESAS= Edmonton symptom assessment scale; HADS= hospital anxiety depression scale; PROM= patient reported outcome measure; SF-12= short form 12.

The patient journey for each participant is detailed in Figure 6-3, Figure 6-4, Figure 6-5, and Figure 6-6. Participants were classified at each potential study visit as "severe" or "not severe" for those who attended the visit. As discussed in Chapter 3, participants were classified as "overall severe" if they scored severe burden in any PROM. For participants who did not attend study visits, reasons were detailed as either "missed" for those who did not attend, "not possible" for those who could not have had a study visit at that time point due to their recruitment date, and "deceased". Using the severity criteria and the definition of probable PC needs detailed in Chapter 3, the population can be divided into two groups: those meeting the definition of PC needs (Figure 6-3), and those without not meeting the definition (Figure 6-4, Figure 6-5, and Figure 6-6). Due to the nature of the patient population being studied, and the length of active follow-up, missed visits were inevitable. I have elected to include participants with missed visits in my analysis as to exclude them would remove a

large proportion of the patient population. Another important reason for including these patients in the analysis is that these participants could have missed study visits due to deteriorating health or hospitalisation, and therefore I would be potentially excluding the participants with the highest need. For the purpose of describing the prevalence of PC needs, I have assumed that during a missed visit a participant had the same status as the last known status, as determined by PROMs. Another possible way to address missing study visit data is to assume that a participant missed a study visit due to deteriorating health and classify them as "severe" for that visit. I have elected not to do this as I feel this will potentially over classify participants as having PC needs. A further option to address missed visits would be to assume a study visit was "not severe", again, I have elected not to do this, as I felt this would potentially under-classify participants with likely PC needs.

Analysis of Figure 6-3, Figure 6-4, Figure 6-5, and Figure 6-6, reveals two broad groups, those with persistently impaired status or those who died following a severe status, and those who had a predominantly not-severe status or had improvement in status. Of those identified as likely having PC needs, 47 (64.5%) participants died following at least one study visit, with no known recovery of overall status. A further 26 (35.6%) of those classified as having likely PC needs had at least two consecutive study visits with severe overall status, without known recovery. The fluctuating nature of heart failure can be seen in these figures, with some participants changing severity category over time from severe, to not severe, and back to severe. A good example of this is patient number 1149. The patient journey figures are also important to understand that, although the mortality is high, many patients with heart failure do well and can improve. Many participants had severe overall impairment at baseline, but improved as time progressed. This highlights the importance of this study and of performing multiple serial assessments, rather than a single one-off assessment in hospital.

Using the definition described in Chapter 3, 73 (26.8%) participants met the definition for PC needs. Of patients, 47 died following a study visit with severe impairment (of any PROM), without known improvement in their status. 26 participants in the PC needs group had two or more consecutive visits with severe impairment of any PROM, without known improvement in their status.

	STUDY VISIT							
Patient	Baseline	4 Month	8 Month	12 month	16 month	20 Month	24 Month	28 Month
1004	Severe	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1008	Severe	Severe	Severe	Deceased	Deceased	Deceased	Deceased	Deceased
1011	Severe	Missed	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1013	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1014	Severe	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1017	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1019	Severe	Not Severe	Severe	Severe	Severe	Severe	Severe	Missed
1026	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1030	Not Severe	Not Severe	Severe	Severe	Severe	Severe	Severe	Severe
1032	Not Severe	Severe	Severe	Missed	Missed	Deceased	Deceased	Deceased
1036	Severe	Severe	Not Severe	Not Severe	Not Severe	Severe	Severe	Not Possible
1038	Severe	Missed	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1043	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1044	Not Severe	Not Severe	Severe	Severe	Severe	Severe	Severe	Not Possible
1052	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1067	Severe	Missed	Missed	Missed	Deceased	Deceased	Deceased	Deceased
1069	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Not Possible
1071	Not Severe	Severe	Severe	Severe	Severe	Severe	Severe	Not Possible
1077	Not Severe	Severe	Not Severe	Severe	Severe	Severe	Severe	Not Possible
1078	Severe	Missed	Severe	Severe	Severe	Missed	Severe	Not Possible
1081	Severe	Severe	Severe	Severe	Not Severe	Severe	Severe	Not Possible
1082	Severe	Severe	Severe	Missed	Missed	Missed	Missed	Deceased
1083	Not Severe	Not Severe	Severe	Missed	Severe	Deceased	Deceased	Deceased
1085	Severe	Severe	Severe	Severe	Missed	Deceased	Deceased	Deceased
1091	Severe	Severe	Severe	Severe	Deceased	Deceased	Deceased	Deceased
1094	Severe	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1096	Severe	Severe	Severe	Severe	Missed	Severe	Not Possible	Not Possible
1098	Severe	Missed	Missed	Deceased	Deceased	Deceased	Deceased	Deceased
1105	Severe	Severe	Missed	Missed	Missed	Missed	Not Possible	Not Possible
1110	Not Severe	Missed	Severe	Missed	Severe	Severe	Deceased	Deceased
1112	Not Severe	Not Severe	Not Severe	Severe	Severe	Severe	Deceased	Deceased
1116	Not Severe	Not Severe	Severe	Severe	Severe	Severe	Not Possible	Not Possible
1119	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1124	Severe	Missed	Missed	Missed	Deceased	Deceased	Deceased	Deceased
1130	Severe	Missed	Missed	Not Possible	Deceased	Deceased	Deceased	Deceased
1132	Severe	Severe	Severe	Missed	Missed	Missed	Not Possible	Not Possible
1142	Not Severe	Severe	Severe	Not Severe	Severe	Severe	Deceased	Deceased
1151	Severe	Severe	Severe	Severe	Severe	Severe	Not Possible	Not Possible
1157	Severe	Not Severe	Missed	Severe	Missed	Not Possible	Deceased	Deceased
1166	Severe	Missed	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1167	Severe	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1174	Severe	Missed	Missed	Deceased	Deceased	Deceased	Deceased	Deceased
1182	Severe	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1198	Severe	Severe	Severe	Severe	Deceased	Deceased	Deceased	Deceased
1205	Severe	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1216	Severe	Missed	Severe	Severe	Missed	Not Possible	Not Possible	Not Possible
1225	Not Severe	Not Severe	Not Severe	Severe	Deceased	Deceased	Deceased	Deceased
1233	Severe	Severe	Missed	Missed	Not Possible	Not Possible	Not Possible	Not Possible
1234	Severe	Severe	Severe	Deceased	Deceased	Deceased	Deceased	Deceased
1235	Severe	Not Severe	Not Severe	Severe	Deceased	Deceased	Deceased	Deceased
1249	Severe	Severe	Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible
1252	Severe	Severe	Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible
1256	Severe	Severe	Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible
1258	Not Severe	Severe	Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible
1261	Severe	Severe	Severe	Severe	Deceased	Deceased	Deceased	Deceased
1266	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1269	Severe	Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1271	Severe	Missed	Severe	Deceased	Deceased	Deceased	Deceased	Deceased
1278	Not Severe	Severe	Severe	Deceased	Deceased	Deceased	Deceased	Deceased
1281	Severe	Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1283	Not Severe	Severe	Severe	Deceased	Deceased	Deceased	Deceased	Deceased
1285	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1290	Severe	Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1295	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1298	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1301	Not Severe	Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1304	Severe	Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1305	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1306	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1315	Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1319	Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1051	Severe	Missed	Missed	Missed	Missed	Deceased	Deceased	Deceased
1135	Not Severe	Severe	Missed	Missed	Missed	Missed	Deceased	Deceased

Figure 6-3 Patient journey- patients with PC needs

	STUDY VISIT							
Patient	Baseline	4 Month	8 Month	12 Month	16 Month	20 Month	24 month	30 Month
1005	Severe	Severe	Not Severe	Deceased	Deceased	Deceased	Deceased	Deceased
1007	Not Severe	Not Severe	Severe	Severe	Not Severe	Not Severe	Not Severe	Not Severe
1039	Severe	Severe	Missed	Severe	Severe	Severe	Not Severe	Not Possible
1074	Severe	Severe	Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible
1079	Severe	Not Severe	Not Severe	Not Severe	Severe	Severe	Not Severe	Deceased
1095	Severe	Missed	Severe	Severe	Severe	Not Severe	Not Possible	Not Possible
1100	Not Severe	Not Severe	Severe	Severe	Not Severe	Not Severe	Not Possible	Not Possible
1115	Severe	Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible
1149	Not Severe	Severe	Not Severe	Severe	Severe	Not Severe	Not Possible	Not Possible
1171	Severe	Missed	Severe	Severe	Not Severe	Deceased	Deceased	Deceased
1189	Severe	Severe	Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1222	Severe	Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible
1001	Not Severe	Not Severe	Not Severe	Deceased	Deceased	Deceased	Deceased	Deceased
1002	Not Severe	Severe	Missed	Not Severe	Not Severe	Not Severe	Not Severe	Missed
1006	Not Severe	Not Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1009	Not Severe	Not Severe	Not Severe	Not Severe	Missed	Missed	Missed	Missed
1010	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe
1012	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Deceased	Deceased	Deceased
1015	Severe	Not Severe	Missed	Not Severe	Missed	Severe	Not Severe	Not Severe
1018	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe
1020	Severe	Not Severe	Not Severe	Not Severe	Deceased	Deceased	Deceased	Deceased
1021	Not Severe	Missed	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe
1022	Not Severe	Not Severe	Missed	Not Severe	Missed	Missed	Missed	Missed
1023	Not Severe	Not Severe	Not Severe	Not Severe	Deceased	Deceased	Deceased	Deceased
1024	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe
1025	Not Severe	Missed	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1027	Not Severe	Missed	Missed	Missed	Missed	Missed	Missed	Missed
1029	Not Severe	Not Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1033	Not Severe	Not Severe	Not Severe	Not Severe	Missed	Not Severe	Not Severe	Not Possible
1034	Not Severe	Missed	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1035	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible
1037	Not Severe	Missed	Missed	Missed	Deceased	Deceased	Deceased	Deceased
1040	Severe	Missed	Missed	Missed	Missed	Missed	Missed	Not Possible
1041	Not Severe	Not Severe	Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible
1042	Severe	Missed	Missed	Missed	Missed	Missed	Missed	Not Possible
1045	Not Severe	Not Severe	Missed	Not Severe	Not Severe	Severe	Not Severe	Not Possible
1046	Not Severe	Missed	Missed	Missed	Missed	Missed	Missed	Not Possible
1048	Severe	Missed	Missed	Missed	Missed	Missed	Missed	Not Possible
1049	Not Severe	Withdrawn	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1050	Not Severe	Not Severe	Not Severe	Missed	Deceased	Deceased	Deceased	Deceased
1053	Not Severe	Not Severe	Not Severe	Not Severe	Deceased	Deceased	Deceased	Deceased
1054	Severe	Missed	Missed	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible
1055	Not Severe	Missed	Missed	Deceased	Deceased	Deceased	Deceased	Deceased
1056	Not Severe	Missed	Missed	Missed	Missed	Missed	Missed	Deceased
1057	Severe	Missed	Missed	Missed	Missed	Missed	Missed	Not Possible
1058	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible
1059	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible
1060	Severe	Not Severe	Missed	Missed	Missed	Missed	Missed	Not Possible
1061	Not Severe	Withdrawn	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1063	Not Severe	Withdrawn	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1064	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible
1065	Severe	Missed	Missed	Missed	Missed	Missed	Missed	Not Possible
1068	Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Missed	Missed
1070	Severe	Not Severe	Not Severe	Severe	Not Severe	Not Severe	Severe	Not Possible
1072	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Severe	Not Severe	Not Possible
1073	Severe	Missed	Not Severe	Not Severe	Not Severe	Not Severe	Missed	Not Possible
1075	Not Severe	Not Severe	Missed	Missed	Missed	Missed	Missed	Missed
1076	Severe	Not Severe	Not Severe	Not Severe	Severe	Not Severe	Not Severe	Not Possible
1080	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible
1084	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible
1086	Not Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1087	Severe	Not Severe	Severe	Not Severe	Not Severe	Deceased	Deceased	Deceased
1088	Not Severe	Missed	Missed	Missed	Missed	Missed	Missed	Not Possible
1089	Not Severe	Not Severe	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
1090	Not Severe	Missed	Missed	Deceased	Deceased	Deceased	Deceased	Deceased

Figure 6-4 Patient journey- patients without PC needs A

	STUDY VISIT							
Patient	**Baseline**	**4 Month**	**8 Month**	**12 Month**	**16 Month**	**20 Month**	**24 month**	**30 Month**
1093	Severe	Not Severe	Not Severe	Not Severe	Not Severe	Severe	Missed	Not Possible
1097	Not Severe	Not Severe	Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible
1099	Severe	Missed	Missed	Missed	Missed	Missed	Not Possible	Not Possible
1101	Not Severe	Not Severe	Missed	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible
1102	Not Severe	Severe	Not Severe	Missed	Missed	Missed	Not Possible	Not Possible
1103	Severe	Missed	Missed	Missed	Missed	Missed	Not Possible	Not Possible
1104	Not Severe	Not Severe	Missed	Not Severe	Not Severe	Missed	Not Possible	Not Possible
1106	Not Severe	Missed	Missed	Missed	Missed	Missed	Not Possible	**Deceased**
1107	Not Severe	Not Severe	Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible
1108	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1109	Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible
1111	Not Severe	Not Severe	Missed	Missed	Not Severe	Not Severe	Not Possible	Not Possible
1113	Not Severe	Missed	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1114	Not Severe	Missed	Not Severe	Severe	Not Severe	Not Severe	**Deceased**	**Deceased**
1118	Not Severe	Missed	Missed	Missed	Missed	Missed	Not Possible	Not Possible
1120	Not Severe	Missed	Missed	Missed	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1121	Not Severe	Missed	Missed	Missed	Missed	Missed	Not Possible	Not Possible
1122	Severe	Missed	Severe	Missed	Missed	Missed	Not Possible	Not Possible
1123	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1125	Not Severe	Not Severe	Not Severe	Missed	Missed	Missed	Not Possible	Not Possible
1126	Severe	Not Severe	Missed	Severe	Not Severe	Severe	Not Possible	Not Possible
1127	Not Severe	Missed	Missed	Missed	Missed	Missed	Not Possible	Not Possible
1129	Severe	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1131	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible
1133	Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible
1134	Severe	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1136	Not Severe	Not Severe	Not Severe	Not Severe	Missed	Missed	Missed	Missed
1137	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible
1138	Not Severe	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1139	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1140	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible
1141	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1143	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1144	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible
1145	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Missed	Not Possible	Not Possible
1146	Not Severe	Missed	Not Severe	Not Severe	Not Severe	Severe	Not Possible	Not Possible
1147	Not Severe	Not Severe	Missed	Missed	Missed	Missed	Not Possible	Not Possible
1152	Not Severe	Not Severe	Not Severe	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1154	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1155	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible
1156	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Missed	Not Possible	Not Possible
1158	Not Severe	Not Severe	Not Severe	Not Severe	Missed	Not Possible	Not Possible	Not Possible
1160	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1161	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1162	Severe	Not Severe	Missed	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1163	Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1164	Not Severe	Missed	Missed	Missed	Missed	**Deceased**	**Deceased**	**Deceased**
1165	Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1168	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1169	Severe	Missed	Missed	Missed	Missed	Not Possible	Not Possible	Not Possible
1172	Not Severe	Not Severe	Missed	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1173	Not Severe	Not Severe	Missed	Not Severe	Not Severe	**Deceased**	**Deceased**	**Deceased**
1175	Not Severe	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1176	Not Severe	Not Severe	Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1178	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1179	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1180	Not Severe	Not Severe	Not Severe	Not Severe	Missed	Not Possible	Not Possible	Not Possible
1181	Severe	Missed	Missed	Missed	Missed	Missed	Missed	Missed
1183	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1184	Not Severe	Severe	Not Severe	Not Severe	Not Severe	**Deceased**	**Deceased**	**Deceased**
1185	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1187	Severe	Not Severe	Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1188	Severe	Not Severe	Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1190	Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1191	Not Severe	Not Severe	Not Severe	Not Severe	Severe	Not Possible	Not Possible	Not Possible

Figure 6-5 Patient journey- patients without PC needs B

	STUDY VISIT							
Patient	**Baseline**	**4 Month**	**8 Month**	**12 Month**	**16 Month**	**20 Month**	**24 month**	**30 Month**
1192	Not Severe	Not Severe	Not Severe	Severe	Not Severe	Not Possible	Not Possible	Not Possible
1194	Not Severe	Not Severe	Not Severe	Not Severe	Severe	Not Possible	Not Possible	Not Possible
1195	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1196	Not Severe	Missed	Missed	Missed	Missed	Not Possible	Not Possible	Not Possible
1197	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1200	Not Severe	Not Severe	Severe	Not Severe	Severe	Not Possible	Not Possible	Not Possible
1201	Not Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1202	Severe	Not Severe	Not Severe	Not Severe	Severe	Not Possible	Not Possible	Not Possible
1203	Not Severe	Not Severe	Missed	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1206	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1207	Severe	Not Severe	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1208	Severe	Not Severe	Not Severe	Not Severe	Not Severe	**Deceased**	**Deceased**	**Deceased**
1209	Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1212	Severe	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible
1218	Not Severe	Missed	Missed	Missed	Missed	Not Possible	Not Possible	Not Possible
1219	Not Severe	Missed	Missed	Missed	Not Possible	Not Possible	Not Possible	Not Possible
1220	Not Severe	Missed	Missed	Missed	Not Possible	Not Possible	Not Possible	Not Possible
1221	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1223	Not Severe	Missed	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible
1224	Not Severe	Missed	Missed	Missed	Not Possible	Not Possible	Not Possible	Not Possible
1227	Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible
1228	Not Severe	Not Severe	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1229	Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible
1230	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible
1236	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible
1237	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible
1238	Not Severe	Not Severe	Not Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible
1239	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible
1240	Not Severe	Not Severe	Missed	Missed	Not Possible	Not Possible	Not Possible	Not Possible
1242	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible
1243	Not Severe	Missed	Missed	Missed	Not Possible	Not Possible	Not Possible	Not Possible
1245	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible
1246	Not Severe	Severe	Not Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible
1250	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible
1251	Not Severe	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible
1254	Not Severe	Missed	Missed	Missed	Not Possible	Not Possible	Not Possible	Not Possible
1255	Severe	Not Severe	Missed	Severe	Not Possible	Not Possible	Not Possible	Not Possible
1257	Not Severe	Missed	Missed	Missed	Not Possible	Not Possible	Not Possible	Not Possible
1262	Severe	Not Severe	Missed	Missed	Not Possible	Not Possible	Not Possible	Not Possible
1263	Not Severe	Missed	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1265	Not Severe	Not Severe	Not Severe	Not Possible	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1267	Not Severe	Not Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1268	Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1272	Not Severe	Not Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1273	Severe	Missed	Missed	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1277	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1279	Not Severe	Missed	Missed	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1280	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1282	Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1286	Severe	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1287	Not Severe	Not Severe	Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1288	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1291	Not Severe	Not Severe	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1292	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1293	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1294	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1299	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1302	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1303	Severe	Missed	Missed	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1307	Not Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1308	Severe	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1310	Not Severe	Missed	Missed	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1313	Not Severe	Not Severe	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1316	Not Severe	Missed	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1317	Not Severe	Missed	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible	Not Possible
1321	Not Severe	Missed	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**
1322	Not Severe	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**	**Deceased**

Figure 6-6 Patient journey- patients without PC needs C

6.4.1 Days alive and out of hospital

As there is no universally accepted tool to determine if a patient with heart failure has PC needs, a sensitivity analysis is required to determine if the criteria I have used to define PC needs are appropriate. Examination of the patient journey as determined by the amount of time lost per patient to hospitalisation or death is an appropriate measure. The DAOH should be lower in the patients deemed to have PC needs.

The DAOH *per* PC needs group are described in Table 6-2. Patients classified as having PC needs spend much fewer days alive and out of hospital during the study. The median DAOH for the entire follow-up period was 394 [172-586] days in the PC needs group and 638 [420-809] days in the not PC needs group ($p<0.001$). As every participant had at least one year of passive follow-up, a more useful comparison is DAOH at one year from recruitment date. The median DAOH at one year was 282 [159-333] in the PC needs group, compared to 346 [296-357] in the not PC needs group ($p<0.001$). Perhaps the most striking difference between the two groups was in the proportion of total follow-up spent alive and out of hospital. The median proportion DAOH for the PC needs group was only 0.59 [0.23-0.93], compared to 0.97 [0.75-0.99] in the not PC needs group ($p<0.001$).

Table 6-2 Days alive out of hospital

	All Participants n=272	PC Needs n=73	Not PC Needs n=199	p
DAOH				
DAOH total follow-up, days	581 [345-783]	394 [172-586]	638 [420-809]	**<0.001**
DAOH 1 year, days	333 [256- 355]	282 [159- 333]	346 [296, 357]	**<0.001**
DAOH proportion of potential follow-up, %	94 [49- 98]	59 [23- 93]	97 [75- 99]	**<0.001**
QOL adjusted DAOH				
QOL adjusted DAOH, days	230 [93- 425]	77 [24- 138]	312 [172- 492]	**<0.001**
QOL adjusted DAOH percentage of follow-up, %	31 [13- 58]	12 [3- 22]	47 [25- 68]	**<0.001**
Symptom adjusted DAOH				
Symptom adjusted DAOH, days	360 [169- 545]	190 [73- 270]	439 [278- 585]	**<0.001**
Symptom adjusted DAOH percentage of follow-up, %	51 [23- 74]	23 [10- 42]	63 [41- 79]	**<0.001**

DAOH= days alive out of hospital; QOL= quality of life.

Another important sensitivity analysis is adjusting each day alive out of hospital for QOL, as described in Chapter 3. The QOL adjusted DAOH results are shown in Table 6-2, Figure 6-7, and Figure 6-8. The median number of overall good days, or QOL adjusted DAOH for the whole cohort was 230 [93-425] for the duration of follow-up. There were much fewer QOL adjusted DAOH in the PC needs versus Not PC needs group, with median QOL adjusted DAOH of 77[24-138] and 312 [172-492] ($p< 0.001$), respectively. As follow-up duration varied for each participant, a more useful metric is to calculate the proportion of potential follow-up which was spent with good QOL, as described in Chapter 3 and expressed as a percentage. The median proportion QOL adjusted DAOH for the whole cohort was 31 % [13-58]. There was a significant difference in the proportion of QOL adjusted DAOH compared to potential follow-up between the groups of PC need, with patients in the PC needs group spending 12 [3-22] % of follow-up with good days out of hospital, compared to 47 [25-68] % in the not PC needs group.

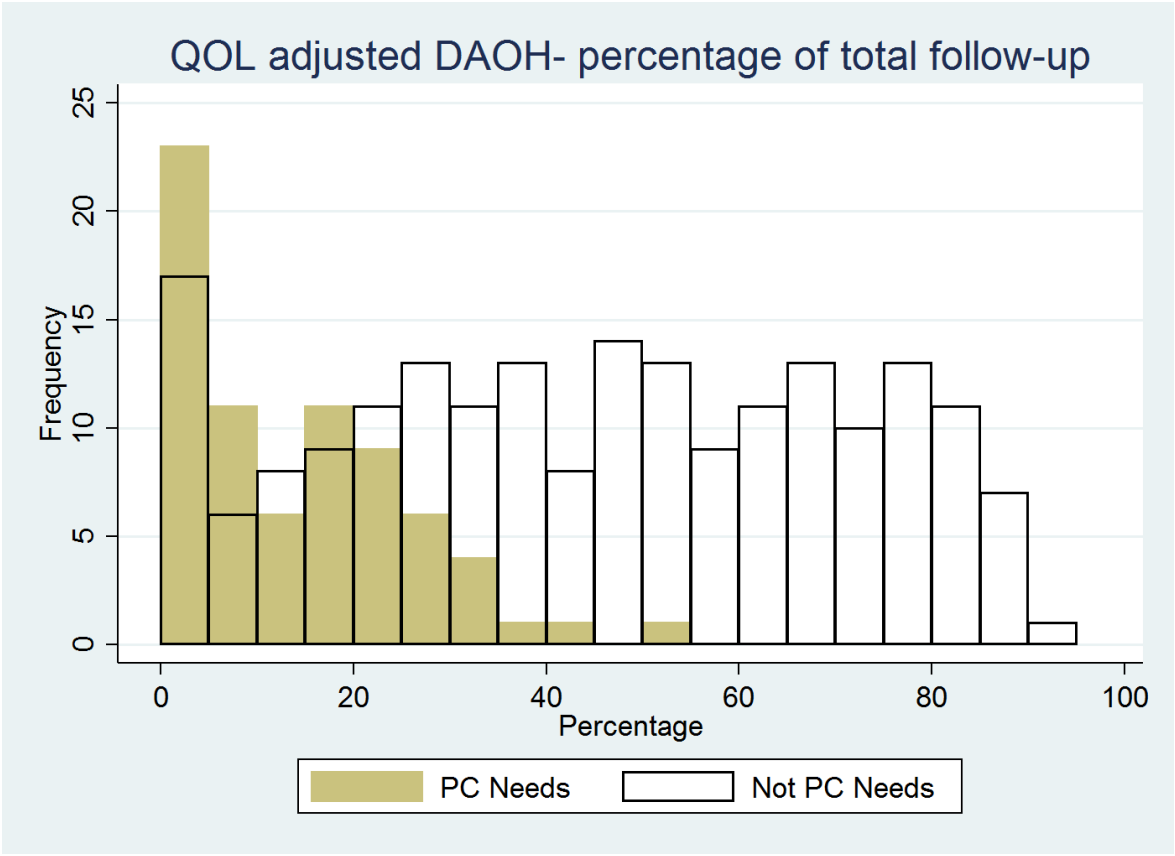


Figure 6-7 QOL adjusted DAOH- histogram

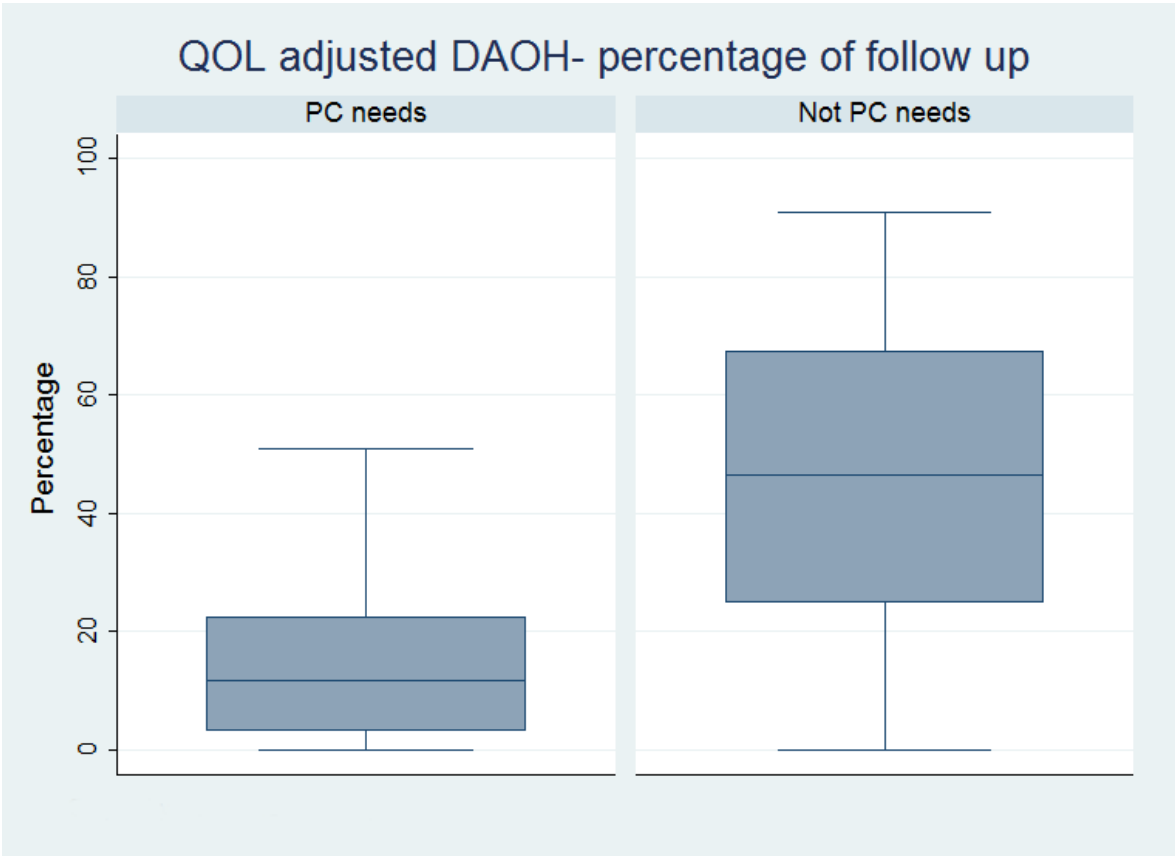


Figure 6-8 QOL adjusted DAOH box plot

Another important sensitivity analysis is to adjust each DAOH for symptom burden, as described in Chapter 3. The results of the symptom adjusted DAOH are shown in Table 6-2, Figure 6-9, and Figure 6-10. The median number of overall good days, after adjusting DAOH for symptom burden, for the whole cohort was 360 [169-545] for the duration of follow-up. There were much fewer symptom adjusted DAOH in the PC needs versus not PC needs group, with median symptom adjusted DAOH of 190 [73-270] and 439 [278-585] ($p< 0.001$), respectively. The median proportion symptom adjusted DAOH for the whole cohort was 51 % [23-74]. There was a significant difference in the proportion of symptom adjusted DAOH compared to potential follow-up between the groups of PC need, with patients in the PC needs group spending 23 [10-42] % of follow-up with good days out of hospital, compared to 63 [41-79] % in the not PC needs group.

The striking, and statistically significant, differences in DAOH, QOL and symptom adjusted DAOH between the two groups of PC need would suggest that the criteria used are appropriate.

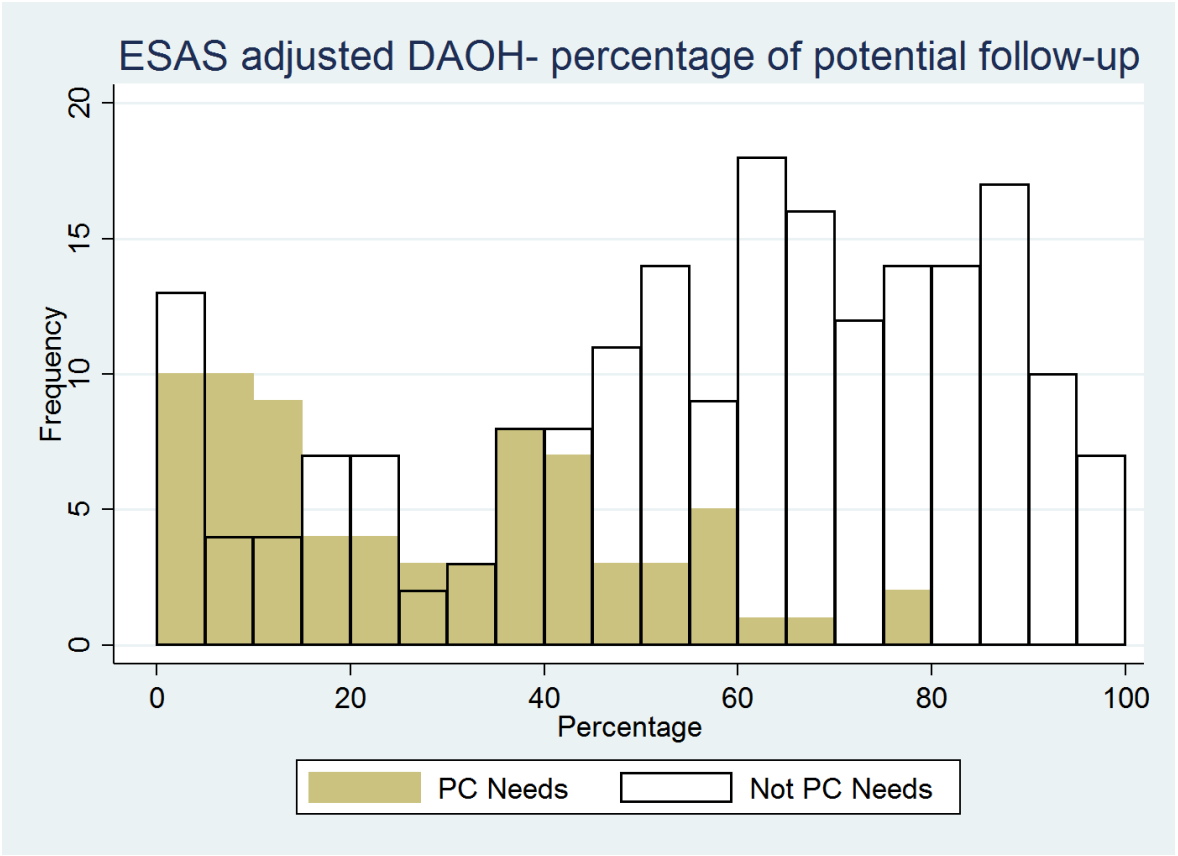


Figure 6-9 Symptom adjusted DAOH histogram per PC needs group

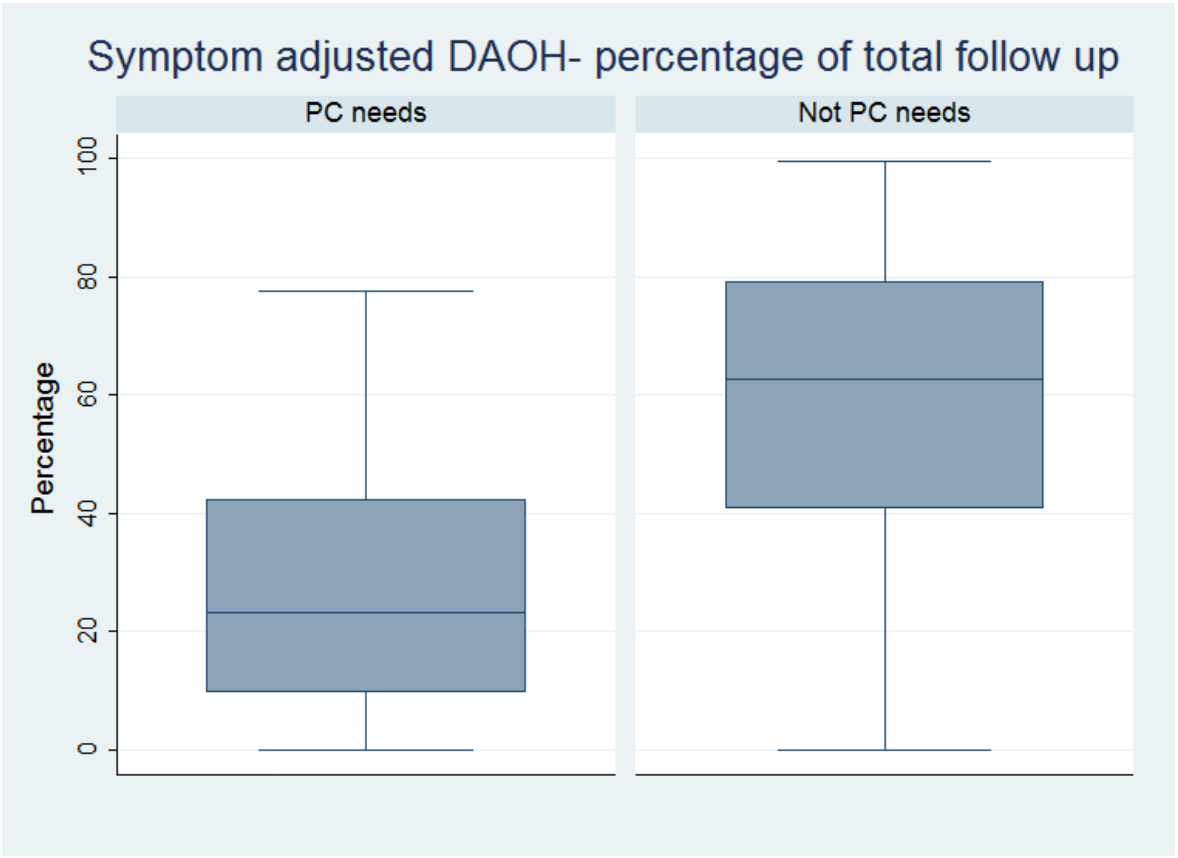


Figure 6-10 Symptom adjusted DAOH box plot per PC needs group

6.5 Baseline demographics clinical features *per* PC needs group

A description of the baseline demographics and physical examination findings *per* PC needs group is provided in Table 6-3. Participants in the PC needs group were younger than those in not-PC needs group, with median ages of 73.6 [66.6-80.5] and 76.6 [70.6-83.0], respectively, although this difference did not reach statistical significance. There was a lower proportion of female participants in the probable PC needs group compared to the unlikely PC needs group, with 37.0 and 50.8% (p= 0.0438), respectively. Both systolic and diastolic blood pressure were lower overall in the probable PC needs group. Other physiological measures were similar between the two groups.

Symptoms of heart failure were similar between the two groups. Orthopnoea was reported by participants in 82.2 and 72.4% of participants in both the probable and unlikely PC needs groups, respectively. Paroxysmal nocturnal dyspnoea was reported in 79.5 and 68.3% participants in both the probable and unlikely PC needs groups, respectively. Ankle swelling was a more commonly reported symptom in participants in the probable compared to unlikely PC needs group, at 84.9 and 73.4% (p= 0.0463), respectively. A similar proportion of ankle swelling was found on physical examination findings, with 86.3 and 72.6 % (p= 0.0186) of probable and unlikely PC needs, respectively. There was a significant difference between the two groups in proportion of participants in each NYHA class with a higher proportion in NYHA class III/IV in the probable compared to unlikely PC needs group. 28.8 compared to 14.1% of the probable compared to unlikely PC needs groups were NYHA class IV, respectively.

Physical examination findings were similar between the two groups, with similar proportions of elevated jugular venous pressure, third heart sound, murmur, pulmonary crackles, and clinical pleural effusions.

Table 6-3 Baseline demographics per PC needs group

	All participants n = 272	PC needs n =73	Not PC needs n = 199	p
Age- yr	76.0 [69.8, 82.4]	73.6 [66.6, 80.5]	76.6 [70.6, 83.0]	0.0628
Female sex- n (%)	128 (47.1)	27 (37.0)	101 (50.8)	**0.0438**
Race or ethnic group- n (%)				0.6667
White	266 (97.8)	71 (97.3)	195 (98.0)	
Black	1 (0.4)	0 (0.0)	1 (0.5)	
Asian	5 (1.8)	2 (2.7)	3 (1.5)	
Other	0 (0.0)	0 (0.0)	0 (0.0)	
Systolic blood pressure- mmHg	134 [118, 155]	127 [112, 152]	136 [120, 158]	**0.0214**
Diastolic blood pressure- mmHg	75 [64, 90]	72 [60, 82]	78.0 [65, 92]	**0.027**
Heart rate- beats/min	82 [68, 102]	81 [71, 100]	82 [68, 103]	0.9054
Body-mass index- kg/m	27.0 [23.5, 31.6]	28.1 [23.6, 31.6]	26.2 [23.5, 31.6]	0.3237
Symptoms- n (%)				
NYHA class				**0.0194**
Class I	0 (0.0)	0 (0.0)	0 (0.0)	
Class II	82 (30.1)	20 (27.4)	62 (31.2)	
Class III	141 (51.8)	32 (43.8)	109 (54.8)	
Class IV	49 (18.0)	21 (28.8)	28 (14.1)	
HF symptoms				
Orthopnoea	204 (75.0)	60 (82.2)	144 (72.4)	0.0971
PND	194 (71.3)	58 (79.5)	136 (68.3)	0.0726
Ankle swelling	208 (76.5)	62 (84.9)	146 (73.4)	**0.0463**
Wheeze	62 (22.8)	14 (19.2)	48 (24.1)	0.3892
Palpitations	10 (3.7)	2 (2.7)	8 (4.0)	0.619
Signs- n (%)				
Elevated JVP (> 4cm)	176 (73.0)	50 (75.8)	126 (72.0)	0.5578
Third Heart Sound	59 (21.8)	17 (23.3)	42 (21.2)	0.7134
Murmur	149 (55.0)	43 (58.9)	106 (53.5)	0.4306
Pulmonary crackles	212 (78.5)	53 (72.6)	159 (80.7)	0.1496
Basal§	210 (99.1)	53 (100)	157 (98.7)	0.412
Middle§	45 (21.2)	15 (28.3)	30 (18.9)	0.1458
Apex§	9 (4.2)	3 (5.7)	6 (3.8)	0.5552
Pleural effusion	95 (35.3)	26 (35.6)	69 (35.2)	0.9498
Right	59 (62.1)	16 (61.5)	43 (62.3)	0.9443
Left	59 (62.1)	15 (57.7)	44 (63.8)	0.5863
Peripheral Oedema	206 (76.3)	63 (86.3)	143 (72.6)	**0.0186**
Ankle*	206 (100.0)	63 (100)	143 (100)	NA
Knee*	125 (60.7)	40 (63.5)	85 (59.4)	0.5833
Thigh*	64 (31.1)	21 (33.3)	43 (30.1)	0.641
Sacrum*	43 (20.9)	13 (20.6)	30 (21.0)	0.9553
Abdomen*	35 (17.0)	12 (19.0)	23 (16.1)	0.6018
Ascites	40 (14.8)	14 (19.2)	26 (13.1)	0.2131

Values are expressed as median [interquartile range]

HF= heart failure; JVP= jugular venous pressure; NYHA = New York Heart Association; PND= paroxysmal nocturnal dyspnoea.

§ percentage of patients with pulmonary crackles

* percentage of patients with peripheral oedema

6.5.1 Past medical history

The past medical history of participants with probable PC needs compared to those with unlikely PC needs is shown in Table 6-4. There was a higher proportion, although not statistically significant, of participants with a prior diagnosis of heart failure in the probable compare to unlikely PC needs group, at 52.1 and 41.2%, respectively. Prior hospitalisation for heart failure was more common in the probable compare to the unlikely PC needs group, although this was not statistically significant. However, participants in the probable PC needs group had a higher prevalence of heart failure hospitalisation in the preceding 6 months compared to those in the unlikely PC needs group, at 13.7 and 6.0% respectively (p=0.04).

Cardiovascular co-morbidities were common, as reported earlier, with similar proportions of atrial fibrillation, hypercholesterolemia, hypertension, peripheral arterial disease, and cerebrovascular disease. 41 (56%) participants in the PC needs groups had suffered a previous myocardial infarction, compared to 70 (35.2%) in the unlikely PC needs group (p 0.0018). Cardiac resynchronisation therapy was rare in both groups, and overall, as were ICDs. Only 8 participants had a cardiac resynchronisation therapy device, and only 4 had an ICD. There were no statistically significant differences between the two groups in terms of device therapy. The low proportion of ICDs and cardiac resynchronisation therapy is notable. Many patients in the cohort will not have met the criteria for such devices, based upon QRS duration and ejection fraction. For some other patients, the index study visit was their first presentation with heart failure, and cardiac resynchronisation is only indicated after optimisation of therapy.

Non-cardiovascular co-morbidities were also common, although not as common as cardiovascular co-morbidities. Most non-cardiovascular co-morbidities had a similar prevalence between the two groups of PC need including COPD, asthma, depression, cancer, hypothyroidism, osteoarthritis, and anaemia. Previously diagnosed diabetes mellitus was more common in the probable versus unlikely PC needs group, at 42.5 and 29.1% (p 0.038), respectively.

Table 6-4 Past medical history per PCneeds group

	All participants n = 272	PC needs n =73	Not PC needs n = 199	p
History of HF- n (%)				
HF diagnosis prior to admission	120 (44.1)	38 (52.1)	82 (41.2)	0.1103
HF hospitalisation	73 (26.8)	27 (71.1)	46 (56.1)	0.1185
HF hospitalisation preceding 6 months	22 (8.1)	10 (13.7)	12 (6.0)	**0.0398**
Cardiovascular- n (%)				
Treated Hypertension	184 (67.6)	51 (69.9)	133 (66.8)	0.6361
Myocardial Infarction	111 (40.8)	41 (56.2)	70 (35.2)	**0.0018**
PCI	38 (14.0)	15 (20.5)	23 (11.6)	0.0581
CABG	42 (15.4)	13 (17.8)	29 (14.6)	0.5129
Hypercholesterolaemia	88 (32.4)	26 (35.6)	62 (31.2)	0.4859
Atrial Fibrillation/Flutter	144 (52.9)	41 (56.2)	103 (51.8)	0.5189
Cerebrovascular disease (CVA/TIA)	52 (19.1)	11 (15.1)	41 (20.6)	0.3037
Peripheral Arterial Disease	37 (13.6)	10 (13.7)	27 (13.6)	0.9778
Primary prevention ICD	4 (1.5)	2 (2.7)	2 (1.0)	0.2949
Pacemaker	18 (6.6)	5 (6.8)	13 (6.5)	0.9258
Conventional[§]	10 (55.6)	4 (80.0)	6 (46.2)	0.1955
CRT-P[§]	3 (16.7)	0 (0.0)	3 (23.1)	0.2393
CRT-D[§]	5 (27.8)	1 (20.0)	4 (30.8)	0.6477
Valve replacement	11 (4.0)	2 (2.7)	9 (4.5)	0.5083
Non-cardiovascular-n (%)				
Diabetes Mellitus	89 (32.7)	31 (42.5)	58 (29.1)	**0.038**
COPD	69 (25.4)	22 (30.1)	47 (23.6)	0.2736
Asthma	23 (8.5)	6 (8.2)	17 (8.5)	0.9323
Depression	37 (13.7)	13 (17.8)	24 (12.2)	0.2325
Cancer	31 (11.4)	7 (9.6)	24 (12.1)	0.5698
Hypothyroidism	35 (12.9)	9 (12.3)	26 (13.1)	0.8723
Osteoarthritis	27 (9.9)	6 (8.2)	21 (10.6)	0.5684
Anaemia	77 (28.3)	23 (31.5)	54 (27.1)	0.4783

CABG= coronary artery bypass graft; COPD= chronic obstructive pulmonary disease; CRT-P= cardiac resynchronisation therapy- pace; CRT-D= cardiac resynchronisation therapy- defibrillator; CVA= cerebrovascular accident; HF= heart failure; ICD= implantable cardioverter defibrillator; PCI= percutaneous coronary intervention; TIA= transient ischaemic attack.

[§] percentage of patients with pacemaker

6.5.2 Drug history- medications started prior to admission

The medications participants were taking prior to admission and those started during admission and on discharge are detailed in Table 6-5 and Table 6-6. Medications prior to the index admission were similar between the two groups of PC need. There were similar proportions of disease modifying therapies such as beta-blockers or RAAS blockers. Hydralazine, nitrates, and ivabradine were rarely prescribed prior to admission in both groups. The only statistically significant difference in drug prescription prior to admission was the PC needs group had a higher proportion prescribed aspirin compared to the group without PC needs, 54.8 and 36.2%, respectively. This is in keeping with the previous finding of a higher proportion of previous myocardial infarction in the PC needs group, as detailed in Table 6-4. Similarly, there was a higher proportion of prescriptions for the anti-platelet drug, clopidogrel, in the PC needs group, although this did not reach statistical significance. The proportions of non-cardiovascular drugs were similar between the two PC needs groups.

The mainstay of pharmacological treatment in hospital for the treatment of symptoms was furosemide, with most participants receiving either a one off or regular intravenous furosemide followed by oral. There were no differences between the two PC needs groups regarding treatment with furosemide. Other medications used in the treatment of acute decompensated heart failure include vasodilators, such as intravenous nitrates, and inotropic agents, such as dobutamine and dopamine. The number and proportion of participants who were treated with these medications was very low, with 6 (2.2%) treated with intravenous nitrates, 4 (1.5%) with dobutamine, and 9 (3.3%) with dopamine. There were no differences between the two PC needs groups other than a higher proportion of participants in the PC needs group were treated with dopamine (p 0.002).

Table 6-5 Pharmacological therapy on admission- per PC needs group

	All participants n = 272	PC needs n =73	Not PC needs n = 199	p
Cardiovascular				
ACEI	108 (39.7)	29 (39.7)	79 (39.7)	1.000
ARB	40 (14.7)	10 (13.7)	30 (15.1)	0.849
Beta-blocker	152 (55.9)	42 (57.5)	110 (55.3)	0.784
MRA	23 (8.5)	8 (11.0)	15 (7.5)	0.460
Hydralazine	8 (2.9)	4 (5.5)	4 (2.0)	0.217
Ivabradine	1 (0.4)	1 (1.4)	0 (0.0)	0.268
Anti-arrhythmic	4 (1.5)	2 (2.7)	2 (1.0)	0.292
Calcium channel-blocker	68 (25.0)	14 (19.2)	54 (27.1)	0.208
Long-acting nitrates	33 (12.1)	11 (15.1)	22 (11.1)	0.403
Statin	171 (62.9)	52 (71.2)	119 (59.8)	0.091
Diabetic medication	70 (25.7)	22 (30.1)	48 (24.1)	0.349
Insulin§	27 (38.6)	6 (27.3)	21 (43.8)	0.290
Sulphonylurea§	33 (47.1)	12 (54.5)	21 (43.8)	0.447
Biguanide§	41 (58.6)	14 (63.6)	27 (56.3)	0.610
Glitazone§	3 (4.3)	0 (0.0)	3 (6.3)	0.547
Other§	8 (11.4)	0 (0.0)	8 (16.7)	0.050
Diuretics	172 (63.2)	53 (72.6)	119 (59.8)	0.065
Digoxin	26 (9.6)	9 (12.3)	17 (8.5)	0.357
Aspirin	112 (41.2)	40 (54.8)	72 (36.2)	**0.008**
Clopidogrel	26 (9.6)	10 (13.7)	16 (8.0)	0.168
Warfarin	78 (28.7)	22 (30.1)	56 (28.1)	0.764
Nicorandil	25 (9.2)	9 (12.3)	16 (8.0)	0.343
Non-cardiovascular				
Bronchodilator	86 (31.6)	29 (39.7)	57 (28.6)	0.105
Steroid tablets*	9 (10.7)	2 (6.9)	7 (12.7)	0.488
Beta-agonist inhalers*	71 (86.6)	23 (82.1)	48 (88.9)	0.498
Anti-cholinergic inhalers*	45 (57.0)	17 (65.4)	28 (52.8)	0.340
Steroid inhalers*	48 (60.8)	22 (78.6)	26 (51.0)	**0.018**
Antidepressants	42 (15.4)	15 (20.5)	27 (13.6)	0.185
SSRI±	17 (40.5)	8 (53.3)	9 (33.3)	0.326
TCA±	19 (45.2)	6 (40.0)	13 (48.1)	0.750
MAOI ±	3 (7.1)	1 (6.7)	2 (7.4)	1.000
Other±	5 (11.9)	1 (6.7)	4 (14.8)	0.639
NSAIDs	8 (2.9)	0 (0.0)	8 (4.0)	0.114
Vitamins	28 (10.3)	9 (12.3)	19 (9.5)	0.504
Antihistamines	11 (4.0)	5 (6.8)	6 (3.0)	0.172

Values are expressed as n (%).

ACE= angiotensin converting enzyme; ARB= angiotensin receptor blocker; MRA= mineralocorticoid receptor antagonist; MAOI= monoamine oxidase inhibitor; SSRI= selective serotonin reuptake inhibitor; TCA= tricyclic antidepressant.

§ percentage of diabetic medication

* percentage of bronchodilator medication

± percentage of antidepressant medication

Prescription of disease modifying therapies was high on discharge from hospital, with 243 (89%) participants taking an ACEi or ARB. 192 (70.6%) participants were prescribed a beta-blocker on discharge, and 91 (33.5%) a mineralocorticoid receptor antagonist. These medications are only indicated in patients with a reduced ejection fraction, 183 (67.3%) participants had an ejection fraction less than 50%.

Table 6-6 Medications started during admission or on discharge- per PC needs group

	All participants n = 272	**PC needs n =73**	**Not PC needs n = 199**	**p**
Cardiovascular				
ACEI	152 (55.9)	39 (53.4)	113 (56.8)	0.680
ARB	91 (33.5)	24 (32.9)	67 (33.7)	1.000
Beta-blocker	192 (70.6)	48 (65.8)	144 (72.4)	0.297
MRA	91 (33.5)	24 (32.9)	67 (33.7)	1.000
Hydralazine	9 (3.3)	5 (6.8)	4 (2.0)	0.061
Ivabradine	1 (0.4)	1 (1.4)	0 (0.0)	0.268
Anti-arrhythmic	7 (2.6)	2 (2.7)	5 (2.5)	1.000
Calcium channel-blocker	28 (10.3)	5 (6.8)	23 (11.6)	0.368
Long-acting nitrates	30 (11.1)	11 (15.3)	19 (9.5)	0.193
Statin	160 (59.0)	42 (58.3)	118 (59.3)	0.890
Diuretics (exc. Furosemide)	22 (8.1)	8 (11.0)	14 (7.0)	0.318
Furosemide	265 (97.4)	70 (95.9)	195 (98.0)	0.390
IV once-off	49 (18.0)	15 (20.5)	34 (17.1)	0.503
IV regular	182 (66.9)	48 (65.8)	134 (67.3)	0.806
Oral once-off	3 (1.1)	1 (1.4)	2 (1.0)	0.118
Oral regular	242 (89.0)	60 (82.2)	182 (91.4)	0.031
Digoxin	76 (27.9)	20 (27.4)	56 (28.1)	1.000
Aspirin	96 (35.4)	30 (41.7)	66 (33.2)	0.200
Clopidogrel	31 (11.4)	7 (9.7)	24 (12.1)	0.671
Warfarin	106 (39.1)	23 (31.9)	83 (41.7)	0.161
Nicorandil	18 (6.6)	4 (5.6)	14 (7.0)	0.788
Inotropes / vasodilators				
IV Nitrate	6 (2.2)	2 (2.7)	4 (2.0)	0.661
Dobutamine	4 (1.5)	2 (2.7)	2 (1.0)	0.292
Dopamine	9 (3.3)	7 (9.6)	2 (1.0)	0.002
IV other	6 (2.2)	1 (1.4)	5 (2.5)	1.000

Values are expressed as n (%).

ACE= angiotensin converting enzyme; ARB= angiotensin receptor blocker; MRA= mineralocorticoid receptor antagonist; IV= intravenous.

6.5.3 Investigations

Electrocardiogram

Details of the ECG findings on admission to hospital are represented in Table 6-7. There were a number of abnormalities in both groups, the most common being the presence of atrial fibrillation on the admission ECG, with a prevalence of 51% in both the probable and unlikely PC needs groups, respectively. A similar proportion of participants had a bundle branch block in both groups, at 32.9 and 28.6%, in the probable and unlikely PC needs groups, respectively. Median QRS duration was higher in the probable PC needs group compared to the unlikely PC needs group at 106 [94-128] and 100 [86-130], although this did not reach statistical significance. The only significant difference between the groups was a higher proportion of pathological Q waves being present in the probable PC needs versus unlikely PC needs group, at 35.6 and 20.2% (p= 0.0087), respectively. This finding is in keeping with the higher prevalence of myocardial infarction seen in the probable PC needs group.

Table 6-7 ECG findings per PC needs group

	All participants n = 272	**PC needs n =73**	**Not PC needs n = 199**	**p**
ECG during admission - n(%)	272 (100)	73 (100)	199 (100)	
Sinus rhythm	138 (50.7)	37 (50.7)	101 (50.8)	0.992
AF/flutter	131 (48.2)	35 (47.9)	96 (48.2)	0.9655
BBB	81 (29.8)	24 (32.9)	57 (28.6)	0.4987
Right[§]	26 (32.1)	10 (38.5)	16 (28.1)	0.2314
Left[§]	55 (67.9)	14 (58.3)	41 (71.9)	
Paced	16 (5.9)	3 (4.1)	13 (6.5)	0.4517
Pathological Q waves	66 (24.4)	26 (35.6)	40 (20.2)	**0.0087**
LVH	54 (19.9)	12 (16.4)	42 (21.1)	0.3925
QRS duration, ms	102 [88, 129]	106 [94, 128]	100 [86, 130]	0.1599
QTc duration, ms	470 [441, 497]	469 [444, 494]	470 [441, 501]	0.9509

AF= atrial fibrillation; BBB= bundle branch block; LVH= left ventricular hypertrophy.
[§] percentage of BBB

Chest X-ray

Chest X-ray findings are detailed in Table 6-8. There were similar frequencies of abnormalities commonly found in decompensated heart failure between the two groups of PC need. These included cardiomegaly, upper lobe venous diversion, interstitial oedema, alveolar oedema and pleural effusions. There was a higher proportion of participants in the unlikely PC group who had bilateral compared to unilateral pleural effusions, although the clinical significance of this is unclear.

Table 6-8 Chest X-ray findings per PC needs group

	All participants (n = 272)	**PC needs (n =73)**		**Not PC needs (n = 199)**		**p**
CXR during admission - n(%)	267 (98.2)	71	(97.3)	196	(98.5)	0.5026
Cardiomegaly (CTR > 0.5)	248 (92.9)	65	(91.5)	183	(93.4)	0.6097
Upper lobe venous diversion	245 (91.8)	64	(90.1)	181	(92.3)	0.5624
Interstitial oedema (Kerley B lines)	112 (41.9)	32	(45.1)	80	(40.8)	0.5337
Alveolar oedema (patchy consolidation)	104 (39.0)	24	(33.8)	80	(40.8)	0.2991
Pleural effusions	140 (52.4)	33	(46.5)	107	(54.6)	0.2409
Right[§]	31 (22.1)	7	(21.2)	24	(22.4)	**0.0282**
Left[§]	16 (11.4)	8	(24.2)	8	(7.5)	
Bilateral[§]	93 (66.4)	18	(54.5)	75	(70.1)	

CTR= cardiothoracic ratio; CXR= chest X-ray.

[§] percentage of patients with pleural effusions

Laboratory results

Laboratory results per PC needs group are detailed in Table 6-9. Median BNP levels were higher in PC compared to no PC needs group, with 807 [471-1810] compared to 680 [417-1329] pg/ml, respectively, although this did not reach statistical significance (p=0.183). A higher proportion (although not significant) of participants in the PC needs group compared to the no PC needs group had detectable troponin, with 65.9 and 48.4%, respectively. Although median troponin levels were numerically higher in the PC needs group compared to the not PC needs group, at 0.06 [0.02-0.13] and 0.02 [0.02-0.11] µg/L, respectively, this difference was not statistically significant. Measures of renal function

(urea, creatinine, eGFR) were similar between the two groups. A numerically higher proportion of participants had renal impairment, as determined by eGFR less than 60 ml/min, in the PC needs group, with 63% compared to 57% in the not PC needs group, although this was not significant. The only biochemical blood tests which were statistically significant between the two groups were potassium and bilirubin, although, as results for both groups were mostly within the normal limits, this likely represents a statically rather than clinically important difference.

Haematology tests were similar between the two groups of PC need. Haemoglobin was similar in the group with PC needs compared to the not PC needs group, with median haemoglobin of 120 [109-136] and 123 [109-138] g/L, respectively.

Table 6-9 Laboratory results per PC needs group

	All participants n = 272	PC needs n =73	Not PC needs n = 199	p
Biochemistry				
BNP level (pg/ml)	724 [420, 1405]	807 [471, 1810]	680 [417, 1329]	0.183
TnI (µg/L)	0.04 [0.02, 0.12]	0.06 [0.02, 0.13]	0.02 [0.02, 0.11]	0.271
TnI ≤ 0.02 µg/L - n(%)	129 (49.6)	30 (44.1)	99 (51.6)	0.500
Sodium (mmol/l)	138 [135, 140]	138 [134, 140]	138 [135, 140]	0.609
Potassium (mmol/l)	4.2 [3.8, 4.6]	4.3 [4.0, 4.6]	4.1 [3.8, 4.5]	**0.035**
Chloride (mmol/l)	103 [99, 106]	103 [98, 106]	103 [99, 107]	0.317
Urea (mmol/l)	8.5 [6.4, 12.4]	8.5 [6.4, 14.3]	8.5 [6.3, 12.0]	0.257
Creatinine (umol/l)	99 [73, 136]	104 [73, 132]	96 [72, 136]	0.268
eGFR (ml/min Derived)	62 [40, 82]	55 [38, 80]	63 [40, 82]	0.647
eGFR <= 60 ml/min-n(%)	159 (58.5)	46 (63.0)	113 (56.8)	0.406
Bilirubin (mmol/l)	16 [10, 23]	13 [9, 21]	17 [11, 26]	**0.034**
AST (mmol/l)	24 [18, 34]	25 [16, 34]	24 [18, 34]	0.768
ALT (mmol/l)	20 [13, 36]	22 [10, 39]	20 [14, 33]	0.974
Alk Phos (mmol/l)	99 [76, 128]	104 [76, 130]	98 [73, 128]	0.611
Albumin (mmol/l)	34 [31, 36]	33 [31, 36]	34 [31, 36]	0.201
TSH (mU/l)	1.60 [0.94, 2.60]	1.50 [0.85, 2.60]	1.60 [0.95, 2.60]	0.629
T4 (pmol/L)	14.00 [0.19, 16.00]	14.40 [12.00, 16.10]	13.50 [0.18, 16.00]	0.077
Urate (mmol/l)	0.51 [0.41, 0.65]	0.55 [0.44, 0.69]	0.51 [0.41, 0.63]	0.093
Glucose (mmol/l)	6.5 [5.6, 8.3]	6.5 [5.7, 7.9]	6.5 [5.5, 8.6]	0.940
Haematology				
Haemoglobin (g/L)	122 [109, 136]	120 [109, 133]	123 [109, 138]	0.444
WCC (x10^9/L)	8.1 [6.4, 10.6]	7.6 [6.2, 9.9]	8.3 [6.6, 10.6]	0.265
HbA1c (mmol/mol)	41 [38, 48]	43 [39, 51]	40 [37, 48]	0.062
MCV (fl)	90.9 [86.1, 95.5]	91.5 [87.3, 95.0]	90.1 [85.9, 95.6]	0.441
Platelets (x10^9/L)	216 [164, 273]	225 [156, 297]	209 [166, 269]	0.494
Lymphocytes (x10^9/L)	1.20 [0.83, 1.60]	1.20 [0.73, 1.76]	1.20 [0.87, 1.60]	0.967

Values are expressed as median [interquartile range] unless specified.
ALT= alanine aminotransferase ; AST= aspirate aminotransferase; eGFR= estimated glomerular filtration rate; HbA1c= haemoglobin A1c; MCV= mean corpuscular volume; BNP= Brain-Type natriuretic peptide; TnI= troponin I; TSH= thyroid stimulating hormone.

Echocardiography

Details of the echocardiographic assessment, per PC needs group, are shown in Table 6-10. Left ventricular volumes (systolic and diastolic), were larger in the probable compared to unlikely PC needs groups, which reached statistical significance for both systolic and diastolic volumes. Other measures of left ventricular size were similar between the two groups. The mean indexed (for body surface area) left ventricular internal diameters in diastole were 3.04 (±0.66) and 2.94 (±0.52) cm, in the PC compared to no PC needs groups,

respectively. A similar, and again not significant, finding was seen in the indexed left ventricular internal diameter in systole. Left ventricular mass, indexed for body surface area, was similar between the two groups, with mean mass of 118 (±34) and 119 (±38) in the two groups.

Measures of left ventricular function, including ejection fraction as measured by Simpson's Biplane method, were similar between the two PC needs groups. Ejection fraction was lower in the PC needs group, but this was not statistically significant, with a mean ejection fraction of 37.6 (±16.9) and 40.4 (16.4), respectively. The markers of diastolic impairment, and prognostic markers, E/e' and left atrial size were similar in both groups. The only statistically significant difference in diastolic function between the two groups, was deceleration time, with a shorter deceleration time in the probable compared to unlikely PC needs group. 89 (32.7 %) patients participating in the PROM part of the study had an ejection fraction $\geq$ 50%, with similar proportions between the two groups of PC need.

Markers of right ventricular structure and function were very similar between the groups, with the only statistically significant difference being a larger mean inferior vena cava size in the probable compared to unlikely PC needs group, at 2.4 (±0.6) and 2.2 (±0.6) cm, respectively. This is perhaps in keeping with a higher prevalence of peripheral oedema reported and found on examination.

There were no differences in the frequency or severity of valvular heart disease between the two groups.

Table 6-10 Echocardiographic findings per palliative care needs group

	All participants n = 272	PC needs n =73	Not PC needs n = 199	p
LV structure				
LViDDi, cm/m^2	2.96 ±0.56	3.04 ± 0.66	2.94 ± 0.52	0.2033
LViSDi, cm/m^2	2.37 ±0.68	2.43 ± 0.78	2.34 ± 0.65	0.3267
LVDVi, ml/m^2	75 ±32	83 ± 37	71.36 ± 29.36	**0.0227**
LVSVi, ml/m^2	49 ±31	58± 35	46 ± 29	**0.0185**
LV mass index, mg/ m^2	119 ±37	118 ± 34	119 ± 38	0.856
LV systolic function				
LVEF Biplane assessment	218 (80.1)	59 (80.8%)	159 (79.9%)	0.8658
LVEF estimated	54 (19.9)	14 (19.2%)	40 (20.1%)	0.8658
LVEF, %	39.63 ±16.55	37.56 ±16.90	40.38 ±16.40	0.2135
EF ≥ 50%	89 (32.7)	21 (28.8)	68 (34.2)	0.467
S-Lateral, m/s	5.54 ±1.99	5.37 ± 1.80	5.61 ± 2.06	0.4063
LV diastolic function				
E, m/s	1.05 ±0.34	1.07 ± 0.34	1.04 ± 0.35	0.5278
a, m/s	0.73 ±0.34	0.62 ± 0.30	0.76 ± 0.34	0.0959
E/a ratio	1.69 ±1.12	2.02 ± 1.27	1.59 ± 1.06	0.1086
E'-Lateral, m/s	0.08 ±0.05	0.08 ± 0.03	0.08 ± 0.06	0.9545
E'-Septal, m/s	0.06 ±0.05	0.06 ±0.02	0.05 ±0.06	0.9875
E'-Average, m/s	0.07 ±0.08	0.08 ± 0.11	0.07 ± 0.06	0.3248
E/E', cm/s	17.45 ±7.57	17.20 ± 6.82	17.54 ± 7.85	0.7489
DT, ms	194.1 ±72.94	174.0 ±60.11	201.45 ± 75.94	**0.0077**
LAVi, ml/m^2	57 ±18	59.46 ±18.56	55.53 ± 17.93	0.1365
RV structure/ function				
RViDD, cm	3.53 ±0.72	3.60 ± 0.80	3.51 ± 0.69	0.379
TV Peak Gradient, ms	2.85 ±0.57	2.88 ± 0.53	2.83 ± 0.58	0.5538
RV Systolic Pressure, mmHg	48.29 ±14.34	49.24 ±13.58	47.90 ± 14.65	0.5373
IVC Diameter, mm	2.24 ±0.56	2.38 ± 0.56	2.18 ± 0.56	**0.0251**
TAPSE, mm	18 ±6	16.56 ± 5.94	18.16 ± 5.73	0.1011
RA Volume, ml	23.32 ±7.8	23.38 ± 7.91	23.30 ± 7.71	0.9404
Valvular disease				
Valve disease	228 (83.8)	61 (83.6)	167 (83.9)	0.9434
Significant Valve Disease*	65 (23.9)	19 (26.0)	46 (23.1)	0.6178
Significant TR§	21 (7.7)	5 (6.8)	16 (8.0)	0.7444

Continuous variables are expressed as mean ± standard deviation unless specified, categorical variables are expressed as n (%).

DT = deceleration time; IVC = inferior vena cava; LAV ; left atrial volume index; LV = left ventricle; LVEF ; left ventricular ejection fraction; LViDDi= left ventricular internal diastolic dimension indexed; LVDVi = left ventricular diastolic volume indexed; LVISDi= left ventricular internal systolic dimension indexed; LVSVi = left ventricular systolic volume indexed; RV = right ventricle; RViDD= right ventricular internal diameter diastole; TAPSE = tricuspid annular plane systolic excursion; TV= tricuspid valve;

* Defined as ≥ moderate-severe left sided valve disease.

§ defined as ≥ moderate-severe tricuspid regurgitation.

6.6 Patient reported outcome measures

HADS

The distribution of baseline summary scores for both the HADS Anxiety and Depression summary scores, *per* PC needs category are displayed in Figure 6-11 and Table 6-11. 263 (96.7%) participants completed the HADS questionnaires at baseline. The median HADS Anxiety summary score was higher in the probable PC needs group compared to the unlikely PC needs group at 9.5 [6.0-13.0] and 6.0 [3.0-9.0] ($p<0.001$), respectively. A statistically significant, higher proportion of participants were classified as having either moderate or severe impairment on the HADS Anxiety summary score in the PC needs group compared to the not PC needs group. Most participants (81.9%) were graded as none/mild impairment in the not PC needs group, compared to 54.3% in the PC needs group.

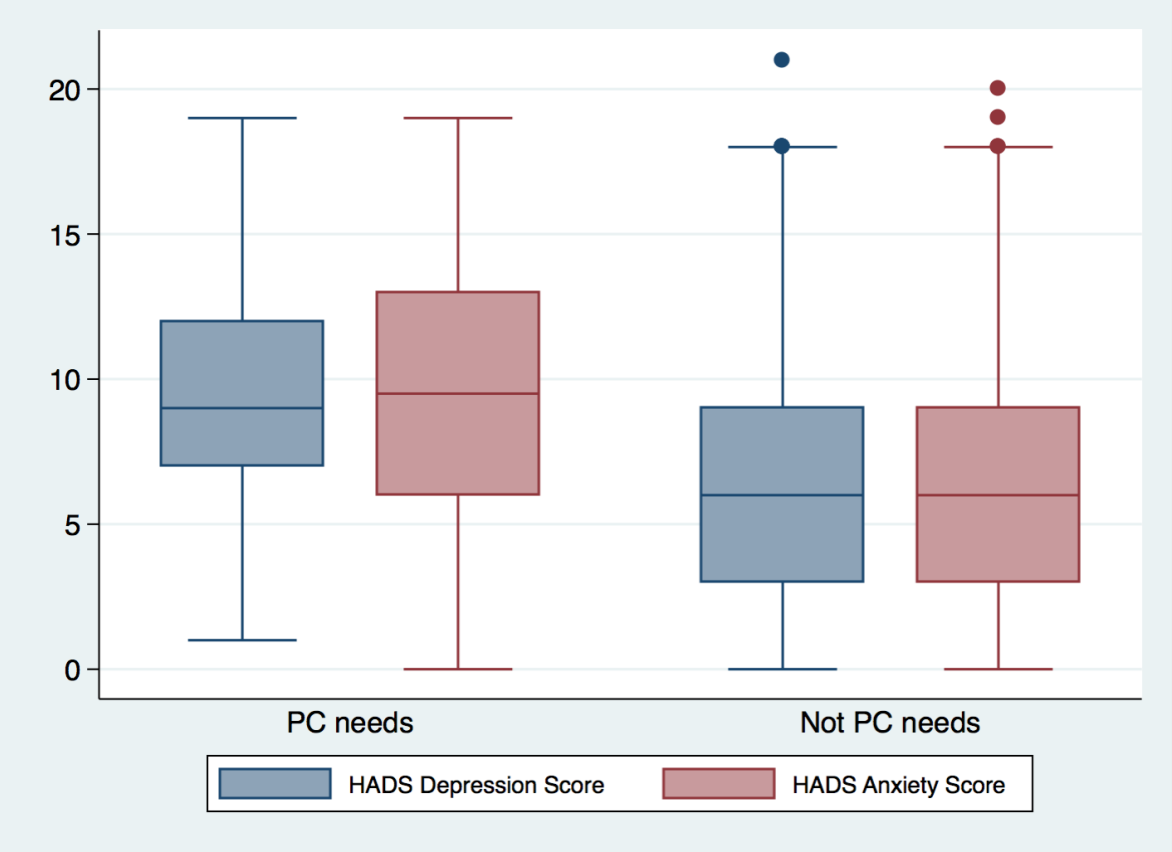


Figure 6-11 HADS summary scores per PC needs category

A similar difference in baseline HADS Depression summary scores were also seen, with higher baseline scores in the PC needs group. The median scores for the

probable and unlikely PC needs at baseline were 9.0 [7.0-12.0] and 6.0 [3.0-9.0] (p<0.001), respectively. A similar trend was present in baseline distribution of severity as determined by the HADS Depression scale. Similar proportions of participants were classified as severe in the two PC needs groups, with 3 and 7 participants. However, most participants in the not PC needs group were classified as none/mild depression at baseline (88.8%). This was a higher proportion compared to those in the PC needs group, where 62% were classified as none/mild depression and 33.8% classified as moderate.

Table 6-11 HADS summary score and severity category per PC needs group

	PC needs n= 73	**Not PC needs n = 199**	**p**
n with HADS Anxiety	70 (95.9)	193 (97.0)	
HADS Anxiety Summary Score, median[IQR]	9.5 [6.0-13.0]	6.0 [3.0-9.0]	**<0.0001**
HADS Anxiety Severity category, n (%)			**<0.0001**
None/mild	38 (54.3)	158 (81.9)	
Moderate	22 (31.4)	28 (14.5)	
Severe	10 (14.3)	7 (3.6)	
n with HADS Depression	71 (97.3)	196 (98.5)	
HADS Depression Summary Score, median[IQR]	9.0 [7.0-12.0]	6.0 [3.0-9.0]	**<0.0001**
HADS Depression Severity category, n (%)			**<0.0001**
None/mild	44 (62.0)	174 (88.8)	
Moderate	24 (33.8)	15 (7.7)	
Severe	3 (4.2)	7 (3.6)	

HADS= hospital anxiety and depression scale; PC = palliative care.

KCCQ

The distribution of baseline overall summary scores for the KCCQ *per* PC needs group are shown in Figure 6-12. The distribution of the composite scores which make up the overall summary score, the summary score, and KCCQ severity category by PC needs group, are detailed in Table 6-12. Every participant completed the KCCQ. This is due to the KCCQ allowing for a missing value or response, where the other PROMs do not. All of the composite scores of the KCCQ were lower in the PC needs group compared to the not PC needs group, with the exception of the Self-efficacy score. The median self-efficacy scores in the PC needs and not PC needs groups were 50.0 [25.0-75.0] and 62.5 [37.5-

87.5] (p=0.158). Figure 6-12 demonstrates the lower baseline KCCQ summary score in the PC versus not PC needs groups, with median scores of 15.9 [8.3-27.3] and 38.5 [26.0-51.8] (p<0.0001). There was also a much higher proportion of participants graded as severe by the KCCQ summary score at baseline in the PC versus not PC needs groups, with 68.5 and 22.6%, respectively. There was a much lower proportion of participants classified as none/mild in the PC compared to not PC needs groups, at 8.2 and 27.1%, respectively.

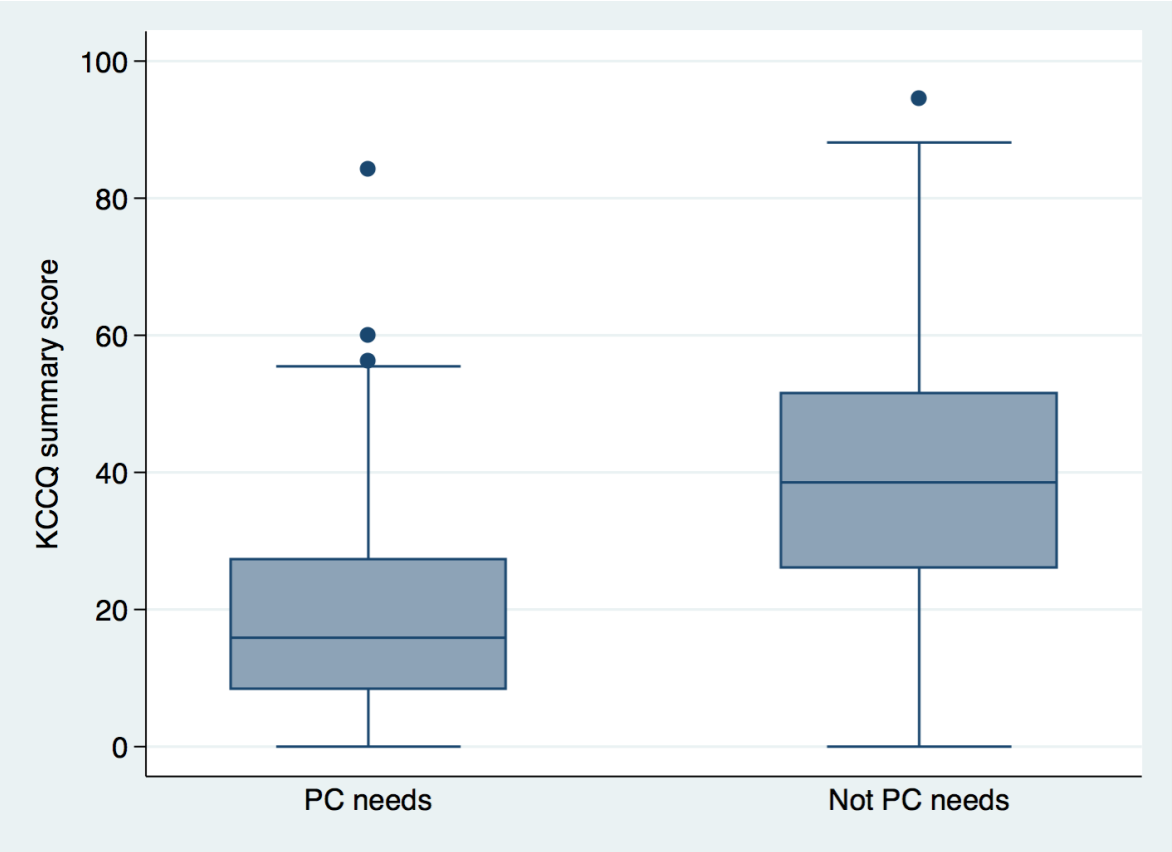


Figure 6-12 KCCQ summary score per PC category

Table 6-12 KCCQ summary scores and severity category per PC needs category

	PC needs n= 73	**Not PC needs n = 199**	**p**
KCCQ completed	73 (100)	199 (100)	
Symptom stability score	0.0 [0.0-25.0]	25.0 [0.0-75.0]	**0.0006**
Symptom frequency score	18.8 [6.2-31.2]	33.3 [18.8-52.1]	**<0.0001**
Symptom burden score	25.0 [0.0-33.3]	41.7 [25.0-58.3]	**<0.0001**
Total symptom score	17.7 [8.3-32.3]	40.6 [21.9-54.2]	**<0.0001**
Self-Efficacy score	50.0 [25.0-75.0]	62.5 [37.5-87.5]	**0.158**
Quality of life score	16.7 [8.3-33.3]	41.7 [16.7-58.3]	**<0.0001**
Social limitation score	7.3 [0.0-16.7]	33.3 [14.6-58.3]	**<0.0001**
Clinical score	17.7 [9.9-30.7]	39.6 [25.0-51.6]	**<0.0001**
Summary score	15.9 [8.3-27.3]	38.5 [26.0-51.6]	**<0.0001**
KCCQ Overall Severity category, n (%)			**<0.0001**
None/mild	6 (8.2)	54 (27.1)	
Moderate	17 (23.3)	100 (50.3)	
Severe	50 (68.5)	45 (22.6)	

Values are expressed as median [IQR] or n (%).
KCCQ= Kansas City Cardiomyopathy Questionnaire; PC = palliative care.

ESAS

The distribution of baseline overall summary scores for the ESAS *per* PC needs group are shown in Figure 6-13. The distribution of different symptom scores which make up the overall ESAS summary score and ESAS severity category by PC needs group, are detailed in Table 6-13. Most participants (98.9%) completed the ESAS at baseline. The median score for every individual symptom was higher in the PC needs group when compared to the not PC needs group, with the exception of nausea. The median score for nausea was 0 [0-4] and 0 [0-2] for probable and unlikely PC needs groups, respectively. The symptoms with the highest scores in the PC needs group were those often characteristic of heart failure, namely tiredness and shortness of breath, with median scores of 8 [5-9] and 8 [6-9], respectively. Patients rated their overall wellbeing as particularly poor in the PC needs group, with a median overall wellbeing score of 7 [4-8]. The overall summary score was higher in the PC compared to not PC need, with median scores of 52.6 [35.8-62.6] and 34.0 [18.0-49.0], respectively. A statistically significant higher proportion of participants were in the severe category for ESAS summary score in the PC compared to not PC group, as shown in Table 6-13. 13 (18.1%) of the PC group compared to 13 (6.6%) of the not PC needs group were classified as severe according to the ESAS.

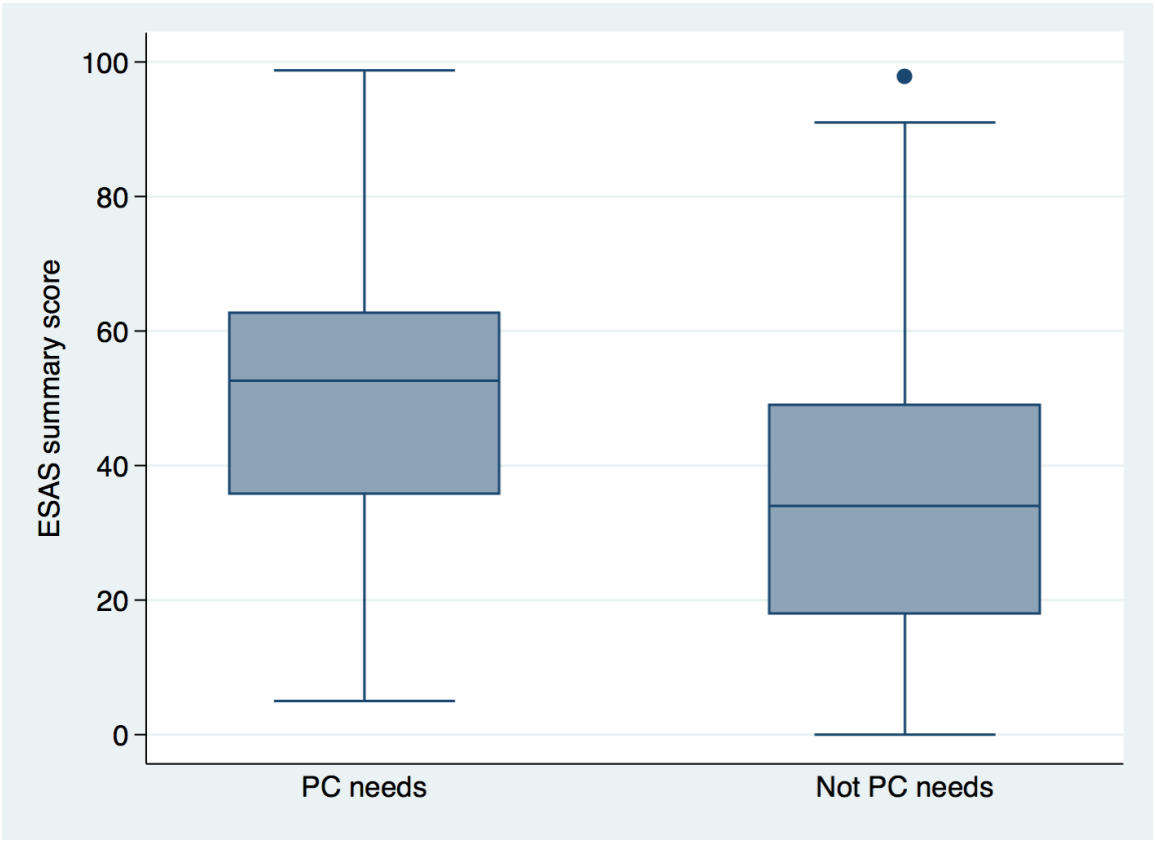


Figure 6-13 ESAS summary score per PC needs category

Table 6-13 ESAS summary score and severity category per PC needs category

	PC needs n= 73	Not PC needs n = 199	p
n with ESAS	72 (98.6)	197 (99.0)	
Pain	4.0 [0.0-6.0]	1.0 [0.0-4.0]	**0.0004**
Tiredness	8.0 [5.0-9.0]	5.0 [3.0-8.0]	**<0.0001**
Drowsiness	6.0 [3.0-8.0]	4.0 [1.0-7.0]	**0.0012**
Nausea	0.0 [0.0-4.0]	0.0 [0.0-2.0]	**0.078**
Lack of appetite	4.0 [0.0-8.0]	3.0 [0.0-6.0]	**0.0414**
Shortness of breath	8.0 [6.0-9.0]	6.0 [3.0-8.0]	**<0.0001**
Depression	5.0 [2.0-8.0]	1.0 [0.0-5.0]	**<0.0001**
Anxiety	4.0 [2.0-8.0]	2.0 [0.0-5.0]	**<0.0001**
Overall wellbeing	7.0 [4.0-8.0]	4.0 [2.0-6.0]	**<0.0001**
ESAS summary score	52.6 [35.8-62.6]	34.0 [18.0-49.0]	**<0.0001**
ESAS Overall Severity category, n (%)			**<0.0001**
None/mild	14 (19.4)	94 (47.7)	
Moderate	45 (62.5)	90 (45.7)	
Severe	13 (18.1)	13 (6.6)	

Values are expressed as median [IQR] or n (%).

ESAS= Edmonton Symptom Assessment Scale; PC = palliative care.

SF-12

The distribution of baseline summary scores for both the SF-12 Physical and Mental summary scores, *per* PC needs category are displayed in Figure 6-14 and Table 6-14. 249 (91.5%) participants completed the SF-12 questionnaire at baseline, 70 (95.9%) and 179 (89.9%) of the PC group and not PC needs group, respectively. Median scores for the various components of the aggregate physical and mental scores are shown in Table 6-14, with all medians being lower (worse) in the PC compared to not PC needs group at baseline.

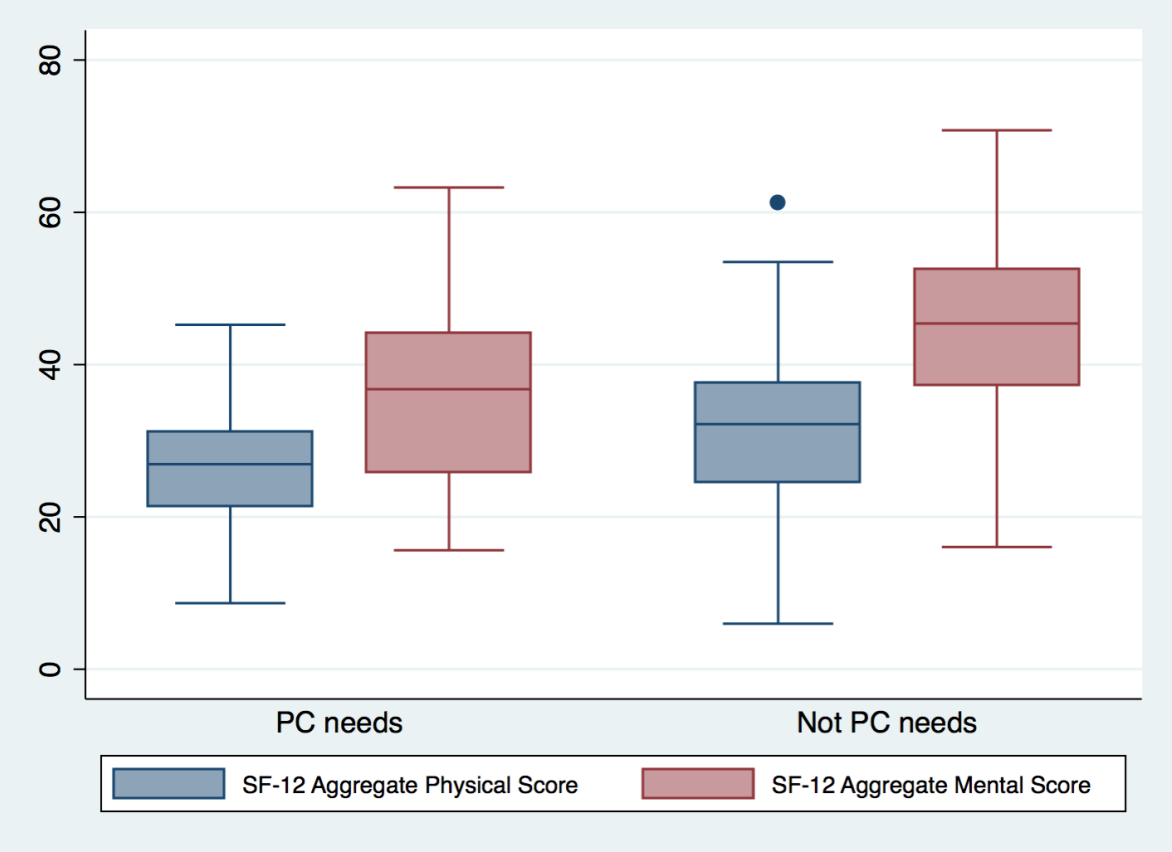


Figure 6-14 SF-12 summary scores per PC needs category

The median aggregate physical scores were 26.9 [21.3-31.2] and 32.2 [24.5-37.6] (p <0.0001) for the PC and not PC needs groups respectively, as shown in Figure 6-14 and Table 6-14. The median aggregate mental score was also lower in the PC compared to not PC needs group, although the overall scores were higher than the aggregate physical scores as shown in Figure 6-14. A higher proportion of participants were classified as moderate or severe for SF-12 Physical aggregate score in the PC compared to not PC needs group, with 21.4 and 14.3% compared to 32.4 and 11.2%, respectively. Fewer participants were classified as

moderate or severe using the aggregate mental wellbeing score in either PC needs group, compared to the aggregate physical burden score. Most participants in the not PC needs group were classified as none/mild (86.0%). A higher proportion of participants in the PC compared to not PC needs group were classified as either moderate or severe using the aggregate mental wellbeing score, with 21.4 and 14.3% compared to 12.3 and 1.7%, respectively.

Table 6-14 SF-12 summary scores and severity category *per* PC needs category

	PC needs n= 73	**Not PC needs n = 199**	**p**
n with SF-12	70 (95.9)	179 (89.9)	
Physical functioning score	22.1 [22.1-22.1]	22.1 [22.1-39.3]	**<0.0001**
Physical role score	20.3 [20.3-29.5]	29.5 [29.5-38.7]	**<0.0001**
Bodily pain score	26.9 [16.7-47.3]	47.3 [26.9-57.4]	**0.0005**
General health score	18.9 [18.9-29.6]	29.6 [29.6-44.7]	**<0.0001**
Vitality score	37.7 [27.6-37.7]	37.7 [27.6-47.7]	**0.005**
Social functioning score	26.3 [16.2-26.3]	36.4 [26.3-46.5]	**<0.0001**
Emotional role score	22.5 [11.3-33.7]	39.3 [28.1-56.1]	**<0.0001**
Mental health score	40.2 [28.0-46.3]	46.3 [40.2-52.3]	**<0.0001**
Aggregate physical score	26.9 [21.3-31.2]	32.2 [24.5-37.6]	**<0.0001**
Aggregate mental score	36.8 [25.9-44.1]	45.4 [37.2-52.6]	**<0.0001**
SF-12 Physical Severity Category			**0.0014**
None/mild	22 (31.4)	101 (56.4)	
Moderate	33 (47.1)	58 (32.4)	
Severe	15 (21.4)	20 (11.2)	
SF-12 Mental Severity Category			**<0.0001**
None/mild	45 (64.3)	154 (86.0)	
Moderate	15 (21.4)	22 (12.3)	
Severe	10 (14.3)	3 (1.7)	

Values are expressed as median [IQR] or n (%).
SF-12= short form 12; PC = palliative care.

ZBI

The summary scores and severity categories for the ZBI are detailed in Table 6-15. 93 (34.1%) of participants' caregivers completed the ZBI caregiver burden questionnaire, with 27 (37.0%) and 66 (33.2%) of caregivers for participants in the PC and not PC needs groups, respectively. Baseline caregiver burden was higher in the PC compared to not PC needs group, with median scores of 24.0 [15.0-38.0] and 12.0 [6.0-22.0] (p0.0008), respectively. Most caregivers in the not PC needs group (72.7%) were classified as none/mild severity using the ZBI, compared to 33.3% of caregivers in the PC needs group. Similarly, a higher proportion of caregivers were classified as moderate or severe in the PC compared to not PC needs, as shown in Table 6-15.

Table 6-15 Zarit Burden Interview summary score and severity category per PC needs category

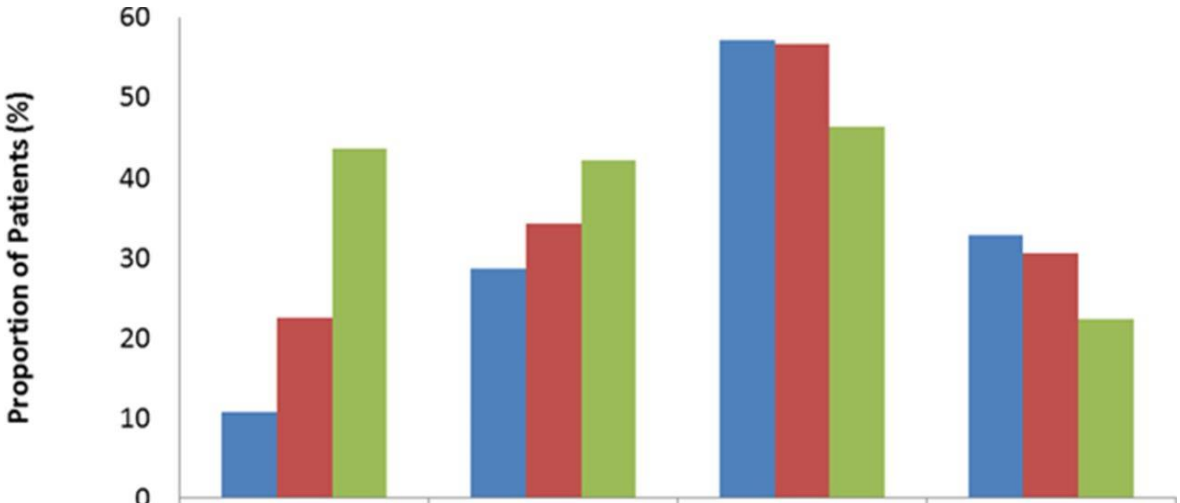
	PC needs n=73	**Not PC needs n=199**	**p**
n with ZBI	27 (37.0)	66 (33.2)	
ZBI summary score	24.0 [15.0-38.0]	12.0 [6.0, 22.0]	**0.0008**
ZBI Severity Category			**0.0018**
None/mild	9 (33.3)	48 (72.7)	
Moderate	12 (44.4)	13 (19.7)	
Severe	6 (22.2)	5 (7.6)	

Values are expressed as median [IQR] or n (%).
ZBI= Zarit burden interview; PC = palliative care.

6.7 Access to palliative care services

Electronic patient records, PC registries, and hospice records were searched to identify participants who accessed specialist PC either as an inpatient or outpatient. Details of participants who accessed hospice care were also recorded. Of the 272 participants who participated in the whole study, 33 (12.1%) accessed specialist PC services. Of the 73 participants who met the definition of PC needs, 19 (26.0%) accessed specialist PC services, compared to 14 (7.0%) of the 199 participants who did not meet the definition of PC needs ($p< 0.001$). Very few participants accessed hospice care, either as an inpatient or an outpatient. Of the 272 participants who participated in the whole study, only 6 (2.2%) accessed some form of hospice care. 5 (6.8%) of participants who met the diagnosis of PC needs accessed hospice care, compared to only one participant (0.5%) of those who did not meet the definition of PC need ($p=0.007$). Some participants who accessed PC services or hospice care may have accessed these services due to established referral pathways from other conditions, such as cancer. It was not possible to determine from electronic records the reason for referral.

The proportion who accessed specialist PC services or hospice care is lower than reported in other cohorts. A recent analysis of the Rochester epidemiology project in the United States of America analysed access to palliative and hospice care in patients with heart failure between 2003 and 2012.[109] The proportions of patients with heart failure who accessed PC over the 9 years of study are shown in Figure 6-15. Of the 1369 patients with heart failure studied, there were 698 deaths. Over the 9 years of study, there was a dramatic increase in the proportion of participants who accessed specialist PC services, with 43.6% accessing PC during a similar follow-up period to my study. There was also a dramatic difference in the proportion of patients who accessed hospice care, with 42.2% of patients with heart failure in the Rochester Epidemiological study compared to only 2.2% in my study over a similar follow-up period. Interestingly, fewer patients with heart failure were hospitalised in the last month of life or died in hospital latterly in the Rochester project. These data are retrospective and not from RCT data, therefore, it is not possible to say that increased PC access resulted in fewer heart failure patients dying in hospital.



	Palliative Medicine consult	Hospice	Hospitalized in last month	In-hospital death
2003-2006	10.8	28.6	57.1	32.8
2007-2009	22.5	34.2	56.7	30.6
2010-2012	43.6	42.2	46.4	22.4

Figure 6-15 Trends in hospice enrolment and palliative care consultations Rochester USA Reproduced with permission from Shannon M. Dunlay *et al*. Circ Heart Fail. 2015;8:489-496.[109]

Although this study is informative for comparison, the healthcare systems in the United States of America and the United Kingdom are quite different, particularly in funding and access to hospice care. Perhaps a more useful comparison is the heart failure audit of England and Wales between 2013 and 2014.[53] This audit included 55 040 patients admitted to hospital because of heart failure. Of these, only 4% of patients accessed PC services. This proportion was lower than the proportion referred and seen by specialist PC services in my study. There is a large discrepancy between the number of patients who met the definition of PC need in my cohort and the number who accessed PC services, although those in the PC needs group were more likely to access PC than those not in the PC needs group.

6.8 Summary

Participants were reviewed frequently and systematically in this study, with a total of 963 individual patient assessments. As well as this active follow-up, participants were followed-up passively using record linkage for a minimum of 1 year, maximum of 2.9 years, and a median of 2.1 years. PROMs were repeated systematically at every patient contact, giving this study a unique opportunity to chart the fluctuation and severity over time in how patients viewed their own health. The number, frequency, high retention in the study, and depth of assessment, make this study the most in depth assessment of PC needs in patients with heart failure. Using the definition of PC needs described earlier, a large proportion of patients in this cohort had PC needs. 72 (27%) of participants met the criteria for PC needs. Participants who were classified as having PC needs had fewer DAOH, and a much lower proportion of the total follow-up was spent alive and out of hospital, suggesting that the criteria used to define PC needs is appropriate. Furthermore, patients meeting the criteria for the definition of PC needs had much worse QOL and symptom adjusted DAOH, again confirming that the group identified was appropriate.

There were few differences between the two groups of PC need in terms of conventional markers of severity of heart failure. Although natriuretic peptide levels were higher in the PC needs group, the difference did not reach statistical significance. Left ventricular size was larger in the PC needs group, but this only reached statistical significance when measured as an estimated diastolic and systolic volume, rather than internal diameter. Systolic function, as measured by ejection fraction, was lower in the group with PC needs, but again, this did not reach statistical significance. Other common prognostic biomarkers were similar between the two groups.

Baseline demographics were similar between the two groups of PC need, with some notable exceptions. A history of myocardial infarction or diabetes was more common in the PC needs group, as was prescription of the anti-platelet aspirin in keeping with higher proportions of prior myocardial infarction. Participants classified as having PC needs were more often NYHA class IV then II/III. Systolic and diastolic blood pressures were lower on admission, and a clinical finding of oedema was more prevalent in the PC needs group.

Pharmacotherapy prescriptions were similar between the two groups of PC need, including proportions of patients treated with disease modifying therapies such as RAAS inhibitors, beta-blockers, and MRAs. Although infrequently prescribed in either group, participants in the PC needs group had a higher prevalence of inotropic prescriptions.

The most marked differences between the two groups at baseline were the summary scores, severity categories, and individual components of each PROM. Participants that were classified as having PC needs had worse scores on each PROM, and were more often classified as severe rather than mild or moderate. Caregiver burden, where available, was higher in the PC needs group, again with a higher proportion classified as having severe burden in the PC needs group.

Despite the patients in this population having a limited life expectancy associated with high symptom burden and low quality of life, very few participants accessed specialist PC services. Even fewer participants accessed hospice care. There appeared to be a marked discrepancy between participants who met the definition of PC needs and who accessed PC services. Furthermore, participants who accessed specialist PC services may have been referred due to another co-morbid condition such as cancer, although this was not possible to ascertain from electronic records.

Prediction of patients who met the definition of PC needs from baseline characteristics and PROMs will be explored in more detail in the following chapter.

Chapter 7 Predicting patients with PC needs

In this chapter I will assess whether it is possible to predict, from the baseline hospital admission data, patients who met the definition of PC needs. Guidelines would suggest that poor functional state, frequent hospitalisations despite optimal therapy, cardiac cachexia, and a clinical judgement of approaching EOL, should be used to determine if a patient requires PC. [3] The most recent ESC guidelines also discuss using performance status as a method of monitoring palliative patients, but do not discuss this as a method to identify patients who should receive PC.[262] During the course of each index hospital admission I asked the treating cardiologist or physician to assess whether they thought the patient had more or less than one year to live. I also asked them whether they thought the patient had PC needs. I will describe whether predicted poor prognosis, predicted PC needs, predictive model for mortality, performance status, or patient reported outcome measures can predict patients who met the definition of PC needs.

7.1 Physician prediction of palliative care needs and prognosis

The questionnaire given to the treating doctor is shown in Appendix 6. Of the 272 patients who participated in the whole study, a physician prediction of PC need was available in 264 (97.1%). The treating physician asked was a cardiologist in 91% of cases and a general internal physician in 9%. The grade of physician who completed the questionnaire was consultant (33.3%), specialist registrar (61.7%), staff grade doctor (4.2%), and senior house officer (0.8%). The results of physician prediction of PC needs compared to patients who did or did not meet the definition of PC needs are shown in Table 7-1. 61 patients were estimated to have PC needs, of these, 22 met the definition of PC needs. The sensitivity of physician prediction of PC needs was 36.1%: the specificity was 75.4%, with an area under the receiver operating curve (AUROC) of 0.56 (95% CI 0.49 to 0.62). The positive and negative predictive values of the physician prediction of PC needs were 30.6 and 79.7%, respectively.

Table 7-1 Physician prediction of PC needs

Physician predicted PC needs	PC needs		
	Yes	No	Total
Yes	22	39	61
No	50	153	203
Total	72	192	264

The results of physician prediction of poor prognosis (defined as less than one year) compared to those who met the definition of PC needs are shown in Table 7-2. 262 physicians gave an estimate of prognosis. 75 patients were predicted to have a prognosis less than one year, of these 26 met the definition of PC needs, giving a sensitivity of 34.7%. 187 patients were predicted to have a prognosis of greater than a year, of these, 141 did not meet the criteria for the definition of PC needs, giving a specificity of 75.4%. The AUROC was 0.55 (95% CI 0.49 to 0.61). The positive and negative predictive values of physician prediction of prognosis at predicting PC needs were 36.1 and 74.2%, respectively. These results are very similar, although there were different proportions of patients in each category, to the physician prediction of PC needs. This suggests that for the physicians asked, their assessment of PC need was linked to their assessment of prognosis.

Table 7-2 Physician prediction prognosis vs PC needs group

Physician predicted prognosis < 1 year	PC needs		
	Yes	No	Total
Yes	26	49	75
No	46	141	187
Total	72	190	262

An analysis of the accuracy of the treating physician in predicting prognosis is shown in Table 7-3. 262 physicians completed the assessment of prognosis, and tried to predict which patients they thought had a prognosis of less than one year. Of these 262 participants, there were 100 deaths. Of the 75 predicted to have a poor prognosis, 47 died, giving a sensitivity of 62.7%. Of the 187 predicted to have a better prognosis (deemed survival greater than one year), 134 were alive at the end of follow-up, giving a specificity of 71.7%. The AUROC was 0.67 (95% CI 0.61 to 0.74). The positive and negative predictive values of physician prediction of prognosis at predicting PC needs were 47.0 and 82.7%,

respectively. A comparison of physician prediction of prognosis less than one year versus survival at one year is shown in Table 7-4. There were 54 deaths during the first year of follow-up. The sensitivity was understandably lower at 42.7%. The specificity was high at 88.2%. Positive and negative predictive values were 59.3 and 79.3%, respectively. The AUROC was 0.65 (05% CI 0.59-0.72).

Table 7-3 Physician prediction prognosis vs survival

Physician predicted prognosis < 1 year	**Died during follow-up**		
	Yes	No	Total
Yes	47	28	75
No	53	134	187
Total	100	162	262

Table 7-4 Physician prediction prognosis versus survival 1 year

Physician predicted prognosis < 1 year	**Died during 1st year of follow-up**		
	Yes	No	Total
Yes	32	43	75
No	22	165	187
Total	54	208	262

These results suggest that physicians were better at predicting prognosis than they were at predicting which patients had PC needs, as defined earlier. The similarities in sensitivity and specificity of physician prediction of prognosis and PC needs at identifying patients with PC needs suggests that physicians link prognosis to PC need.

7.2 Physician completed assessments of palliative care need

During the baseline assessment, I completed the AKPS and the NAT-PD-HF assessments. These are both assessments which are completed by physician. The AKPS is an end of the bed assessment, whereas the NAT-PD-HF is an assessment based upon discussions with the patient (and caregiver where available).

7.2.1 Australia Modified Karnofski Performance Scale

The AKPS is a functional, bedside assessment commonly used in patients with cancer to monitor PC need.[230] The physician marks a score between 0 and 100, indicating physical performance. Higher scores indicate better performance. An example of the AKPS is shown in page 18 of the case report form, Appendix 3.

All participants had an AKPS assessment completed. The overall mean and median were 72.6 (15.3) and 70 [60-80], respectively. The range of scores were from 40 to 100. A score of 40 indicates a participant is in bed more than 50% of the time. Patients in the PC needs group had lower scores on the AKPS compared to those who did not meet the definition of PC needs, with mean values of 65.9 (14.0) and 75.0 (15.0) ($p<0.001$), respectively. Median values were also lower in the PC need group compared to the not PC need group, at 60 [60-80] and 80 [60-90] ($p<0.001$), respectively.

7.2.2 Needs Assessment Tool-Progressive Disease- Heart Failure

The NAT-PD-HF is a single page assessment which can be completed by any member of the healthcare team. This has specifically been developed for use in patients with heart failure, and aims to identify patients with heart failure who have PC needs. An example of the NAT-PD-HF is provided in page 19 of the case report form, Appendix 3. The NAT-PD-HF is divided into three sections: patient well-being assessment; ability to care for the patient; and caregiver wellbeing assessment. Each section has specific questions, which the healthcare professional answers whether they have no concern, some/potential concern, or significant concern. I have classified the NAT-PD-HF overall as significant level of concern if any of the responses were answered “significant level of concern”.

The results of the NAT-PD-HF are detailed in Table 7-5 and Table 7-6. Participants in the PC needs group scored a higher percentage of "significant concern" in the first three questions regarding patient wellbeing. These were "Is the patient experiencing unresolved physical symptoms?", "Does the patient have problems with daily living activities?", and "Does the patient have psychological symptoms that are interfering with wellbeing?". There was also a small, but statistically significant difference regarding caregiver wellbeing in the question "Is the caregiver or family experiencing grief over the impending or recent death of the patient that is interfering with their wellbeing or functioning?" Other than these questions, there were no statistically significant differences between patients who met the diagnostic criteria for PC needs and those who did not. For the purposes of using the NAT-PD-HF as a potential tool to identify patients with heart failure with PC needs, I defined 'significant level of concern' as assessed by the NAT-PD-HF, as scoring 'significant concern' for any of the questions regarding patient wellbeing (Table 7-5).

Table 7-5 NAT-PD-HF patient wellbeing component

	All participants			PC needs			Not PC needs			p
	No concern	Some concern	Significant concern	No concern	Some concern	Significant concern	No concern	Some concern	Significant concern	
PATIENT WELLBEING										
1. Is the patient experiencing unresolved physical symptoms?	107 (39.5)	110 (40.6)	54 (19.9)	15 (20.5)	32 (43.8)	26 (35.6)	92 (46.5)	78 (39.4)	28 (14.1)	**< 0.001**
2. Does the patient have problems with daily living activities?	109 (40.1)	114 (41.9)	49 (18.0)	16 (21.9)	33 (45.2)	24 (32.9)	93 (46.7)	81 (40.7)	25 (12.6)	**< 0.001**
3. Does the patient have psychological symptoms that are interfering with wellbeing?	197 (73.0)	62 (23.0)	11 (4.1)	41 (56.9)	27 (37.5)	4 (5.6)	156 (78.8)	35 (17.7)	7 (3.5)	**< 0.001**
4. Does the patient have concerns about how to manage his/her medication and treatment?	208 (77.0)	54 (20.0)	8 (3.0)	52 (71.2)	52 (71.2)	2 (2.7)	156 (79.2)	35 (17.8)	6 (3.0)	0.336
5. Does the patient have concerns about spiritual or existential issues?	245 (90.4)	20 (7.4)	6 (2.2)	61 (83.6)	11 (15.1)	1 (1.4)	184 (92.9)	9 (4.5)	5 (2.5)	0.017
6. Does the patient have financial or legal concerns that are causing distress or require assistance?	257 (94.5)	14 (5.1)	1 (0.4)	67 (91.8)	5 (6.8)	1 (1.4)	190 (95.5)	9 (4.5)	0 (0.0)	0.232
7. From the health delivery point of view, are there health beliefs, cultural or social factors involving the patient or family that are making care more complex?	260 (95.6)	7 (2.6)	5 (1.8)	71 (97.3)	1 (1.4)	1 (1.4)	189 (95.0)	6 (3.0)	4 (2.0)	0.876
Values are expressed as n(%)										

Table 7-6 NAT-PD-HF caregiver wellbeing component

	All participants			PC needs			Not PC needs			p
	No concern	Some concern	Significant concern	No concern	Some concern	Significant concern	No concern	Some concern	Significant concern	
ABILITY OF CAREGIVER OR FAMILY TO CARE FOR PATIENT										
1. Is the caregiver or family distressed about the patient's physical symptoms?	50 (39.1)	59 (46.1)	19 (14.8)	11 (28.9)	18 (47.4)	9 (23.7)	39 (43.3)	41 (45.6)	10 (11.1)	0.127
2.Is the caregiver or family having difficulty providing physical care?	83 (64.8)	33 (25.8)	12 (9.4)	20 (52.6)	13 (34.2)	5 (13.2)	63 (70.0)	20 (22.2)	7 (7.8)	0.143
3. Is the caregiver or family having difficulty coping?	97 (75.8)	27 (21.1)	4 (3.1)	27 (71.1)	9 (23.7)	2 (5.3)	70 (77.8)	18 (20.0)	2 (2.2)	0.538
4. Is the caregiver have difficulty managing the patient's medication and treatment regimes?	111 (86.7)	16 (12.5)	1 (0.8)	34 (89.5)	4 (10.5)	0 (0.0)	77 (85.6)	12 (13.3)	1 (1.1)	0.842
5. Does the caregiver or family have financial or legal concerns that are causing distress or require assistance?	118 (93.7)	7 (5.6)	1 (0.8)	35 (94.6)	1 (2.7)	1 (2.7)	83 (93.3)	6 (6.7)	0 (0.0)	0.334
6. Is the family currently experiencing problems that are interfering with their functioning or inter-personal relationships, or is there a history of such problems?	117 (92.9)	7 (5.6)	2 (1.6)	33 (89.2)	4 (10.8)	0 (0.0)	84 (94.4)	3 (3.4)	2 (2.2)	0.262
CAREGIVER WELLBEING										
1. Is the caregiver or family experiencing physical, practical, spiritual, existential or psychological problems that are interfering with their wellbeing or functioning?	20 (16.5)	101 (83.5)	0 (0.0)	5 (14.3)	30 (85.7)	0 (0.0)	15 (17.4)	71 (82.6)	0 (0.0)	0.791
2. Is the caregiver or family experiencing grief over the impending or recent death of the patient that is interfering with their wellbeing or functioning?	104 (83.2)	16 (12.8)	5 (4.0)	26 (70.3)	7 (18.9)	4 (10.8)	78 (88.6)	9 (10.2)	1 (1.1)	**0.012**

Values are expressed as n(%)

7.3 Multivariable model

To identify independent predictors that could potentially be used to highlight patients at risk of developing PC needs, markers of prognosis, physician completed assessments, and PROMs from baseline were compared by calculating univariable and multivariable odds ratios and 95% confidence intervals. The prognostic variables used were age, sex, NYHA classification, eGFR, history of diabetes, systolic blood pressure, ejection fraction, natriuretic peptide, and serum sodium. These variables were the most commonly used in a recently published systematic review of prognostic models in heart failure, both acute and chronic.[263] I have also included physician completed assessments, namely the AKPS and NAT-PD-F, and also the PROMs. Patients were classified as having "significant level of concern" overall on the NAT-PD-HF if they scored "significant" in any of the patients wellbeing components of the NAT-PD-HF. I categorised the PROMs into severity category, as this could be more useful in clinical practice to identify patients with potential PC needs. As many of the PROMs had comparatively few patients classified as severe at baseline, other than KCCQ, the PROMs were grouped by "none/mild" and "moderate/severe".

The results of the multivariable analysis are shown in Table 7-7.

Table 7-7 Univariable and multivariable analysis of predictors of PC needs

Variable	n	Univariate odds ratio	Univariate 95% CI	Univariate p-value	n	Multivariate odds ratio	Multivariate 95% CI	Multivariate p-value
Prognostic variables								
Age (per year increase)	262	0.98	(0.95, 1.02)	0.337	231	1.01	(0.97, 1.05)	0.520
Gender (Female)	262	0.66	(0.35, 1.22)	0.185	231	0.48	(0.21, 1.10)	0.084
Diabetes Mellitus	262	1.89	(0.98, 3.64)	0.058	231	1.30	(0.57, 2.95)	0.528
NYHA Class	262			0.043	231			0.110
Class III vs II	262	0.87	(0.43, 1.74)	0.685	231	0.36	(0.14, 0.93)	0.036
Class IV vs II	262	2.25	(0.95, 5.28)	0.064	231	0.45	(0.13, 1.54)	0.201
Systolic blood pressure (per mmHg increase)	262	0.99	(0.98, 1.00)	0.089	231	0.99	(0.98, 1.01)	0.328
eGFR (per ml/min increase)	262	1.00	(0.99, 1.01)	0.971	231	1.00	(0.99, 1.02)	0.910
Ejection Fraction (per 5% decrease < 50)	262	0.99	(0.87, 1.13)	0.905	231	1.07	(0.90, 1.26)	0.453
Log BNP level (pg/ml) (per unit increase)	262	1.14	(0.74, 1.75)	0.557	231	1.28	(0.73, 2.22)	0.385
BMI (per kg/m2 increase)	262	1.01	(0.96, 1.06)	0.712	231	1.05	(0.98, 1.12)	0.174
Sodium (per mmol/l increase)	262	0.99	(0.93, 1.05)	0.640	231	1.00	(0.93, 1.08)	0.952
Physician completed assessment								
AKPS Score(per 10 unit increase)	272	0.96	(0.94, 0.98)	< 0.001	231	0.98	(0.94, 1.01)	0.138
NAT-PD-HF - Significant Level of Concern	272	0.43	(0.24, 0.77)	0.004	231	0.90	(0.35, 2.32)	0.830
PROMs								
HADS Depression Severity (Mod/Sev)	267	4.85	(2.53, 9.32)	< 0.001	231	1.61	(0.61, 4.23)	0.337
HADS Anxiety Severity (Mod/Sev)	263	3.80	(2.09, 6.90)	< 0.001	231	1.74	(0.66, 4.62)	0.264
KCCQ Overall Summary Score Severity	272			< 0.001	231			< 0.001
Moderate vs Mild/None	272	1.53	(0.57, 4.11)	0.399	231	1.41	(0.40, 4.91)	0.592
Severe vs Mild/None	272	10.00	(3.93, 25.4)	< 0.001	231	7.18	(1.77, 29.1)	0.006
ESAS-R Severity (Mod/Sev)	269	3.78	(1.98, 7.22)	< 0.001	231	2.04	(0.82, 5.11)	0.127
SF-12 Physical Severity (Mod/Sev)	249	2.83	(1.57, 5.07)	< 0.001	231	1.28	(0.58, 2.84)	0.543
SF-12 Mental Severity (Mod/Sev)	249	3.42	(1.79, 6.53)	< 0.001	231	0.78	(0.30, 2.06)	0.618

AKPS= Australia Modified Karnofsky Performance Scale; BNP= brain type natriuretic peptide; eGFR= estimated glomerular filtration rate; ESAS= Edmonton Symptom Assessment Scale; HADS= Hospital Anxiety and Depression Scale; KCCQ= Kansas City Cardiomyopathy Questionnaire; NAT-PD-HF= Needs Assessment Tool Progressive Disease Heart Failure.

Of the 272 patients who participated in the study, 231 had complete data for the purposes of the multivariable analysis. None of the conventional predictors of prognosis, when measured at admission, predicted patients who were subsequently classified as having PC needs. Neither of the physician completed assessments, the AKPS and NAT-PD-HF, predicted PC needs in a multivariable analysis. The only variables which independently predicted PC need at baseline, were a severe score on KCCQ (KCCQ < 25), and NYHA class II. That NYHA class II is an independent predictor of PC needs is counter-intuitive. After analysis for correlation between variables, NYHA class and KCCQ severity were strongly correlated. I therefore, removed NYHA class from the multivariable analysis due to collinearity of these variables. The results of the multivariable analysis using categorical variables for each PROM is shown in Table 7-8. The multivariable analysis was repeated using continuous variables for each PROM summary score, as shown in Table 7-9.

Table 7-8 Multivariable analysis of prediction of PC need using categorical PROM variables

Variable	n	Multivariate odds ratio	Multivariate 95% CI	Multivariate p-value
Prognostic variables				
Age (per year increase)	231	1.01	(0.97, 1.05)	0.695
Gender (Female)	231	0.45	(0.20, 1.02)	0.056
Diabetes Mellitus	231	1.27	(0.57, 2.84)	0.558
Systolic blood pressure (per mmHg increase)	231	0.99	(0.98, 1.01)	0.282
eGFR (per ml/min increase)	231	1.00	(0.99, 1.01)	0.980
Ejection Fraction (per 5% decrease < 50)	231	1.06	(0.90, 1.24)	0.473
Log BNP level (pg/ml) (per unit increase)	231	1.16	(0.68, 2.00)	0.584
BMI (per kg/m^2 increase)	231	1.04	(0.97, 1.10)	0.278
Sodium (per mmol/l increase)	231	0.99	(0.92, 1.07)	0.852
Physician completed assessment				
AKPS Score (per 10 unit increase)	231	0.98	(0.95, 1.01)	0.186
NAT-PD-HF - Significant Level of Concern	231	0.94	(0.38, 2.36)	0.901
PROMs				
HADS Depression Severity (Mod/Sev)	231	1.60	(0.63, 4.08)	0.322
HADS Anxiety Severity (Mod/Sev)	231	1.89	(0.74, 4.85)	0.186
KCCQ Overall Summary Score Severity	231			**0.002**
Moderate vs Mild/None	231	0.96	(0.30, 3.12)	0.950
Severe vs Mild/None	231	4.37	(1.25, 15.3)	**0.021**
ESAS-R Severity (Mod/Sev)	231	1.91	(0.78, 4.68)	0.159
SF-12 Physical Severity (Mod/Sev)	231	1.34	(0.61, 2.94)	0.460
SF-12 Mental Severity (Mod/Sev)	231	0.79	(0.31, 2.00)	0.612

AKPS= Australia Modified Karnofsky Performance Scale; BNP= brain type natriuretic peptide; eGFR= estimated glomerular filtration rate; ESAS= Edmonton Symptom Assessment Scale; HADS= Hospital Anxiety and Depression Scale; KCCQ= Kansas City Cardiomyopathy Questionnaire; NAT-PD-HF= Needs Assessment Tool Progressive Disease Heart Failure.

Table 7-9 Multivariable analysis of prediction of PC need continuous PROM variables

Variable	n	Multivariate odds ratio	Multivariate 95% CI	Multivariate p-value
Prognostic variables				
Age (per year increase)	231	1.00	(0.96, 1.04)	0.941
Gender (Female)	231	0.51	(0.23, 1.11)	0.088
Diabetes Mellitus	231	1.39	(0.63, 3.10)	0.415
Systolic blood pressure (per mmHg increase)	231	0.99	(0.97, 1.00)	0.149
eGFR (per ml/min increase)	231	1.00	(0.99, 1.02)	0.709
Ejection Fraction (per 5% decrease < 50)	231	1.04	(0.89, 1.22)	0.622
Log (BNP level (pg/ml)) (per unit increase)	231	1.12	(0.66, 1.91)	0.674
BMI (per kg/m^2 increase)	231	1.02	(0.96, 1.09)	0.468
Sodium (per mmol/l increase)	231	0.98	(0.91, 1.05)	0.558
Physician completed assessment				
AKPS Score (per 10 unit increase)	231	0.98	(0.95, 1.01)	0.241
NAT-PD-HF - Significant Level of Concern	231	0.81	(0.33, 1.99)	0.641
PROMs				
HADS Depression summary score (per unit increase)	231	0.99	(0.89, 1.11)	0.896
HADS Anxiety summary score (per unit increase)	231	1.04	(0.94, 1.15)	0.493
KCCQ Overall Summary Score (per unit increase)	231	0.97	(0.94, 1.00)	**0.029**
ESAS-R summary score (per unit increase)	231	1.00	(0.98, 1.02)	0.941
SF-12 Physical summary score (per unit increase)	231	0.99	(0.93, 1.04)	0.649
SF-12 Mental summary score (per unit increase)	231	0.97	(0.92, 1.02)	0.234

AKPS= Australia Modified Karnofsky Performance Scale; BNP= brain type natriuretic peptide; eGFR= estimated glomerular filtration rate; ESAS= Edmonton Symptom Assessment Scale; HADS= Hospital Anxiety and Depression Scale; KCCQ= Kansas City Cardiomyopathy Questionnaire; NAT-PD-HF= Needs Assessment Tool Progressive Disease Heart Failure.

Using a backwards selection method, a best fit multivariable model was created first using categorical variables for each PROM, then using continuous variables for each PROM summary score. The results of these best fit models are shown in Table 7-10 and Table 7-11, respectively. The independent predictors of PC needs, when assessed at baseline were KCCQ less than 25, HADS anxiety score of moderate or severe, lower AKPS score, and male sex, when using the PROMs as categorical variables. When using the PROMs as continuous variables, the strongest independent predictors of PC need were lower KCCQ summary score, lower AKPS score, and male sex.

The AUROC for the multivariable model using PROM data as categorical variables was 0.80. The AUROC for the multivariable model using PROM data as continuous variables was 0.81. Therefore, categorical variables were used in the final model for ease of interpretation.

Table 7-10 Multivariable model prediction PC needs- categorical PROM variables

Variable	n	Multivariate odds ratio	Multivariate 95% CI	Multivariate p-value
Gender (Female)	231	0.39	(0.19, 0.80)	0.010
AKPS Score (per 10 unit increase)	231	0.97	(0.95, 1.00)	0.020
HADS Anxiety Severity (Mod/Sev)	231	2.14	(1.02, 4.46)	0.044
KCCQ Overall Summary Score Severity	231			< 0.001
Moderate vs Mild/None	231	1.21	(0.40, 3.70)	0.738
Severe vs Mild/None	231	6.90	(2.33, 20.4)	< 0.001

AKPS= Australia Modified Karnofsky Performance Scale; HADS= Hospital Anxiety and Depression Scale; KCCQ= Kansas City Cardiomyopathy Questionnaire.

Table 7-11Multivariable model prediction PC needs- continuous PROM variables

Variable	n	Multivariate odds ratio	Multivariate 95% CI	Multivariate p-value
Gender (Female)	231	0.44	(0.22, 0.88)	0.020
AKPS Score (per 10 unit increase)	231	0.97	(0.95, 1.00)	0.026
KCCQ Overall Summary Score (per unit increase)	231	0.95	(0.93, 0.97)	< 0.001

AKPS= Australia Modified Karnofsky Performance Scale; KCCQ= Kansas City Cardiomyopathy Questionnaire.

7.4 Summary

Common prognostic predictors in heart failure, when assessed in the first few days of admission, did not predict patients that met the definition of PC needs. Physician completed tools used in other terminal conditions to monitor PC needs, namely the AKPS and NAT-PD-HF, identified patients who went on to meet the definition of PC needs. Only AKPS was predictive of PC needs after multivariable analysis. All of the PROMs, assessed in the first few days of admission, were predictive of PC needs, but only the KCCQ was an independent predictor of PC needs after multivariable analysis.

Physicians' clinical acumen had a modest correlation in identifying patients with PC needs during an index heart failure hospitalisation. Physicians were better at predicting prognosis than predicting PC needs. Two best-fit multivariable models were created (using backwards selection), one with categorical and one with continuous variables for baseline PROMs. Both models had similar AUROC values. Both models had greater accuracy for predicting patients with PC needs than physician assessment. The model using continuous PROM variables is perhaps more useful clinically as there is only one PROM required, and one physician completed assessment.

That KCCQ was the strongest predictor of PC needs, is somewhat of a self-fulfilling prophecy as participants had to have a severe PROM (either before death, or persistently severe without improvement) to meet our chosen definition of PC needs, and KCCQ had the highest proportion of participants categorised as severe. However, this information has been shown to be clinically relevant. Clinicians will know that if a patient has a low summary score during an admission due to heart failure, they are at risk of not only reduced days alive out of hospital, but also persistently impaired QOL. These data are in keeping with the analysis of the large, multicentre, acute heart failure study EVEREST.[112] The authors of this study used different, although similar, criteria for the definition of PC needs. They defined PC needs as persistently impaired QOL (defined as KCCQ less than 45 at one-week post discharge and at 6 months) or death before 6 months. In a multivariable analysis, they found that KCCQ less than 25 was the strongest predictor of PC need (i.e. meeting the above definition). The EVEREST authors found that some

predictors of prognosis also predicted PC need, whereas my study did not. There are a number of possible explanations for this. Firstly, their definition of PC needs included death, whereas my study used severe impairment preceding death. Secondly, the cohort studied in EVEREST were exclusively HF-REF, and most prognostic variables and models have been tested and validated in HF-PEF, where my study included all ejection fractions. Thirdly, I assessed prognostic variables close to day of admission, where EVEREST assessed on day of discharge. Markers such as natriuretic peptide are potentially more powerful predictors of prognosis on discharge than admission.[264, 265] This potentially reflects the dynamic physiological changes which can occur during a heart failure hospitalisation, such as reduction in natriuretic peptide or improvement in renal function with diuresis. It would appear that a KCCQ score taken either on admission or discharge is predictive of patients with heart failure who have or will go on to develop PC needs.

Chapter 8 Heart failure at end of life

In this chapter I will evaluate EOL in patients in with heart failure. I will describe how and where patients with heart failure died, and compare those with and without PC needs, as defined in Chapter 3. I will also compare preferred place of death to actual place of death. Lastly, I will assess EOL care by reporting the results of the EOL questionnaire VOICES.

8.1 Mortality

Of 272 participants, during the mean follow-up of 2.1 years, there were 103 (37.9%) deaths. Of the whole cohort of 313 patients, there were 118 (36.5%) deaths. 15 (36.7%) of the patients who did not participate in the questionnaire or active follow-up aspects of the study died. There were no statistically significant differences between those who participated in the whole study and those who did not. The Kaplan-Meier survival analysis *per* PC needs group is shown in Figure 8-1.

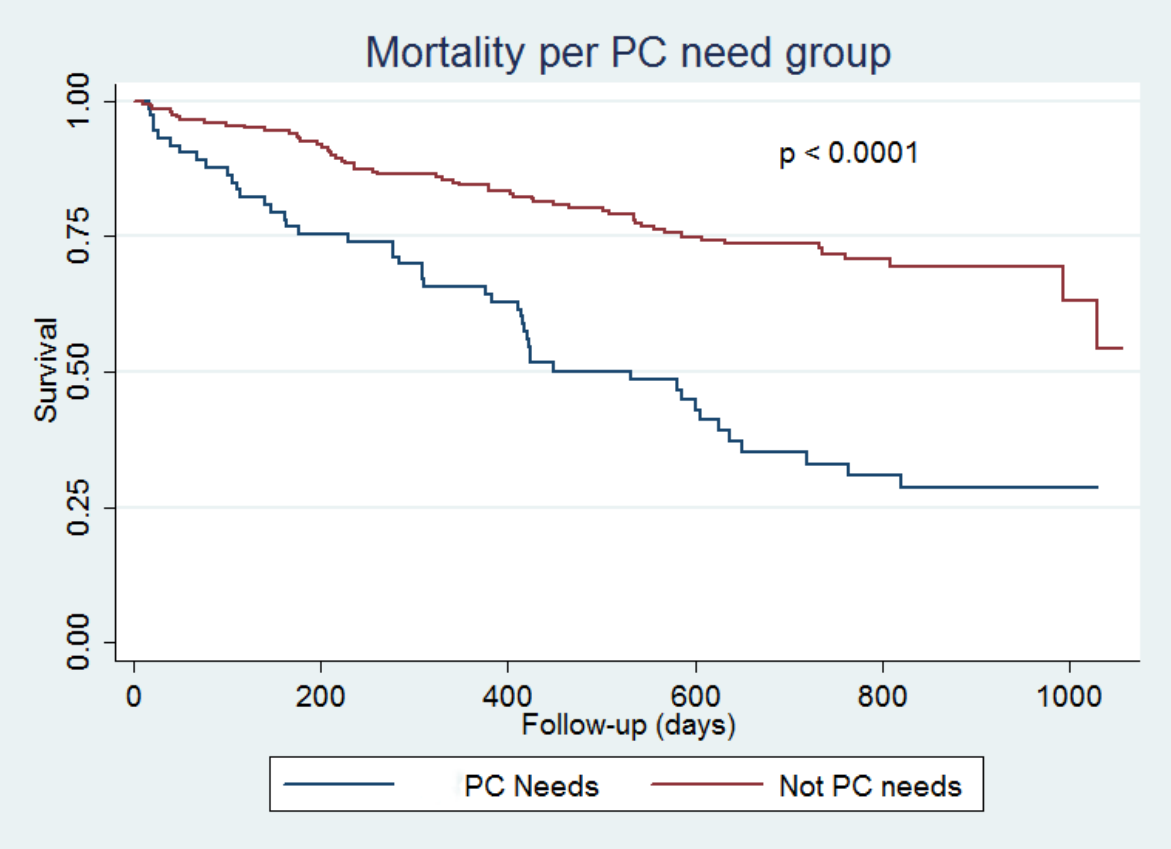


Figure 8-1 Kaplan-Meier overall survival *per* PC needs group

There is clear separation of the survival curves for overall mortality between the two PC groups, this occurred early and continued throughout the follow-up period. Participants in the PC needs group had higher mortality rates than those in the no PC needs group, p <0.0001. This is not surprising as I have used mortality as a component of the definition of PC needs. If participants had a severe impairment on any PROM and died without known recovery of status, they were in the PC needs group. The total mortality for the follow up period was understandably higher in the PC needs group compared to the no PC needs group, with 47 (64.4%) and 56 (28.1%) (p<0.0001).

8.1.1 Cause of death

Cause of death was available through record linkage with the Scottish Morbidity Record via the Greater Glasgow and Clyde SafeHaven. Cause and location for death was available for 108 (91.5%) of all deaths in the cohort, and 96 (93.2%) of participants who completed the PROM and active follow-up phases of the study. Details regarding cause and location of death were not available in 10 (8.5%) participants, due to inaccuracies in record linkage at the time the death certificate was produced. Cause of death was defined as the primary reason for death documented on the official death certificate. The International Classification of Diseases (ICD) version 10, was used to classify cause of death.[266]

Details of recorded cause of death for the whole cohort are detailed in Table 8-1. Causes of death were more likely to be from cardiovascular than non-cardiovascular causes, with 65 (60.2%) and 43 (39.8), respectively. There were no differences between participants who completed the PROM component of the study and those who did not (p=0.536). Of the cardiovascular causes, the most common cause of death recorded was myocardial infarction, with 49.2%. The next most common cardiovascular cause recorded as the primary cause of death was heart failure, with 15.4%. Arrhythmia and stroke were infrequent cardiovascular causes of death, with 3.1 and 9.2%, respectively. The most common non-cardiovascular causes of death recorded were those classified as diseases of the respiratory system or cancer, with 32.6 and 18.6%. The proportion of non-cardiovascular causes is higher than has been reported in RCTs of patients with heart failure.[267] However, there has been a rise in the proportion of deaths attributable to non-cardiovascular deaths with increasing

use of disease modifying therapy, such as beta-blocker therapy. Another difference between this cohort and other reported studies is the low proportion of participants who had a primary cause of death recorded as heart failure, with only 9.3% overall. There are a number of possible explanations for these discrepancies. Firstly, my cohort was unselected and had an older, and likely frailer population with a greater proportion of co-morbidities. Secondly, most RCTs adjudicate deaths, which did not happen with my cohort, potentially leading to a lower classification of heart failure as the primary cause of death. Lastly, my cohort included not only HF-REF, but also HF-PEF. RCTs of HF-PEF have a higher proportion of non-cardiovascular death than those of HF-REF.

Table 8-1 Cause of death all - participants

	All participants n = 313	Completed PROMS n =272	Did not complete PROMS n = 41	p
All deaths	118 (37.7)	103 (37.9)	15 (36.6)	
Cause of death available	108 (91.5)	96 (93.2)	12 (80.0)	0.086
Cardiovascular	65 (60.2)	59 (61.5)	6 (50.0)	0.536
Heart failure*	10 (15.4)	8 (13.6)	2 (33.3)	0.055
Myocardial infarction*	32 (49.2)	31 (52.5)	1 (16.7)	
Arrhythmia*	2 (3.1)	1 (1.7)	1 (16.7)	
Stroke*	6 (9.2)	5 (8.5)	1 (16.7)	
Other CV*	15 (23.1)	14 (23.7)	1 (16.7)	
Non-Cardiovascular	43 (39.8)	37 (38.5)	6 (50.0)	0.536
Respiratory diseases§	14 (32.6)	14 (37.8)	0 (0.0)	0.177
Neoplasms§	8 (18.6)	7 (18.9)	1 (16.7)	
Diseases of the GU system§	6 (14.0)	5 (13.5)	1 (16.7)	
Infectious and parasitic diseases§	5 (11.6)	4 (10.8)	1 (16.7)	
Diseases of the digestive system§	4 (9.3)	3 (8.1)	1 (16.7)	
Primary disorders of muscles§	2 (4.7)	1 (2.7)	1 (16.7)	
Unspecified fall§	2 (4.7)	1 (2.7)	1 (16.7)	
T2DM§	1 (2.3)	1 (2.7)	0 (0.0)	
Churg-Strauss§	1 (2.3)	1 (2.7)	0 (0.0)	

Values are expressed as n (%).
CV= cardiovascular; GU = genitourinary; PROMs= patient reported outcome measures; T2DM = Type 2 diabetes mellitus.
*= % of cardiovascular deaths
§ = % of non-cardiovascular deaths

The causes of death *per* group of PC need are detailed in Table 8-2. There were no significant differences in cause of death between the two groups of PC need.

Table 8-2 Causes of death *per* PC need group

	All participants n = 272	PC needs n =73	Not PC needs n = 199	p
All deaths	103 (37.9)	47 (64.4)	56 (28.1)	
Cause of death available	96 (93.2)	46 (97.9)	50 (89.3)	
Cardiovascular	59 (61.5)	29 (63.0)	30 (60.0)	0.835
Heart failure*	8 (13.6)	4 (13.8)	4 (13.3)	0.871
Myocardial infarction*	31 (52.5)	14 (48.3)	17 (56.7)	
Arrhythmia *	1 (1.7)	1 (3.4)	0 (0.0)	
Stroke *	5 (8.5)	2 (6.9)	3 (10.0)	
Other CV *	14 (23.7)	8 (27.6)	6 (20.0)	
Non-Cardiovascular	37 (38.5)	17 (37.0)	20 (40.0)	0.871
Diseases of the respiratory system§	14 (37.8)	9 (52.9)	5 (25.0)	0.259
Neoplasms§	7 (18.9)	3 (17.6)	4 (20.0)	
Diseases of the GU system§	5 (13.5)	2 (11.8)	3 (15.0)	
Infectious and parasitic diseases§	4 (10.8)	0 (0.0)	4 (20.0)	
Diseases of the digestive system §	3 (8.1)	2 (11.8)	1 (5.0)	
Primary disorders of muscles§	1 (2.7)	1 (5.9)	0 (0.0)	
Unspecified fall§	1 (2.7)	0 (0.0)	1 (5.0)	
T2DM §	1 (2.7)	0 (0.0)	1 (5.0)	
Polyarteritis with lung involvement§	1 (2.7)	0 (0.0)	1 (5.0)	

Values are expressed as n (%).
CV= cardiovascular; GU = genitourinary; T2DM = Type 2 diabetes mellitus.
* = % of CV deaths
§ = % of non-CV deaths

8.1.2 Place of care and death

Preferred place of care/death

All participants who took part in the PROM stage of the study were asked to consider, in a hypothetical scenario, where they would prefer to be cared for in the event of a deterioration in their health. Participants were given the following options as answers; home, hospital, care facility, hospice, or undecided. Participants were then asked to consider, again in a hypothetical scenario, where they would prefer to spend the last few days and hours of their life in the event of a deterioration in their health. Again participants were given the following options as possible answers; home, hospital, care facility, hospice, or undecided.

The answers provided at baseline are provided in Table 8-3. 256 (94.1%) of participants gave answers to the above questions regarding preferred place of

care and death. Most participants expressed a preference to be cared for, and indeed spend their last few days and hours, at home if possible, with 61.3 and 55.9%, respectively. A similar proportion of participants wished to spend their last few days or hours in a hospital (8.2%), care facility (5.9%), or hospice (6.3%).

Table 8-3 Preferred place of care and death

	All participants n = 272	Probable PC needs n =73	Unlikely PC needs n = 199	p
Answered questions	256 (94.1)	70 (95.9)	186 (93.5)	
Preferred place of care				0.389
Home	157 (61.3)	40 (57.1)	117 (62.9)	
Hospital	17 (6.6)	3 (4.3)	14 (7.5)	
Care facility	24 (9.4)	6 (8.6)	18 (9.7)	
Hospice	6 (2.3)	3 (4.3)	3 (1.6)	
Undecided	52 (20.3)	18 (25.7)	34 (18.3)	
Preferred place of death				0.263
Home	143 (55.9)	35 (50.0)	108 (58.1)	
Hospital	21 (8.2)	6 (8.6)	15 (8.1)	
Care facility	15 (5.9)	2 (2.9)	13 (7.0)	
Hospice	16 (6.3)	4 (5.7)	12 (6.5)	
Undecided	61 (23.8)	23 (32.9)	38 (20.4)	

Values are expressed as n (%).
PC = palliative care.

A comparison between preferred place of death in my cohort and other heart failure cohorts is shown in Figure 8-2. In their study, Formiga *et al* asked 80 patients admitted to hospital with decompensated heart failure to consider their place of care if recovery seemed unlikely.[42] Of these, 50% wanted to be cared for at home, a further 40% wanted to continue care in hospital, and 10% were unsure. Of those who preferred to be cared for in hospital, 53% of these said this due to worry regarding the burden they would place on their caregivers. As part of their study, Stachan *et al* asked 107 patients admitted to hospital with decompensated heart failure to consider their preferred place for death.[165] This was a highly selected cohort, consisting of patients with NYHA class IV symptoms and an ejection fraction less than 25%. Most patients in this cohort expressed a preference for EOL care at home (44%), with a further 26% expressing a wish for EOL care in hospital. 25% of this cohort were undecided regarding their preference for EOL care location. A higher proportion of participants in my study expressed a wish to spend their EOL at home (60%), with a similar proportion undecided to that reported by Strachan *et al*, at 24%. Much fewer

participants expressed a wish for EOL care to take place in hospital in my study, at only 8%.

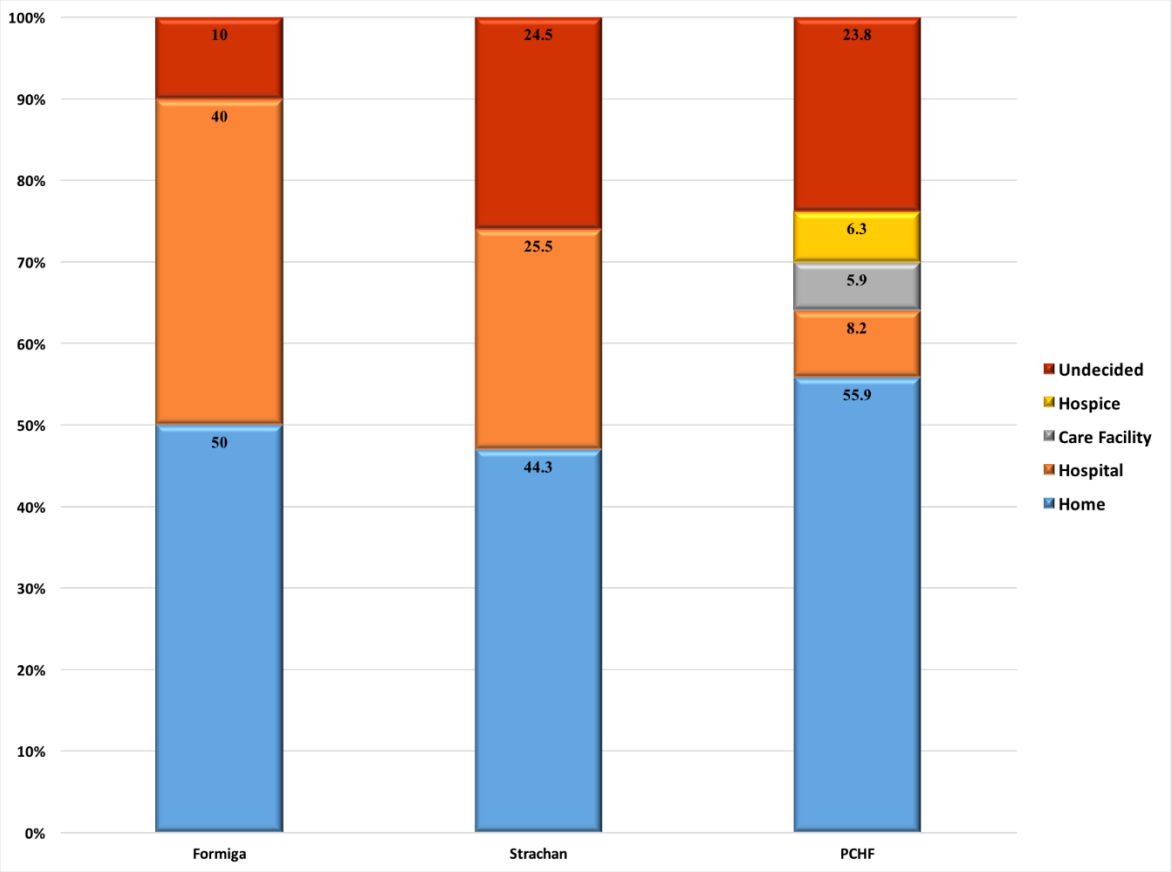


Figure 8-2 Preferred place of death comparison other cohorts

Actual place of death

The details of location of death were available for 92% of all participants in the study, and 93% of those who completed PROMs. The actual place of death for the whole cohort are shown in Table 8-4. Most participants (68.5%) died in hospital, compared to only 18 (16.7%) at home and a further 14 (14.6%) in other facilities such as care homes or hospices. A higher proportion of patients who did not agree to take part in the whole study and complete PROMs or attend follow-up died in hospital, although this difference was not statistically significant.

Table 8-4 Location of death- all participants

	All participants n = 313	Completed PROMS n =272	Did not complete PROMS n = 41	p
All deaths	118 (37.7)	103 (37.9)	15 (36.6)	
Location of death available	108 (91.5)	96 (93.2)	12 (80.0)	0.086
Location of death				
Home	18 (16.7)	17 (17.7)	1 (8.3)	0.804
Hospital	74 (68.5)	65 (67.7)	9 (75.0)	
Other	16 (14.8)	14 (14.6)	2 (16.7)	

Values are expressed as n (%).
PROMS= patient reported outcome measures.

The actual location of death for the participants who took part in the whole study, broken down into those who met the definition of PC need and those who did not, are shown in Table 8-5. Again, most participants died in hospital, with 67.7% of the cohort. Only 17 (17.7%) participants died at home, with a further 14 (14.6%) dying at other care facilities. A higher percentage of participants died in other facilities in the group who met compared to those who did not meet the definition of PC need, with 19.6 and 10.0%, respectively. The differences in place of death by palliative care need group did not reach statistical significance as shown in Table 8-5.

Table 8-5 Location of death per PC need group

	All participants n = 272	PC needs n =73	Not PC needs n = 199	p
All deaths	103 (37.9)	47 (64.4)	56 (28.1)	
location of death available	96 (93.2)	46 (97.9)	50 (89.3)	
Location of death				
Home	17 (17.7)	7 (15.2)	10 (20.0)	0.394
Hospital	65 (67.7)	30 (65.2)	35 (70.0)	
Other	14 (14.6)	9 (19.6)	5 (10.0)	

Values are expressed as n (%).

A comparison of actual place of death in cohorts of patients with heart failure is shown Figure 8-3. Place of death was reported in the Assessment and Treatment with Lisinopril and Survival (ATLAS)[38] and Sudden Cardiac Death in Heart Failure Trial (SCD HeFT)[39] RCTs, where 53 and 58% died in hospital, respectively. A recent study assessing place of death by using death certificates in three European countries in 2007, reported similar proportion of patients with a primary diagnosis of heart failure who died in hospital.[40] Most deaths in patients

with heart failure in Finland, France, and England occurred in hospital, with 58%, 61%, and 68% respectively. The proportion of patients who died at home ranged from 20-35%, with the lowest proportion of home deaths in these studies in England. A similar proportion of participants in my study died in hospital, although this was even higher than previously reported at 68%. Furthermore, a lower proportion of participants in my study died at home compared to other studies reporting place of death in patients with heart failure.

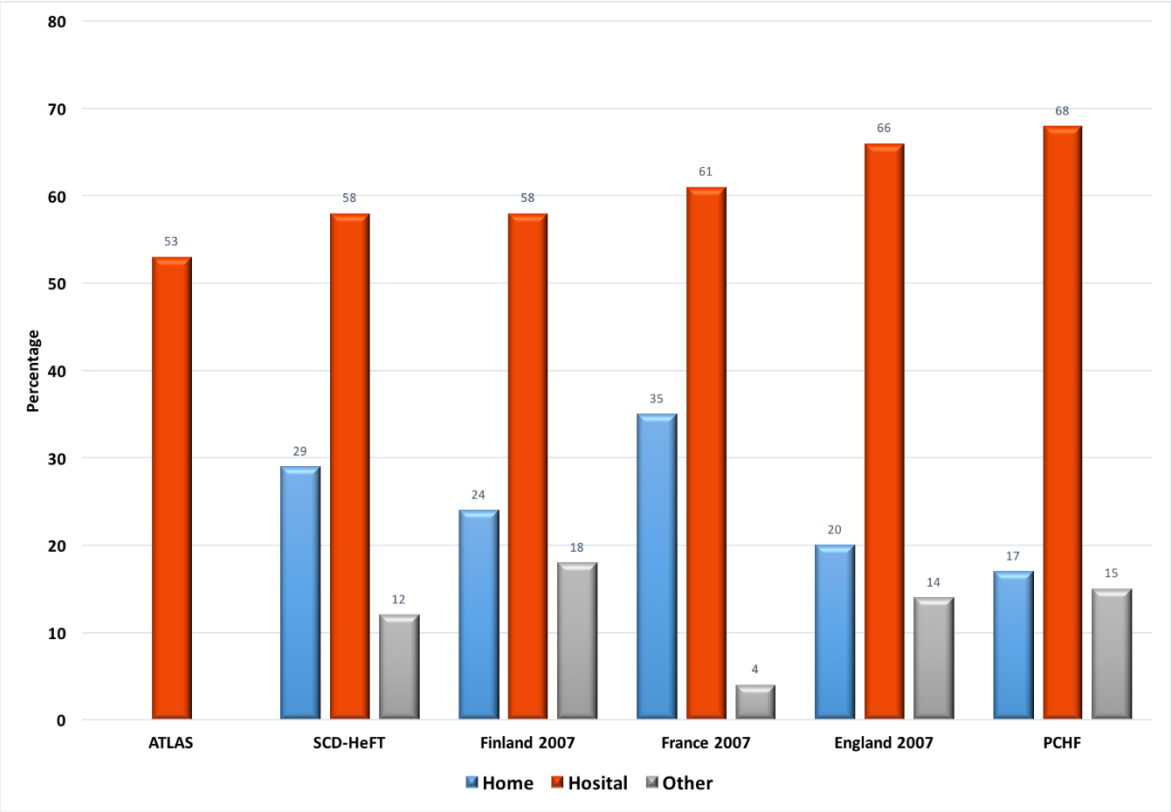


Figure 8-3 Actual place of death comparison other cohorts
ATLAS= Assessment and Treatment with Lisinopril and Survival; PCHF= palliative care in heart failure; SCD-HeFT= Sudden Cardiac Death in Heart Failure Trial.

Of the 96 deaths where location of death was available, data regarding preferred place of death was known at baseline in 94 participants. Of these 72 (76.5%) expressed a preferred place of death and 22 (23.5%) were either undecided or did not have a preferred place of death. A comparison of location of death compared to preferred place of death is shown in Table 8-6. As described above, most participants expressed a preference to spend their EOL at home. Of the 50 participants who expressed a wish to die at home, and who had location of death data available, only 9 (18%) achieved their preferred place of death. Most (n= 37, 74%) died in hospital. Overall, only 18 (25%) of the 72

patients who expressed a preference for location of EOL, achieved their preferred place of death.

Table 8-6 Preferred place versus actual place of death

	Preferred place of death				
	Home	Hospital	Care home	Hospice	Undecided
Location of death					
Home	9 (18.0)	3 (30.0)	2 (40.0)	0 (0.0)	3 (13.6)
Hospital	37 (74.0)	6 (60.0)	2 (40.0)	5 (71.4)	13 (59.1)
Other*	4 (8.0)	1 (10.0)	1 (20.0)	2 (28.6)	6 (27.3)

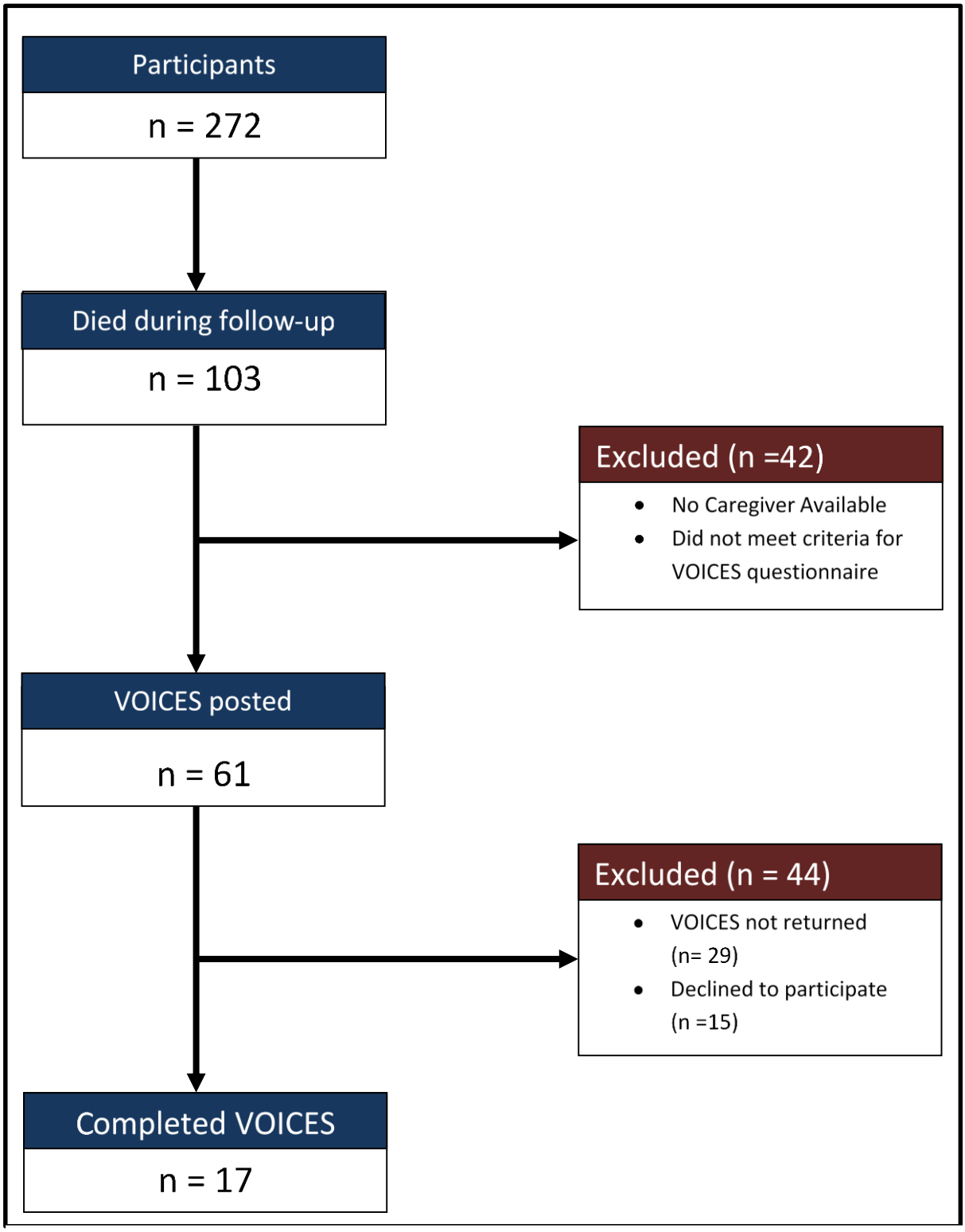
Values are expressed as n (%).
* Either care home or hospice.

8.2 End of life care assessment- VOICES

The VOICES questionnaire has been designed and used by the Department of Health to assess EOL care, from the perspective of informal caregivers.[101] The VOICES questionnaire is a postal questionnaire which describes care in the last three months of life, the last two days of life, and care at the EOL. The questionnaire is designed to be completed by caregivers after what is perceived to be adequate grieving time, but still close enough to a death to allow accurate reflection. For this reason, the authors advise posting the questionnaire 6-12 months following a death.

8.2.1 Completion of VOICES questionnaire

The proportion of participants' caregivers who completed the VOICES questionnaire is displayed in Figure 8-4. Of the 272 participants who took part in the study and completed PROMs, 103 died during follow-up. Of these, 61 were eligible to participate in the VOICES EOL survey. 42 participants were excluded, either because the timing of their death would not allow 6 months' lag before posting the questionnaire, or the participants had no known or available caregiver. Of the 61 VOICES questionnaires posted, 17 were returned.



VOICES = Views Of Informal Caregivers Evaluation of Services questionnaire.

Figure 8-4 VOICES questionnaire CONSORT diagram

15 caregivers returned the reply slip stating they did not wish to participate in this part of the study and a further 29 did not return any of the VOICES documentation. OF the 17 VOICES questionnaires returned, 7 were from caregivers who met the definition of PC needs, and 10 were from caregivers of participants who did not meet the definition of PC needs.

8.2.2 VOICES results- assessment of care in last 3 months of life

Of those completing the VOICES questionnaire, the reported length of illness was between 1 and 6 months in 5.9%, between 6 and 12 months in 17.7%, and over 1 year in 82.4%. 14 (82.4%) caregivers reported that their relative or friend spent some time at home in the last 3 months of life, with a further 2 (11.8%) spending that time in a care home, and 1 respondent reporting their relative or friend did not spend any time in either.

Community care

A summary of the evaluation of community services in the last three months of life is shown in Table 8-7. Most informal caregivers felt that the community care services worked well together, with 61.6% of respondents reporting that care worked well together to some extent or definitely. One caregiver did not feel that care services worked well together, and one caregiver did not know. Three caregivers felt that their relative or friend did not receive any care services in the community in the las three months of life. 50% of respondents felt they got as much support in the community as they wanted, with a only one caregiver reporting they got support but not as much as they wanted or required. One caregiver felt they did not get enough support, even though they tried to get more. 28.6% of caregivers did not get enough support, but did not seek additional support. Most patients who tried to see their general practitioner (GP) got to see their preferred GP most (18.8%), a lot (18.8%), or some of the time (31.2%). 2 caregivers reported that their relative almost never got to see their preferred GP. Most caregivers felt they were able to discuss their fears or worries with the GP, with only 12.5% % reporting they tried to discuss these but were not able to do so. One care giver reported having fears or worries, but did not attempt to discuss these with the GP. Caregivers generally reported good access to home visits, with 67.7% reporting very easy or fairly easy access to

getting a GP home visit. 2 caregivers felt it was fairly difficult getting a home visit, no caregivers felt it was very difficult to get a home visit. Out of hours care was generally rated highly by caregivers. 84.9% of respondents reported excellent or good care provided in the community out of hours, with only 3 caregivers reporting fair or poor care.

Table 8-7 Community care in the last 3 months of life

	All participants	PC needs	Not PC needs	p
Care services worked well together				
Yes, definitely	5 (38.5)	2 (40.0)	3 (37.5)	1.000
Yes, to some extent	3 (23.1)	1 (20.0)	2 (25.0)	
No, they did not work well together	1 (7.7)	0	1 (12.5)	
Did not receive any care	3 (23.1)	2 (40.0)	1 (12.5)	
Don't know	1 (7.7)	0	1 (12.5)	
Got enough help and support at home from services				
Yes, as much as we wanted	7 (50.0)	2 (33.3)	5 (62.5)	0.394
Yes, some but not as much as we wanted	1 (7.1)	1 (16.7)	0	
No, although we tried to get more	1 (7.1)	1 (16.7)	0	
No, but we did not ask for more	4 (28.6)	2 (33.3)	2 (25.0)	
Did not need help	1 (7.1)	0	1 (12.5)	
Saw preferred GP				
Always or almost always	3 (18.8)	1 (14.3)	2 (22.2)	0.575
A lot of the time	3 (18.8)	2 (28.6)	1 (11.1)	
Some of the time	5 (31.2)	3 (42.9)	2 (22.2)	
Never or almost never	2 (12.5)	1 (14.3)	1 (11.1)	
Did not try to see a particular GP	3 (18.8)	0	3 (33.3)	
Did not have to see GP	0	0		
Able to discuss fears or worries with GP				
No fears or worries to discuss	3 (18.8)	0	3 (33.3)	0.148
Yes, as much as I wanted	9 (56.2)	5 (71.4)	4 (44.4)	
Yes, but not as much as I wanted	1 (6.2)	1 (14.3)	0	
No, although I tried to discuss	2 (12.5)	0	2 (22.2)	
No, but I did not try to discuss	1 (6.2)	1 (14.3)	0	
Ease of getting a home visit				
Very easy	5 (31.2)	2 (28.6)	3 (33.3)	0.650
Fairly easy	6 (37.5)	2 (28.6)	4 (44.4)	
Fairly difficult	2 (12.5)	1 (14.3)	1 (11.1)	
Very difficult	0	0	0	
Don't know	1 (6.2)	0	1 (11.1)	
Wanted home visit, but GP would not	0	0	0	
Does not apply, did not want home visit	2 (12.5)	2 (28.6)	0	
Out of hours care				
Excellent	6 (49.2)	2 (33.3)	4 (50.0)	0.867
Good	5 (35.7)	3 (50.0)	2 (25.0)	
Fair	1 (7.1)	0	1 (12.5)	
Poor	2 (14.3)	1 (16.7)	1 (12.5)	
Don't know	0	0	0	

GP= general practitioner; PC= palliative care.

Pain relief in last 3 months

Caregivers were asked to report on how adequately pain was controlled in the various healthcare settings that their relative was cared for in the last three months of life. A summary of the assessment of pain control are shown in Table 8-8. Most patients appeared to have suffered from pain in the last three months of life. 42.8% of caregivers reported that pain was only relieved partially or not at all in the community. A similar proportion of caregivers reported only partial pain relief in the four patients cared for in care homes (50%). Of the 14 patients who spent some of their last three months in hospital, 2 did not experience any pain. Of those who spent time in hospital and experienced pain, 58.3% of caregivers reported inadequate pain relief. Only two participants with caregivers who completed the VOICES questionnaire spent any time in a hospice. Of these, only one caregiver reported that their relative or friend experienced pain, and this was relieved partially. There were no statistically significant differences between the two groups of PC need regarding pain relief in the last 3 months of life.

Table 8-8 Pain control in the last 3 months of life

	All participants n = 17	PC needs n =7	Not PC needs n = 10	p
Pain control at home				
Does not apply, not pain	3 (21.4)	1 (16.7)	2 (25.0)	1.000
Completely, all of the time	4 (28.6)	2 (33.3)	2 (25.0)	
Completely, some of the time	1 (7.1)	1 (16.7)	0	
Partially	5 (35.7)	2 (33.3)	3 (37.5)	
Not at all	1 (7.1)	0	1 (12.5)	
Don't know	0	0	0	
Pain control in Care home				
Does not apply, not pain	0	0	0	1.000
Completely, all of the time	1 (25.0)	0	1 (33.3)	
Completely, some of the time	1 (25.0)	0	1 (33.3)	
Partially	2 (50.0)	1 (100.0)	1 (33.3)	
Not at all	0	0	0	
Don't know	0	0	0	
Pain control in Hospital				
Does not apply, not pain	2 (14.3)	1 (20.0)	1 (11.1)	0.850
Completely, all of the time	5 (35.7)	1 (20.0)	4 (44.4)	
Completely, some of the time	0	0	0	
Partially	6 (42.9)	3 (60.0)	3 (33.3)	
Not at all	1 (7.1)	0 (0.0)	1 (11.1)	
Don't know	0	0	0	
Pain control in Hospice				
Does not apply, not pain	1 (50.0)	0	1 (50.0)	na
Completely, all of the time	0	0	0	
Completely, some of the time	0	0	0	
Partially	1 (50.0)	0	1 (50.0)	
Not at all	0	0	0	
Don't know	0	0	0	

na= not applicable; PC= palliative care.

Respect and dignity in last three months of life

As part of the VOICES questionnaire, informal caregivers are asked to report whether they felt specific healthcare professionals treated their relatives or friends with respect and dignity. The results of these questions are displayed in Table 8-9. No caregivers reported that their friend or relative was never treated with respect by any healthcare professional. Of those cared for by community nurses, 66.7% of caregivers felt the healthcare professionals treated their relative or friend with respect and dignity always or most of the time. Only one caregiver reported their friend or relative being treated with respect and dignity some of the time. 81.3% of caregivers reported that their relative or friends' GP treated them with respect and dignity always or most of the time, with 3 caregivers reporting some of the time. Of the four participants who were cared for in a care-home in the last three months of life, all four were treated with respect and dignity, either always or most of the time. Hospital doctors and nurses were evaluated similarly regarding their treatment of relatives or friends of caregivers, with 78.5 and 78.6% of caregivers reporting treatment with respect and dignity always or most of the time, respectively. Of the two participants, with caregivers completing the VOICES questionnaire, who were cared for in a hospice, hospice staff were reported to treat the two participants with respect and dignity always.

Table 8-9 Respect and dignity shown to patient in last 3 months of life

	All participants n = 17	PC needs n =7	Not PC needs n = 10	p
Community nurse				
Always	5 (55.6)	2 (50.0)	3 (60.0)	1.000
Most of the time	1 (11.1)	1 (25.0)	0	
Some of the time	1 (11.1)	0	1 (20.0)	
Never	0	0	0	
Don't know	2 (22.2)	1 (25.0)	1 (20.0)	
General practitioner				
Always	11 (68.8)	4 (57.1)	7 (77.8)	0.342
Most of the time	2 (12.5)	2 (28.6)	0 (0)	
Some of the time	3 (18.8)	1 (14.3)	2 (22.2)	
Never	0	0	0	
Don't know	0	0	0	
Care home staff				
Always	2 (50.0)	0	2 (66.7)	1.000
Most of the time	2 (50.0)	1 (100.0)	1 (33.3)	
Some of the time	0	0	0	
Never	0	0	0	
Don't know	0	0	0	
Hospital doctor				
Always	8 (57.1)	3 (60.0%)	5 (55.6)	0.287
Most of the time	3 (21.4)	0	3 (33.3)	
Some of the time	3 (21.4)	2 (40.0%)	1 (11.1)	
Never	0	0	0	
Don't know	0	0	0	
Hospital nurse				
Always	9 (64.3)	3 (60.0)	6 (66.7)	1.000
Most of the time	2 (14.3)	1 (20.0)	1 (11.1)	
Some of the time	3 (21.4)	1 (20.0)	2 (22.2)	
Never	0	0	0	
Don't know	0	0	0	
Hospice doctor				
Always	1 (50.0)	0	1 (50.0)	na
Most of the time	1 (50.0)	0	1 (50.0)	
Some of the time	0	0	0	
Never	0	0	0	
Don't know	0	0	0	
Hospice nurse				
Always	2 (100.0)	0	2 (100.0)	na
Most of the time	0	0	0	
Some of the time	0	0	0	
Never	0	0	0	
Don't know	0	0	0	

na= not applicable; PC= palliative care.

Overall care in the last three months of life

As part of the VOICES questionnaire, informal caregivers were asked to make an assessment of care from various healthcare professionals and make an overall assessment of care in the last three months of life of their friend or relative. Caregivers were asked to make an assessment of standard of care by selecting an answer from poor, fair, good, excellent, or don't know. The results of these questions are shown in Table 8-10 and Table 8-11.

Table 8-10 Assessment of care in last three months

	Community nurse n = 9	GP n =16	Care home staff n = 4	Hospital doctor n = 13	Hospital nurse n = 13	Hospice care n = 2
Assessment of care						
Excellent	5 (55.6)	7 (43.8)	3 (75.0)	5 (38.5)	6 (46.2)	1 (50.0)
Good	1 (11.1)	4 (25.0)	1 (25.0)	4 (30.8)	4 (30.8)	0
Fair	1 (11.1)	1 (6.2)	0	1 (7.7)	2 (15.4)	1 (50.0)
Poor	1 (11.1)	4 (25.0)	0	3 (23.1)	1 (7.7)	0
Don't know	1 (11.1)	0	0	0	0	0

Values are expressed as n (%).
GP= general practitioner.

Care from community nurses was generally rated highly, with 6 (66.7%) caregivers evaluating care delivered by community nurses as excellent or good. 2 (22.2%) rated fair or poor standard of care by community nurse in the last three months of life. GPs were rated highly, many caregivers felt the care delivered by GPs was excellent or good, 43.8% and 25.0%, respectively. Of the four participants in care-homes who had a caregiver complete the VOICES questionnaire, all four caregivers rated the care received there as either excellent (3 caregivers) or good (1 caregiver). Hospital doctors were rated similarly to community nurses and GPs, with 38.5 and 30.8% of caregivers rating hospital doctors' care in the last three months of life as either excellent or good. 3 (23.1%) hospital doctors were rated as poor by caregivers. Hospital nurses were rated highly overall, with 77.0% being rated by caregivers as delivering excellent or good care in the last three months of life, with only one caregiver reporting poor care, and a further 2 (15.4%) reporting fair care. Of the

two participants who accessed hospice care with caregivers who completed the VOICES questionnaire, one reported excellent care and one fair care.

Table 8-11 Overall assessment of care in last 3 months of life

	All n = 17	PC needs n =7	Not PC needs n = 10	p
Overall Care last 3 months				0.164
Outstanding	2 (11.8)	1 (14.3)	1 (10.0)	
Excellent	4 (23.5)	2 (26.8)	2 (20.0)	
Good	5 (29.4)	3 (42.9)	2 (20.0)	
Fair	5 (29.4)	0	5 (50.0)	
Poor	1 (5.9)	1 (14.3)	0	
Don't know	0	0	0	

Values are expressed as n (%).
PC= palliative care.

The caregivers' evaluation of overall care is shown in Table 8-11, including distribution of care assessment by palliative care needs group. This particular question in the VOICES questionnaire had the additional option of rating care as outstanding, in addition to the options available in Table 8-10. Again, more caregivers felt that overall care was positive, with 64.2% reporting good-outstanding care. 2 (11.8%) caregivers felt care was outstanding, 4 (23.5%) felt care was excellent, and 5 (29.4%) felt care was good. 5 (29.4%) and 1 (5.9%) caregivers reported overall care in the last three months of life of their friend or relative as fair and poor, respectively. There was no statistical difference in the proportion of participants in each care standard category between those with PC needs and those without. This may have been due to small numbers of responses received for the VOICES questionnaire.

8.2.3 Assessment of care in last two days of life

Caregivers completing the VOICES questionnaire were also asked to reflect on various aspects of care in the last two days of life of their relative or friend. The results of these questions, overall and by PC needs group, are shown in Table 8-12 and Table 8-13.

Caregivers were asked to reflect on location care took place in the last two days of life. 5 (29.4%) reported care taking place at home all of the time, 3 (17.6%)

in a care home, 7 (41.2%) in hospital, and 2 (11.8%) in a hospice. This proportion is different to the location of death recorded by the whole cohort, perhaps reflecting the presence of an informal caregiver, enabling a higher proportion of participants to spend their last two days at home. Most felt were treated with respect and dignity by doctors in the last two days of life, with 10 (66.7%) treated with respect and dignity either always or most of the time. No caregiver reported their friend or relative never being treated with respect and dignity in the last two days. 2 (13.3%) were treated with respect and dignity only sometimes in the last two days of life. Caregivers reported a higher proportion of patients being treated with respect and dignity by nurses in the last two days of life, with 93.4% of caregivers reporting nurses treated their relatives with respect and dignity either always or most of the time.

Most caregivers reported that their friends or relatives received enough help to meet their personal care needs in the last two days of life. Only two caregivers reported feeling that there was not enough support to meet these needs. A similar proportion of caregivers reported that there was enough nursing support in the last two days of life, again with 2 (13.4%) caregivers reporting that there was not enough nursing support. Most caregivers (73.4%) reported there was enough privacy at the bed space in the last two days of life. Two caregivers reported that they did not think there was enough privacy.

There were no statistically significant differences between the groups of palliative care need in the caregiver perceived standards of care described in Table 8-12.

Table 8-12 Assessment of care in last 2 days of life

	All participants	PC needs	Not PC needs	p
Location of care last 2 days of life				
At home all the time	5 (29.4)	3 (42.9)	2 (20.0)	0.762
Care home all the time	3 (17.6)	1 (14.3)	2 (20.0)	
Hospital all the time	7 (41.2)	3 (42.9)	4 (40.0)	
Hospice all the time	2 (11.8)	0	2 (20.0)	
Other	0	0	0	
Treated with dignity and respect by doctors last 2 days of life				
Always	9 (60.0)	4 (66.7)	5 (55.6)	1.000
Most of the time	1 (6.7)	0	1 (11.1)	
Some of the time	2 (13.3)	1 (16.7)	1 (11.1)	
Never	0	0	0	
Don't know	3 (20.0)	1 (16.7)	2 (22.2)	
Treated with dignity and respect by nurses last 2 days of life				
Always	10 (66.7)	5 (83.3)	5 (55.6)	0.139
Most of the time	4 (26.7)	0	4 (44.4)	
Some of the time	1 (6.7)	1 (16.7)	0	
Never	0	0	0	
Don't know	0	0	0	
Enough help to meet personal care needs in last 2 days				
Strongly agree	2 (13.3)	1 (16.7)	1 (11.1)	0.944
Agree	8 (53.3)	3 (50.0)	5 (55.6)	
Neither agree nor disagree	2 (13.3)	1 (16.7)	1 (11.1)	
disagree	1 (6.7)	0	1 (11.1)	
Strongly disagree	1 (6.7)	1 (16.7)	0	
Does not apply	1 (6.7)	0	1 (11.1)	
Don't know	0	0	0	
Enough nursing care to meet needs in last 2 days				
Strongly agree	4 (26.7)	2 (33.3)	2 (22.2)	1.000
Agree	7 (46.7)	3 (50.0)	4 (44.4)	
Neither agree nor disagree	1 (6.7)	0	1 (11.1)	
disagree	1 (6.7)	0	1 (11.1)	
Strongly disagree	1 (6.7)	1 (16.7)	0	
Does not apply	0	0	0	
Don't know	1 (6.7)	0	1 (11.1)	
Enough privacy bed space last 2 days				
Strongly agree	4 (26.7)	2 (33.3)	2 (22.2)	1.000
Agree	7 (46.7)	3 (50.0)	4 (44.4)	
Neither agree nor disagree	1 (6.7)	0	1 (11.1)	
disagree	1 (6.7)	0	1 (11.1)	
Strongly disagree	1 (6.7)	1 (16.7)	0	
Does not apply	0	0	0	
Don't know	1 (6.7)	0	1 (11.1)	

PC= palliative care.

15 caregivers answered the VOICES questions regarding pain relief in the last two days of life. Of the 13 participants who experienced pain, most received good or excellent pain relief in the last two days of life, 4 (30.7%) and 5 (38.5%), respectively. 3 (23%) caregivers reported that pain relief was poor in the last two days of life. A similar proportion of caregivers reported adequate control of other symptoms in the last two days of life, with 5 (33.3%) reporting this as excellent and 5 (33.3%) good. A further 5 (33.3%) caregivers rated symptom control in the last two days of life as either fair or poor.

Caregivers were asked to rate EOL care in terms of the emotional and spiritual support that their friend or relative received in the last two days of life, the proportion of answers given are shown in Table 8-13. Two caregivers did not know what this was. Just over half of caregivers (8 caregivers) reported that their relative or friend received excellent or good emotional support in the last two days of life. 5 rated the standard of emotional support given in the last two days as either fair or poor. 11 caregivers reported that they felt spiritual support was required. Of these, 1 (9.1%) and 4 (36.4%) caregivers reported excellent and good spiritual support in the last two days of life, respectively. 4 (36.4%) caregivers rated the quality of spiritual support as either fair or poor.

Caregivers were asked to rate the amount of support that was provided to enable achievement of preferred place of death. 15 caregivers answered this question, with one stating this was not applicable, and another reporting they did not know the answer to this question. Of the other 13 caregivers, 4 (30.8%) rated support for preferred place of death as excellent, 5 (38.5%) as good, 3 (23.1%) as fair, and 1 (7.8%) as poor.

There were no statistically significant differences between the groups of PC need regarding evaluation of EOL care in the last two days of life, as demonstrated in Table 8-13.

Table 8-13 Assessment of symptom and emotional support last 2 days of life

	All participants	PC needs	Not PC needs	p
Pain relief in last 2 days of life				
Excellent	4 (26.7)	2 (33.3)	2 (22.2)	1.000
Good	5 (33.3)	2 (33.3)	3 (33.3)	
Fair	0	0	0	
Poor	3 (20.0)	1 (16.7)	2 (22.2)	
Does not apply	3 (20.0)	1 (16.7)	2 (22.2)	
Don't know	0	0	0	
Relief of other symptoms in last 2 days of life				
Excellent	5 (33.3)	2 (33.3)	3 (33.3)	1.000
Good	5 (33.3)	2 (33.3)	3 (33.3)	
Fair	3 (20.0)	1 (16.7)	2 (22.2)	
Poor	2 (13.3)	1 (16.7)	1 (11.1)	
Does not apply	0	0	0	
Don't know	0	0	0	
Emotional support in last 2 days of life				
Excellent	4 (26.7)	2 (33.3)	2 (22.2)	0.760
Good	4 (26.7)	1 (16.7)	3 (33.3)	
Fair	2 (13.3)	1 (16.7)	1 (11.1)	
Poor	3 (20.0)	2 (33.3)	1 (11.1)	
Does not apply	0	0	0	
Don't know	2 (13.3)	0	2 (22.2)	
Spiritual support in last 2 days of life				
Excellent	1 (6.7)	1 (16.7)	0	0.811
Good	4 (26.7)	2 (33.3)	2 (22.2)	
Fair	2 (13.3)	1 (16.7)	1 (11.1)	
Poor	2 (13.3)	1 (16.7)	1 (11.1)	
Does not apply	4 (26.7)	1 (16.7)	3 (33.3)	
Don't know	2 (13.3)	0	2 (22.2)	
Support to achieve preferred place of care in last 2 days of life				
Excellent	4 (26.7)	2 (33.3)	2 (22.2)	1.000
Good	5 (33.3)	2 (33.3)	3 (33.3)	
Fair	1 (6.7)	0	1 (11.1)	
Poor	3 (20.0)	2 (33.3)	1 (11.1)	
Does not apply	1 (6.7)	0	1 (11.1)	
Don't know	1 (6.7)	0	1 (11.1)	

PC= palliative care.

8.2.4 Assessment of communication at end of life

As part of the VOICES questionnaire caregivers were asked to reflect on how well health professionals communicated with both patients and their caregivers leading up to death, and with caregivers following death. The distribution of answers to these questions are shown in Table 8-14. Caregivers were asked to comment on whether their friend or relative knew that they were likely to die. 57% reported that their friend or relative certainly or probably did know they were going to die. 6 (35.5%) caregivers felt that their friend or relative probably did not know they were likely to die, and one felt that their friend or relative definitely did not know they were likely to die. Caregivers often did not know

whether or not their friend or relative was told they were dying in a sensitive way. Most caregivers (47.1%) responded that their relative did not know they were dying.

Caregivers were asked whether they were contacted in enough time before their friend or relative died. 2 (11.8%) caregivers reported that they were not. Most other caregivers were either with their friend or relative already or were contacted in enough time (76.4%). Caregivers were asked if the news of the death of their friend or relative was broken in a sensitive manner, and all reported that it was. 13 (76.5%) caregivers felt they were given enough support at the time of death, either definitely or to some extent. One caregiver reported not getting enough support at the time of death.

Caregivers were asked to reflect on whether they thought they or their relatives or friends were involved in decisions about their health as much as they would have wanted. Most caregivers (85.7%), felt that their relative or friend were involved with decision making as much as they would have wanted. 2 (13.3%) caregivers, felt that their relative or friend would have liked to be more involved in decision making processes. 11 (64.7%) caregivers felt they were involved in decision making as much as they would have liked, with a further 5 (29.4%) feeling they would have liked to be more involved, and one caregiver reported feeling that they were too involved. 2 (17.6%) caregivers reported that some decisions were not in keeping with their friend or relative's wishes, although most felt this was not the case or not applicable (82.3%).

Of the caregivers completing the VOICES questionnaire, none accessed any formal bereavement counselling, with half stating they would have liked to.

Table 8-14 Assessment of communication at end of life

	All participants	PC needs	Not PC needs	p
Did patient know they were likely to die				
Yes, certainly	4 (23.5)	1 (14.3)	3 (30.0)	0.735
Yes, probably	4 (23.5)	1 (14.3)	3 (30.0)	
Probably not	6 (35.5)	3 (42.9)	3	
No, definitely	1 (5.9)	1 (14.3)	0	
Not sure	2 (11.8)	1 (14.3)	1 (10.0)	
Did the person who broke news he/she was likely to die do so sensitively				
Yes, definitely	1 (5.9)	1 (14.3)	0	0.166
Yes, to some extent	1 (5.9)	0	1 (10.0)	
No, not at all	0	0	0	
Don't know	4 (23.5)	0	4 (40.0)	
Does not apply, they did not know he/she was dying	3 (17.6)	2 (28.6)	1 (10.0)	
Does not apply, they did not tell him/her they were dying	8 (47.1)	4 (57.1)	4 (40.0)	
Were you contacted in enough time to see him/her before he/she died				
Yes	4 (23.5)	1 (14.3)	3 (30.0)	0.637
No	2 (11.8)	1 (14.3)	1 (10.0)	
I was there already	9 (52.9)	5 (71.4)	4 (40.0)	
It was not clear they were going to die soon	2 (11.8)	0	2 (20.0)	
I could not have got there anyway	0	0	0	
Were family given enough support at the time of death				
Yes, definitely	7 (41.2)	3 (42.9)	4 (40.0)	1.000
Yes, to some extent	6 (35.3)	3 (42.9)	3 (30.0)	
No, not at all	1 (5.9)	0	1 (10.0)	
Don't know	3 (17.6)	1 (14.3)	2 (20.0)	
After his/her death did staff deal with the family in a sensitive manner				
Yes	15 (88.2)	7 (100.0)	8 (80.0)	0.485
No	0	0	0	
Don't know	0	0	0	
Does not apply	2 (11.8)	0	2 (20.0)	
Over the past 3 months was he/she involved in decision about his/her care as much as you wanted				
Involved as much as wanted to be	12 (70.6)	6 (85.7)	6 (60.0)	0.338
Would have liked to be more involved	2 (11.8)	1 (14.3)	1 (10.0)	
Would have liked to be less involved	0	0	0	
Don't know	3 (17.6)	0	3 (30.0)	
Over the past 3 months, were you involved in decision about his/her care as much as you wanted				
Involved as much as wanted to be	11 (64.7)	5 (71.4)	6 (60.0)	1.000
Would have liked to be more involved	5 (29.4)	2 (28.6)	3 (30.0)	
Would have liked to be less involved	1 (5.9)	0	1 (10.0)	
Don't know	0	0	0	
Were any decision made about his/her care that he/she would not have wanted				
Yes	3 (17.6)	2 (28.6)	1 (10.0)	0.404
No	11 (64.7)	5 (71.4)	6 (60.0)	
Don't know	3 (17.6)	0	3 (30.0)	
Have you talked to anyone from health or social services or a bereavement service?				
Yes	0	0	0	1.000
No, but I would have liked to	8 (50.0)	4 (57.1)	4 (40.0)	
No, but I did not want to	8 (50.0)	3 (42.9)	5 (50.0)	
Not sure	0	0	0	

PC= palliative care.

8.3 Summary

Despite the numerous advances in the treatment of heart failure, particularly HF-REF, patients admitted to hospital in this cohort were a very high risk group, in terms of mortality risk. During a median follow-up of 2.1 years, 37.9% of the cohort died. Unsurprisingly, the participants who met the definition of PC needs had a much higher mortality rate, with 64.4% versus 28.1% dying during follow-up, $p<0.001$. This difference likely reflects the use of mortality in the definition of PC needs (which is appropriate), however, death was not a mandatory condition to meet the definition. Most deaths in my cohort were classified as cardiovascular, with the highest proportion of deaths being further sub-classified as due to myocardial infarction. A lower than expected proportion of deaths were classified as due to heart failure. This is perhaps due to the non-adjudicated nature of the deaths. Despite cardiovascular deaths being more common, there was still a high proportion of deaths classified as non-cardiovascular (39%). Of these, most were classified as due to respiratory disease, followed by cancer, with 37.8% and 18.9% of non-cardiovascular deaths respectively due to these causes. This proportion of non-cardiovascular deaths perhaps reflects the nature of the population studied, with an elderly population with a high proportion of co-morbidities.

As previously described in other smaller studies, most patients with heart failure, when asked, expressed a preference to spend their EOL at home. Despite this preference for place of death, most patients in my study did not die at home. By far the most common location of death was hospital. This was a consistent finding with other studies which have recorded place of death in patients with heart failure, although an even higher proportion of hospital deaths was seen in my study. This is potentially an area where PC could have a positive influence.[268] However, this needs to be explored further in adequately powered RCTs.

Although only 17 informal caregivers completed the VOICES questionnaire, this still provides a useful, although not exhaustive, insight into EOL care in patients with heart failure. In general, most caregivers were positive about the care received in the community by their relative or friend in the last three months of life. Most felt the various services available in the community worked well

together, and out of hours care was viewed positively. Most caregivers felt their relative or friend could access their preferred GP during working hours. 4 out of 14 caregivers did not feel like they had enough access to support services in the last three months of life, although they did not seek additional support, perhaps suggesting they were not aware of extra support that may have been available. Pain was only partially relieved between 36 and 50% of the time, depending on care setting. Overall, most caregivers felt that their relative or friend was treated with respect and dignity, with no caregiver reporting this never happened.

Caregivers mostly reported positively regarding care in the last two days of life. However, 2 (13.4%) caregivers felt there was not enough nursing support or help to meet the personal needs of their relative or friend in the last two days of life. 2 caregivers also reported not enough privacy at the bed-space in the last two days of life. 20% of caregivers felt relief of pain or other symptoms was poor. Emotional and spiritual support was also rated as fair or poor in 5 (33.3%) and 4 (26.7%) patients, respectively. One quarter of caregivers felt support to achieve preferred place of death was fair or poor, in keeping with the observed discrepancy between preferred and actual place of death. Although communication at EOL was rated highly in general, 6 (35.5%) caregivers felt their relative or friend did not know they were dying. A further 5 (29.4%) caregiver felt they would have liked to have been more involved in decisions about care. No caregivers reported accessing any form of bereavement service, with half of respondents reporting they would have liked to have accessed this service.

A useful comparison can be made between my study and the National Survey of Bereaved People in England, 2015.[103] In the most recent cycle of this survey, the VOICES questionnaire was completed by 21 320 bereaved relatives. Overall care in the last three months of life was rated as either good, excellent, or outstanding in 74.9%. 25.1% of caregivers reported overall care as either fair or poor. The overall rating of care in the last three months was less favourable from the 17 caregivers in my study who completed the VOICES questionnaire. Of these, 35.3% rated overall care to be fair or poor.

An important reason for using the VOICES EOL questionnaire in this study was to determine if this could be used as a potential outcome measure in a subsequent

RCT of early PC in heart failure. I have found the return rate to be particularly low, lower than reported in the DOH EOL surveys. This was surprising as, unlike the Department of Health survey, I had previously made contact with most of the caregivers who the questionnaire was posted to and in most cases established a rapport. I was aware that many participants in my study did not have an informal caregiver or close friend or relative, which would result in low return rate. I also found the timing of the VOICES questionnaire difficult to administer, as this was quite prescriptive. The questionnaire itself is large, and perhaps represents too high a participant burden. My opinion regarding the VOICES EOL questionnaire is that it would not be useful as an outcome measure in an RCT, in its current form, although it may be informative.

Chapter 9 Discussion

9.1 Main findings of the study

Heart failure is common and associated with significant morbidity and mortality. There have been a number of evidence based therapies which have been shown to improve prognosis and reduce morbidity, particularly in patients with HF-REF. Despite these improvements, for many patients, heart failure is a life-limiting disease. There has recently been more focus on providing PC and treatments for patients with organ failure, including heart failure. This has been recognised by numerous editorials, and now is acknowledged in international guidelines.[3, 269] However, the extent of patients which have, or would potentially benefit from, a palliative intervention has not been described. I believe that this study and thesis has systematically addressed this important research and clinical question.

I have systematically reviewed the published literature available describing the potential PC needs in patients with heart failure. My search strategy identified over 60 publications, including more recently published RCTs. Half of the studies identified used qualitative research methods and half used either quantitative or a mix of the two methodologies. Many of the studies identified described highly selected cohorts, either patients with exclusively NYHA class III/IV or patients already attending or referred to PC services. Most of the cohorts did not fully describe the patient population studied in detail, with important data such as severity of heart failure (including ejection fraction and NYHA clas), drug history, or natriuretic peptide levels missing. Most of the studies identified described only a 'snap-shot' assessment, at one time-point. This methodology would not capture the potential fluctuation that heart failure is thought to have, and ultimately would not describe the patient journey. Another key weakness of the current literature identified was the focus on exclusively patients with HF-REF. HF-REF is the most prevalent type of heart failure and appears to have the highest mortality associated, however, the proportion of patients with HF-PEF is potentially increasing and underrepresented in the studies identified. Even though HF-REF was studied more often, descriptions of proportions of patients receiving disease modifying therapies were lacking. This is crucial to report in any study describing either

the prevalence of PC needs or the effect of PC on patients with heart failure, as pharmacotherapy can improve QOL. My study and thesis addressed these issues, and ultimately, provides a description of the prevalence of PC needs in a contemporary and very well described cohort of patients admitted to hospital because of heart failure.

A total of 829 unselected, near-consecutive, patients with suspected heart failure were screened for inclusion in the study. Of these, 313 met the ESC diagnostic criteria for definition of heart failure. Of these 313 patients with confirmed heart failure, 272 (86.9%) agreed to participate in the whole study and complete the PROMs at baseline and at follow-up visits. The 41 patients who declined or were unable to take part in the PROM and follow-up parts of the study were older, with a higher proportion women and with lower BMI. There were no other statistically significant differences at baseline between those who participated and those who did not in the whole study.

The patients enrolled in the study were elderly with a median age of 76, and had numerous co-morbidities. Just under half of participants were women (47%), and most participants were white, reflecting the catchment area for the Western Infirmary, Glasgow. The most common co-morbidities were hypertension, ischaemic heart disease, atrial fibrillation, diabetes mellitus, and COPD. Most patients were NYHA class III (52%), with 30% class II, and 18% class IV. Pulmonary rales was the most common finding on physical examination, with 79%, followed by peripheral oedema (76%). That 30% of patients were NYHA class II (symptoms on mild exertion) is in some ways surprising, as one would expect patients admitted to hospital to be symptomatic on minimal exertion or at rest (NYHA class III/IV). However, these findings are in keeping with a recent study which reported that most patients admitted to hospital due to heart failure are comfortable at rest, but short of breath on exertion, compared to those that are short of breath at rest.[270]

Most patients in the study had HF-REF (67.3%), in keeping with previous studies locally, and in keeping with a large contemporary meta-analysis.[61, 250] Valve disease was common, with significant valve disease (defined as ≥ moderate-severe aortic or mitral valve lesion) present in 23.9% of patients. Markers of disease severity, namely ejection fraction and BNP, were very similar between

my cohort and other large unselected heart failure cohorts. Prescription levels of disease modifying therapy were high in my cohort. 70.5% of patients who took part in the PROMs and follow-up parts of the study were prescribed either ACEI/ARB, with 70.6% prescribed a beta-blocker, and 33.5% a MRA. Very few participants had an ICD or CRT device before the index admission.

In this study I have completed one of the most detailed quantitative assessments describing the influence heart failure has on the lives of patients. I have used PROMs to describe the patients' perspective, rather than the often reported investigators perspective. I have made detailed assessments of QOL (using two different measures), mood disturbance (using two measures), symptom burden, and caregiver burden. Although each of these different PROMs have been used in patients with heart failure before, this breadth of assessment has not been used in such a large and well defined cohort as this one. I have shown that patients with heart failure suffer from a variety of symptoms, including some symptoms which are more commonly associated with other terminal conditions (like cancer) such as pain and nausea. During the index hospitalisation 114 (41.9%) participants had PROMs scores in the severe range of at least one PROM. Of these participants, 48.2% had severe impairment of at least two PROMs. The KCCQ, which has been widely used in a number of studies and cohorts of patients with heart failure, appeared to be the most sensitive PROM at identifying patients with severe impairment, with 34.9% of participants having severe impairment at baseline. This compared to 9.7% in the severe category in the ESAS, 14.1% in SF-12-Physical, 6.5% in HADS- Anxiety, 5.2% in SF-12-Mental, and 3.7% in HADS-Depression. The mean KCCQ scores in my cohort were consistent with other hospitalised cohorts of patients with heart failure, suggesting that the results are robust and genuine. The importance of using a variety of PROMs to assess different facets of influence of heart failure on patients' lives is demonstrated by the difference between the number of patients who were severe in any category and those who were severe in KCCQ.

Participants were offered follow-up visits, either in the study centre or at home, every 4 months for the duration they were in the study, with a minimum of 8 months and a maximum of 28 months. At each study visit all of the PROMs were completed/ offered to each participant, and caregiver where available. There were a total of 691 study visits, giving a total number of assessments during the

study of 963. 37% of all study visits were carried out in patients' homes. This allowed this study to have a very high retention rate given the length of the study and the age and frailty of the participants. Excluding patients who did not attend due to death, 78% of potential study visits were completed. This makes this study one of the most in-depth longitudinal studies assessing the patient journey in patients with heart failure. This, combined with the unselected recruitment and rigorous diagnostic process, makes this study unique.

Participants were followed-up actively at study visits and also passively, using medical record linkage. This resulted in a very complete follow-up for hospitalisations, and deaths. In keeping with other cohorts, and data based on death certificates, participants in this study were at risk of early death following or during their index admission. During the follow-up period there were 103 deaths, 37.9% of the participants who participated in the PROMs aspect of the study. Most deaths were cardiovascular (61.5%). This relatively high proportion of non-cardiovascular deaths for a heart failure cohort perhaps reflects the high proportion of participants with co-morbidities. Participants were asked where there preferred place of death would be, in a hypothetical scenario. In keeping with other studies, most participants stated a preference to spend their EOL at home. However, there was a stark mismatch between preferred place of death and actual place of death. Of the 94 patients who died, where place of death was known, 50 (53%) stated a preference to spend their EOL at home. Of these, 37 (74%) died in hospital. Most participants 63 (67%) died in hospital. The proportion of patients with heart failure dying in hospital is similar to that reported in a recent study reporting place of death in three countries in Europe (including England and Wales) in 2007.[40] My study is the largest study of unselected patients with heart failure to compare preferred to actual place of death. EOL care was also evaluated using the VOICES questionnaire. Unfortunately, there was a lower than expected response rate, possible due to a lack of informal caregiver for many participants. Of the 61 VOICES EOL questionnaires posted to informal caregivers of deceased participants, 17 (27.9%) were returned. The VOICES questionnaire does still provide useful insight into the EOL care in patients with heart failure. 11 (64.7%) respondents reported overall care in the last three months of life to be either good, excellent, or outstanding. Only 2 (11.8%) felt that care was

outstanding. 6 (35.3%) informal caregivers felt that overall care was either fair or poor. These results are worse than the latest National EOL Survey in England and Wales, completed by 21 320 bereaved caregivers.[103] In that survey, overall care was rated as good-excellent in 74.1%. Whether this discrepancy is due to my cohort being exclusively of patients with heart failure is unclear. It is not possible to make direct comparisons due to the large discrepancy in size between the two surveys. The results of the VOICES questionnaire in my study, combined with the discrepancy between preferred and actual place of care, do suggest that improvements could be made in EOL care.

As described above, participants were followed-up actively, between 8 and 28 months following their index heart failure hospitalisation. At each of these assessments, each PROM was repeated. By classifying patients as having severe impairment (defined as scoring in the severe category in any PROM) or not-severe, I was able to describe the patient journey in detail. Using this method, I was able to describe a group of patients who suffered from persistently severe impairment (of either QOL, symptom burden, or mood) over time, or died without improvement in their overall status. Using these criteria to define PC need, 73 (26.8%) participants enrolled in the study had PC needs. A higher proportion of patients in this group were men. Physical examination findings were similar other than a higher proportion of patients presenting with signs of peripheral oedema, and patients in the PC needs group having lower median blood pressures. There was a higher proportion of patients in NYHA class IV in the group meeting the definition of PC needs. Patients in the PC needs group were more likely to have a past history of myocardial infarction or diabetes mellitus, and were more likely to have been admitted to hospital due to heart failure in the preceding 6 months. The only difference in drug prescription prior to admission was a higher proportion of patients being prescribed aspirin in the PC needs group, in keeping with the higher proportion of previous myocardial infarction. There were no differences in prescription of drugs on discharge or during admission, other than a higher use of the inotropic agent dopamine in the PC needs group. Biochemical markers of disease severity, and predictors of prognosis, such as BNP and troponin, were higher in the PC needs group, although these differences did not reach statistical significance. There were no statistically significant differences on laboratory testing during the index

admission between the two groups, other than a lower bilirubin level in the PC needs group. The clinical significance of this difference is uncertain given both median bilirubin results were within the normal reference limits. Ejection fraction was lower in the PC needs group, but this difference was not significant. LV indexed diastolic and systolic volumes were higher in the PC needs group (p=0.02). There was a higher proportion of HF-REF in the PC needs group, although the difference was not significant. There were no significant differences in left atrial or right ventricular size and function between the two groups.

The most marked differences between the two groups of PC need were in the PROMs measured. Patients in the PC needs group had worse overall summary scores across all PROMs, all of which were statistically significant. There were also higher proportions of patients classified as moderate or severe by all PROM in the PC needs group. Participants in the PC needs group not only had a reduced life expectancy, but also spent fewer DAOH. An important additional analysis, adjusting DAOH for QOL and symptom burden, showed that patients in the PC needs group had much fewer good days spent alive and out of hospital. This confirms that the definition of PC needs is robust and appropriate to identify a group of patients who have persistently impaired lives with low QOL and a reduced life expectancy.

Of the 272 patients who participated in the whole study, 33 (12.1%) accessed specialist PC services (SPCS), that is, they were on a specialist PC register. Of the patients classified as having PC needs, 19 (26.0%) accessed SPCS, where 14 (7.0%) of the 199 patients who were not in the PC needs group accessed SPCS, p <0.001. Very few patients in either group accessed hospice care, either as an inpatient or day care services. Only 6 of the 272 participants accessed any form of hospice care. Although patients in the PC needs group were more likely to access SPCS, the majority of those identified as meeting the definition of PC needs did not.

I have shown what many believe in clinical practice, that predicting which patients go on to develop PC needs is difficult. I was able to formally assess this by asking the attending physician to try to predict if each patient had PC needs. The physicians' predictions only correlated modestly with patients who met the

definition of PC needs. The attending physicians were better at predicting prognosis at 1 year than predicting PC needs, although this correlation was also moderate. I have also demonstrated that the most commonly used variables in predictive models for prognosis do not reliably identify or predict patients who have PC needs. This finding i contrary to contemporary guidelines which suggest using physicians' prediction of poor prognosis as one method for selecting patients who should be referred for specialist PC input.[3] Using multivariable logistic regression analysis, I have shown that a combination of a PROM (low KCCQ summary score) and a structured physician completed assessment (low AKPS score) is more accurate at predicting patients with PC needs than physicians' clinical assessment or prediction of prognosis. The strongest independent predictor of PC needs, following multivariable analysis, was a KCCQ summary score of less than 25 (when using KCCQ as a categorical variable). This finding is consistent with the previous analysis of the acute heart failure study, EVEREST, in which KCCQ less than 25 during admission was the strongest predictor of persistently impaired QOL or death.[112]

9.2 Strengths

My study has a number of strengths which make this one of the most robust and detailed assessments of PC needs in patients with heart failure. Firstly, screening was rigorous and systematic. I screened for new heart failure admissions at least 5 days per week, for almost two years. As well as personally reviewing all admissions to the medical receiving unit, I screened echocardiogram requests. Given the median length of stay for a patient with heart failure was 9 days, I believe I was able to screen almost all patients with heart failure who were admitted to hospital in the Western Infirmary during the study. I was very prescriptive when employing the ESC diagnostic criteria to diagnose heart failure, and therefore feel that all of the patients in this cohort had heart failure. I used natriuretic peptides, echocardiography, CXR, and clinical examination to confirm or refute the diagnosis. I believe this makes my cohort one of the most robust contemporary heart failure cohorts. Furthermore, a detailed echocardiogram was performed, making assessment of left ventricular systolic and diastolic function, left and right ventricular size, and valve structure and function. All echocardiograms were performed by myself, but blindly analysed by an expert in echocardiography (consultant cardiologist, Dr Piotr

Sonecki). This was a crucial aspect of the screening process, particularly in making the diagnosis of HF-PEF, as this can be difficult and requires a number of assessments to be made. These are often not routinely performed in clinical practice in the West of Scotland.

Although a strictly consecutive cohort was not possible, as some patients are unable to consent due to cognitive impairment, and some patients refused consent, I was able to recruit a near-consecutive cohort of patients with heart failure. This makes the results of this study more generalisable than most of the previous published studies assessing PC need in patients with heart failure. I have also reduced selection bias as much as possible by employing this strategy. In my systematic review of the literature I showed that most of the previous published studies of PC needs in patients with heart failure were from small, highly selected cohorts, often exclusively of HF-REF.

Another issue identified in the systematic review of the current literature was the limited description available of use of pharmacotherapy and device therapy in previous studies describing PC needs. I have extensively documented admission and discharge medications, including all potential disease modifying therapies. The patients studied with HF-REF, where disease modifying therapies are available, were in general discharged from hospital on disease modifying therapy where tolerated. This is important in any study assessing the PC needs of patients with heart failure, as these therapies could change the course of the condition and symptom burden.

Another strength of my study was the size, with a large number of participants recruited, and long follow-up period with regular study assessments. As described above, many of the studies reviewed focused on small numbers of highly selected cohorts, with resultant low power and high selection bias, and ultimately reduced generalisability. I have recruited a large contemporary cohort, of well described patients with heart failure, and systematically followed them up over a median of 2.1 years. A total of 691 study assessments were carried out, which gives this study a unique perspective into the patient journey. Patients were not only passively followed-up with record linkage to ensure as complete follow-up as possible, but they were offered active follow-up with study visits for a minimum of 8 months and a maximum of 28 months. Only

two other studies describing the potential PC needs of patients with heart failure enrolled similar or greater number of patients. The first enrolled community patients with heart failure.[183] This study is important and informative, but lacks the robustness of diagnosis that my study offers. The diagnosis was a clinical diagnosis of heart failure, which is flawed due to the variety of other conditions which can present with similar symptoms. The analysis of the EVEREST study is also important, firstly due to its size, but also that participants had repeat assessments at one and 26 weeks.[112] Although this was a highly selected clinical trial cohort, only including HF-REF, and used a different definition of PC needs (KCCQ summary score <45 on two measurements or death before week 26), the results were similar to my own. In their multivariable analysis, the strongest predictor of PC needs was a KCCQ summary score of < 25 during baseline hospitalisation.

Perhaps the greatest strength of my study was the use of quantitative measures to describe the effect heart failure has on patients' QOL, symptoms, and mood. I used a combination of well validated and robust measures to give an overall assessment of the burden placed on patients by heart failure. I also made an objective assessment of caregiver burden using a well validated questionnaire. Many studies have performed these assessments in patients with heart failure previously, however no study has performed all of these PROMs, and repeatedly over time, in an unselected cohort. Using quantitative PROMs again increases the generalisability of the results.

9.3 Weaknesses

There are a number of unavoidable weaknesses in this study. Perhaps the most important to address is the definition of PC needs. There is no single assessment that categorises patients as having PC needs in heart failure. There is a WHO definition of PC, and this defines what PC aims to do for a patient, but there is no universal definition of PC needs. I have used this definition of PC to define a group of patients who I think had PC needs. Not only did I adapt and interpret this definition of PC, but I also consulted with experts in both PC and heart failure, including the only consultant cardiologist in the UK with a specialist interest in PC (Dr Karen Hogg). Through these discussions we were able to reach a consensus on how PC needs should be defined, as described in the methods

chapter. I believe this definition is appropriate, incorporates the principles of the WHO definition of PC, and importantly, is intuitive for the practicing physician to understand. Ultimately, the definition of PC needs I have chosen was designed to identify a group of patients who have the worst persistently impaired lives (as measured by frequent hospitalisations, poor QOL, high symptom burden) and a reduced life expectancy. The reason for identifying these patients is that they are likely to be the group who would benefit most from a palliative intervention. I have shown that the group identified as having PC needs had a worse patient journey, and ultimately had much fewer good days out of hospital with more days lost to either death, hospitalisation, or impairment of QOL.

Another potential weakness of my study is the use of cut-off scores to define severity in each PROM. For most of the PROMs there were published severity categories available, or cut-offs which were associated with worse outcomes. The ESAS was one PROM which, although used frequently in PC studies of patients with cancer, had no defined cut-off scores to categorise severity. I have used an intuitive and common-sense approach to divide the overall score of the ESAS into thirds, with categories for none/mild impairment, moderate, and severe. I believe the cut-offs or categories used are appropriate as patients with severe ESAS category had worse scores in all other PROM categories, and were more likely to be classified severe in other PROM categories. Using cut-offs will invariably classify some patients who would have been close to the severe group in each PROM being labelled as not having PC needs. Again, the purpose of this study was to try and describe a group of patients with persistently the worst QOL, symptom burden, and mood, and a reduced life expectancy, which may benefit from PC. I believe this has been achieved and now this group of patients can be targeted for a palliative intervention in a RCT. This is similar to the first use of ACEI in patients with heart failure. First, the therapy was used in the most severe group, in the case of CONSENSUS, patients with NYHA class IV and low ejection fraction were targeted. After a benefit was shown in this group, the therapy was trialled in other categories of patients (NYHA II, and patients without overt symptoms).

Another potential weakness of the study was the number of patients who withdrew or were lost to active follow-up (failed to attend study visits). I have

chosen not to exclude these patients. I have done this as to eliminate these patients would reduce the overall generalisability of the study by introducing a form of selection bias, as only those who were fit/ able enough to complete follow-up would be assessed. I feel excluding these patients would eliminate a large group of patients who were perhaps those with the highest need, as they may have missed study assessments due to deteriorating health. There are various statistical ways of dealing with drop outs, or missed appointments. One method is to impute an assumed value. Another method would be to assume that a patient missed an appointment due to deteriorating health and classify them as "severe" for that missed assessment. For the purposes of the defining patients with PC needs, I have not done this. I have assumed that the patient's overall status did not change from the previous assessment.

Another potential weakness of the study was the time between assessments. I elected to use 4 monthly assessments instead of shorter time intervals. I did this for logistical reasons, based on the amount of time available for myself and the study nurse to complete the large number of assessments. To increase the frequency of visits to 3 monthly, or more frequent, would have required me to truncate follow-up. I felt 4 month visits allowed for the maximum number of follow-up visits and study duration.

The VOICES survey had a low response rate compared to the published national VOICES surveys. This reduces the value of the VOICES component of this study, but I believe this part of the study is still useful and informative about the caregivers' perspective regarding EOL care. I suspect the difference in methodology between my study and the VOICES national survey explains the low response rate in my study. I only posted the VOICES questionnaire if I definitively knew that the deceased participant had an informal caregiver, whereas the VOICES national survey posted to registered next of kin.

An unavoidable weakness of the study is the exclusion of patients with dementia. Although these patients are potentially a group which are underserved by all services, and potentially have the highest levels of PC need, it would not be possible or appropriate to include these patients. Firstly, they would be unable to participate, and secondly, they would be unable to complete the PROMs.

9.4 Future research based on this study

One of the main objectives of this study was to identify a group of patients with heart failure who may benefit from a palliative intervention. Not only have I described a group of patients who had either a sustained, severe impairment of QOL, symptom burden, or mood, or died following severe impairment, but I have also shown there is a marked discrepancy between these patients with PC needs and those who received PC. Although there has now been a number of recent RCTs that are suggestive that a palliative intervention in patients with heart failure would be beneficial, these have been small studies, with ambiguous primary outcomes such as change in QOL. To truly say that a patient has PC needs, we must prove that there is a benefit to patients from a palliative intervention. My study will inform the design of a RCT which will answer this question. I have identified a suitable target population, specifically those who met the definition of PC needs for such a study. I have also shown that it is possible to identify these patients using a validated QOL questionnaire, the KCCQ, and a bedside physician completed assessment, the AKPS. This study also provides crucially important data to power the sample size for any future RCTs testing a palliative intervention. I have demonstrated the usefulness of the novel metric, DAOH, and more importantly, QOL adjusted DAOH. This measure, used as the primary endpoint in a RCT of early PC in heart failure, will allow comparison of the patient journey between two groups. I have also shown that patients are willing to discuss EOL preferences, and this is another potential endpoint in a RCT, comparing achieved preference for EOL care. I believe this would be a more appropriate secondary endpoint, as palliative care needs are not limited to patients who die. I found the VOICES EOL questionnaire to be very informative, but I feel this will be less useful in a RCT setting due to low return rates.

I envisage an RCT comparing standard practice to early referral and utilisation of specialist PC services, in conjunction with usual care. My study also provides some of the potential target areas for intervention, as individual patients would have different needs. I have shown that some patients experience marked mood disturbance with low mood and anxiety, perhaps these patients could be targeted with cognitive-behavioural, pharmacological, and psychological therapies. I have also shown that patients with heart failure experience a

variety of symptoms which could be specifically monitored and targeted, such as focused treatment of pain and nausea. I have also demonstrated that some patients and their caregivers would have welcomed better communication between services, and better communication regarding their prognosis, treatment options, and EOL preferences. Some of these communication issues could potentially be addressed or highlighted through use of an appropriate anticipatory care plan. Such an anticipatory care plan could be standardised in an RCT setting. I believe that the NAT-PD-HF, although not identified as an independent predictor of PC need after multivariate analysis, would still be a very useful tool for monitoring the progress and highlighting specific needs of individual patients. These specific and individual needs could be targeted by the PC and heart failure teams during the study. Further research, based on the data gathered in my study, will be able to provide the construct validation for the NAT-PD-HF for such a purpose.

9.5 Conclusions

Patients admitted to hospital because of heart failure experience a variety of symptoms, frequently experience mood disturbance, and have markedly impaired QOL. Not only does heart failure impair the lives of patients, but also that of their caregivers. I have demonstrated the fluctuating nature of the syndrome of heart failure by describing the patient journey in detail. Following a hospitalisation due to heart failure, many patients have reduced number of good days spent out of hospital, with frequent and prolonged hospitalisations, reduced QOL, and reduced life expectancy. 26.8% of patients in this study met the definition PC needs. Despite these apparent PC needs, very few patients accessed SPCS, and even fewer accessed hospice care. Ultimately to prove a need for treatment, we should first prove a benefit. My study provides the basis for the design of, and the justification for, a RCT which will test whether early PC can improve the lives of patients with a diagnosis of heart failure.

Appendices

Appendix 1- Systematic review table

Supplementary Appendix: Table 1A: Quantitative studies

Study (year) *Country*	Cohort description									Aims	Design	Outcome measures	Main Findings
	Participants	Recruitment	n	Age (mean)	Male (%)	NYHA (%)	Mean EF (%)	HF diagnosis definition	HF-PEF included				
Scott[161] (2000) *USA*	• Outpatients with End Stage HF	10 outpatient inotrope infusion programs. Selected Cohort.	20	69	90	IV (100)	NA	NA	NA	Describe patient and caregiver HRQOL.	Cross-sectional. Quantitative. Telephone interview.	QOL: • MLHF • QLI Mental health • MHI-5	•1/3 of caregivers felt unprepared for the stress associated with caring for someone with end-stage HF. •Most felt positive regarding caregiving.
	• Caregivers		18	63	11					Describe influence of caring on caregiver.		Caregiver preparedness: • QPS Caregiver Burden: • CRA	•78% reported daily activities focused on ADL of patient, with 55% having to eliminate things from their schedule. •All pts reported physical burden, more so than emotional, particularly impairment in sexual activity, diet , walking, and climbing stairs. •55% of caregivers and 50% of pts experienced anxiety , with 65% and 45% respectively experiencing depression. 75% of patients fell below the age-adjusted normative values for mental health scores.
Anderson[113] (2001) UK	• Outpatients with end stage HF	Heart failure clinic, tertiary centre.	66	67	83	III/IV (49)	29	NA	NA	Describe and compare symptoms	Quantitative. Cross-sectional.	Self-designed questionnaire consisting of checklist of 20	• PC and HF patients had similar number of symptoms per patient.

	• Outpatient palliative patients (cancer or HIV)	Consecutive patients. From Palliative care services and clinics	213							and service use between HF and palliative patients.		different symptoms.	• Symptom type differed between PC and HF patients. • HF patients less likely to access support services
Fried[134] (2002) USA	• CHF with reduced life expectancy • COPD with reduced life expectancy • Cancer with reduced life expectancy	Sequential charts screened from Cardiology, Pulmonary and Oncology outpatient practices, as well as inpatients.	66 81 79	75	77	NA	NA	NA	NA	Describe patients' preference for care in relation to burden of care.	Quantitative, cross-sectional. Interview at home.	Self-designed questionnaire using 4 scenarios: burden of treatment; possible outcomes; likelihood of outcomes.	• Most patients would accept a low burden treatment unless high likelihood of functional or cognitive impairment.
Barnes[114] (2006) UK	CHF outpatients from 16 GP practices	Identified and recruited by GPs Largely unselected cohort Age > 60	540	NA 80% >70 39%> 80	54	I/II (61) III/IV (39)	NA	Clinical diagnosis of HF	NA	Explore prevalence and burden of symptoms in elderly patients with CHF	Quantitative, Longitudinal Qualitative interview for 40 participants	QOL: • KCCQ • SF-36 Mood: • GDS-5 Symptoms • NYHA	• Symptom burden high and common, particularly SOB and fatigue, which was experienced daily in half of participants • Over half of participants reported symptoms of depression
Walke[169] (2007) USA	CHF outpatients	Sequential charts reviewed and patients contacted by telephone Selected cohort Age > 60	59	75	63	III/IV(100)	(100% EF= <20%)	NA	No	Examine the prevalence and severity of symptoms over time	Quantitative Longitudinal every 4 months for 2 years	Symptoms • ESAS	• Symptoms not only highly prevalent, but frequently reported as moderate or severe • >50% of HF patients reported physical discomfort, fatigue, and problems with appetite • Pain increased in severity over time in patients with HF
	COPD outpatients		74	72	50	NA							
Fitzsimons[132] (2007) UK	HF inpatients	Selected cohort Identified by clinical team	6	na	67	III/IV(100)	(100% EF= <30%)	NA	no	Explore patient perceived PC needs of	Mixed methods: quantitative	QOL • SF-36 Mood • HADS	• Patients with HF reported poor physical and general health on SF-36

										patients with non-cancer diagnosis	and qualitative, Cross-sectional	Semi-structured interview	• Depression and anxiety not reported at clinically significant levels on HADS • Themes important to patients identified through interview were physical deterioration, increased dependence, and family burden. Patients also experienced limited access to resources
	Renal failure Respiratory failure		6 6	NA NA	50 50	NA NA							
Bekelman[1] [16, 117] (2007) USA	CHF	Recruited by Cardiologists at outpatient clinic	60	75*	63	NA	NA	Cardiologist's clinical diagnosis of HF	NA	Identify the relationship between spiritual well-being and depression	Cross-sectional, quantitative	Mood • GDS-SF Spiritual well-being • FACIT-Sp QOL • KCCQ Physical symptoms • MSAS-SF	• >30% of patients had clinically significant depression • Greater spiritual well-being was associated with less depression • Depression was associated with a greater number of physical symptoms
Gott[137] (2007) UK	CHF in primary care	Decedents with KCCQ assessments from larger longitudinal study of HF	27	NA	NA	II (66) III (33)	NA	Clinical diagnosis of HF	NA	Assess change in QOL prior to death and dying trajectory	Quantitative, longitudinal	QOL • KCCQ	• Physical function fluctuated in the months leading up to death • No clear dying trajectory was identified
Opasich[157] (2008) Italy	HF inpatients	Selected cohort, inpatients with NYHA III-IV	46	71	57	III (26) IV (74)	28	NA	NA	Explore physical and emotional symptoms mostly related to global health status in HF	Cross-sectional, quantitative ESAS repeated x2 daily for 5 days	QOL • KCCQ Symptoms • ESAS	• Many symptoms identified, HF patients had poor global health status • Most distressing symptoms reported were general discomfort, tiredness, anorexia and dyspnoea

Goebel[136] (2009) USA	CHF outpatients	Randomly sampled patients attending outpatient visits	95	67	100	NA	NA	Clinical diagnosis of systolic or diastolic HF	Yes	Describe and compare symptoms of pain in patients with HF	Cross-sectional, quantitative	Mood • PHQ-2 • GAD-2 Symptoms • BPI	• Patients with HF experienced similar severity, interference, distress and location of pain to patients without HF • Pain is not an uncommon symptom in HF
	Other outpatients		539	62	100								
Bekelman[120] (2009) USA	CHF outpatients	Selected patients from cardiology outpatient	60	75*	63	NA	NA	Cardiologist's clinical diagnosis of HF	NA	Compare need for PC between HF and cancer population	Cross-sectional, quantitative	Mood • GDS-SF Spiritual well-being • FACIT-Sp QOL • KCCQ Physical symptoms • MSAS-SF	• Similar physical symptoms , depression, and spiritual well-being scores were reported between cancer and HF patients • Similar physical symptom burden, mood, and spiritual well-being scores were seen regardless of ejection fraction
	Advanced cancer	Oncology clinics	30	64*	40								
Evangelista[131] (2009) USA	CHF outpatients	Tertiary HF clinic Selected cohort	300	54	74	I (11) II (34) III (45) IV (12)	32.3	NA	No, inclusion EF <40%	Describe the prevalence of pain in patients with HF and determine relationship of pain and QOL	Cross-sectional, quantitative	QOL • MLWHF Pain • SF-36	• Pain was common in CHF (67%) and more so in worse NYHA class (89% of NYHA IV) • Worse QOL (overall and physical) correlated with presence of pain
O'leary[156] (2009) Ireland	CHF outpatients	Specialist HF clinic Selected cohort NYHA III/IV Deteriorating clinic condition	50	77*	78	III/IV (100)	28	NA	NA	Compare PC needs of patients with HF to patients with cancer	Cross-sectional, quantitative + qualitative interview	QOL • SF-36 Mood • HADS Symptoms • ESAS	• Similar symptom burden was experienced between patients with HF and cancer • There was no difference between anxiety and depression scores between patients with cancer and HF

													• Similar levels of QOL, with the exception of HF patients having better social functioning scores.
	Cancer outpatients	Referred to community specialist PC service	50	75*	50								
Strachan[165] (2009) Canada	HF inpatients	ADHF from 5 tertiary hospitals Selected cohort NYHA IV Age >55 EF < 25%	106	76	65	IV (100)	NA	NA	no	Identify opportunities to improve EOL care in hospitalized patients with HF	Cross-sectional, quantitative	Investigator designed questionnaire covering 5 areas: • Medical + nursing care • Communication + decision making • Social relationships + support • Advanced care planning	• Most preferred place of death was home • Obstacles identified to achieving home death included burden (58%), no caregiver available (22%), pain (30%), and no health care services (48%) • Most expected to have a life expectancy of > 1 year or did not know • 46% wanted to know their prognosis • 50% wanted to have a discussion about CPR, 42% had not discussed CPR with anyone, • Most patients wanted some form shared decision making regarding CPR
Allen[112] (2011) USA	HF inpatients	RCT inpatients with EF ≤ 40% Recruited from 359 sites Selected population	1458	67	75	I (4) II (42) III (48) IV (6)	27	Clinical signs of HF + low EF	No	Identify patients at risk of poor QOL and death following HF hospitalization	Quantitative Longitudinal	QOL • KCCQ	• High 6 month mortality (33%) • 13.2% of survivors had persistently unfavorable QOL
Raphael[158] (2011) UK	HF outpatients with ICD	Selected population with ICD	54	72	80	Overall score mean 1.8	37	NA	No	Assess patients' attitudes to and opinions of EOL care	Quantitative Cross-sectional	EOL • Investigator designed questionnaire	• Most patients were aware of why ICD was implanted, but few were aware of options for device deactivation.

												assessing ICD deactivation	• Most patients would like to be involved in any discussions about device deactivation, and advanced care planning.
Bekelman[118] (2011) USA	HF outpatients attending HF PC clinic	Selected population	50	51*	72	I (2) II (28) III (57) IV (13)	28	NA	NA	Assess PC needs (QOL, symptoms, mood) serially in outpatients attending PC program	Quantitative Longitudinal Retrospecti-ve	QOL • KCCQ Mood • PHQ-9 • GAD-7 Symptoms • MSAS-SF	• Common symptoms were depression(50%), anxiety (33%), pain (47%), fatigue (62%), dyspnea (46%), and sleep disturbance (44%). • Most of population not in terminal year of life, 1 year mortality 14% • Advanced care discussed in 48%, Hospice and resuscitation discussed in 16%
Habal[140] (2011) Canada	HF oupatients attending heart function clinic in quaternary care academic centre	Selected population LVSD	41	57	83	I (17) II (39) III (29) IV (15)	NA	NA	No	Determine patients' awareness, comprehension, utilisation of ACD, determine knowledge of CPR and preference	Quantitative Cross-sectional	Semi-structured interview	• Most (76%) did not know what an ACD was • Most would like to discuss ACD (78%) • Most would prefer full resuscitation at the time of interview • Of 19 patients with ICD, 47% would want ICD deactivation if deterioration of clinical condition, only 2 patients recalled having previously discussed device deactivation
Janssen[147] (2011) The Netherlands	Outpatients with severe HF Outpatients with COPD	Selected population, NYHA III/IV Selected population,	80 105	76 66	68 62	III/IV (100)	na	na	na	Assess the severity of symptoms, presence of co-morbidities, and provision of	Quantitative Cross-sectional	Symptoms • VAS Mood • HADS	• Numerous symptoms were common, and rated as moderate to severe: Dyspnoea (75%); Fatigue (84%); Coughing (50%); weakness (85%); loss of appetite (45%);

		GOLD stage III/IV								services in outpatients with advanced COPD and HF			insomnia (50%); low mood (53%); pain (41%); thirst (46%); frequent micturition (65%) • Symptom frequency and severity were similar between COPD and HF, although there was more severe dyspnoea in pts with COPD and more pain, itch and nocturnal micturition in pts with HF • Pts with both COPD and HF were generally satisfied with their management
Janssen[148] (2012) The Netherlands	Caregivers of outpatients with severe HF Caregivers of outpatients with advanced COPD Caregivers of outpatients with advanced CRF	Selected population, NYHA III/IV	45 73 41	67 63 59	20 23 42	III/IV (100) (patients)	na	na	na	To assess caregiver burden as well as positive aspects of caregiving in advanced organ disease	Quantitative Cross-sectional	Caregiver burden • FACQ PC Care dependency • CDS	• Caregiver strain scores were relatively low • Scores were comparable across different conditions • Scores for positive caregiving appraisals and family well being were relatively positive
Dunlay[128] (2012) USA	New HF outpatients Olmstead County	Unselected cohort, retrospective study	608	74	55	I/II (35) III/IV (65)	NA	Framingham criteria	Yes	Assess use of ACD	Quantitative Longitudinal	Mood • PHQ-9 QOl • SF-12 Social support • ESSI EOL • Medical record	• 27% of participants died within mean follow up 1.8 years • Only 249 had an ACD • Of those with an ACD, less than half addressed CPR, mechanical ventilation or haemodialysis
Howie-Esquivel[143] (2012) USA	HF inpatients	Recruited as inpatient, screening NA	47	63	64	II (21) III (34) IV (45)	NA	NA	Yes	Assess communication wishes regarding	Quantitative, Cross-sectional	QOL • KCCQ EOL	• Most patients wished for more information about their condition

										EOL care; identify relationship between communication and clinical characteristics		• Semi-structured interview	• 44% wanted more information regarding prognosis • 51% of patients could recall discussions regarding resuscitation during hospitalization
Udeoji[168] (2012) USA	HF outpatients	Selected population, NHA IV excluded, HF-REF only	62	56*	82	na	33	na	no	Evaluate the prevalence and severity of pain in patients with HF	Quantitative, Cross-sectional	Symptoms • ESAS	• Symptoms were common and often reported as severe: pain (52%), fatigue (76%), reduced general wellbeing (84%), dyspnoea (76%), drowsiness (76%)
Evangelista[130] (2012) USA	HF outpatients referred for PC consultation	Selected population, Tertiary centre, Patients with ICD/ VAD excluded, life expectancy < 6 months excluded	36	54	72	II (70) III (30)	25	NA	NA	1) Assess feasibility of referring pts recently hospitalized with HF to PC + standard care 2) Compare PC consultation to standard care 3) Examine relationship between clinical characteristics and QOl, mood, symptom burden 4) Assess multivariate model in predicting QOL, mood,	Quantitative, longitudinal	Symptoms • ESAS Mood • PHQ-9 QOL • MLHF	• PC consultation focused on ACP (100%), symptom management (81%), illness understanding (69%), and caregiver burden (50%) • Impaired QOL, mood disturbance, and symptom burden common in both groups • Pts referred to PC were similar to the control group regarding symptoms, QOl, and Mood at baseline • PC group showed better QOL, symptoms, and mood at 3 months
	HF patients hospitalized	Recruited from a larger RCT, selected population	36	53	72	II (72) III (28)	26	NA	NA				

										Symptom burden			
Brunner-La Rocca[48] (2012) Europe	HF outpatients	Pts participating in a RCT (BNP guided treatment) Selected population	622	77	59	≥ II (76)	35	Previous hospitalization with CHF	Yes	Assess willingness to trade survival time for QOL and resuscitation preferences	Quantitative, Longitudinal	QOL • MLHF • SF-12 Mood • GDS EOL • TTO tool	• 89% of participants completed time trade-off questionnaire, although this decreased at subsequent visits • At baseline, 74% of pts were not willing to trade survival time for improved QOL, this increased significantly at month 12 and again at month 18 • Willingness to trade survival time for increased QOL increased with age, female sex, GDS, reduced activity status, gout, constipation and oedema. This was not reliably predictable from these factors however. • 97% of pts completed the resuscitation questionnaire • 39% did not wanting resuscitation, where 51% did
Malik[152] (2013) UK	HF outpatients HF caregivers	Recruited from outpatient clinics and inpatient wards Selected patients	51	73	75	II (18) III (74) IV (8)	25*	NA	NA	Compare experiences of caring for breathless patient with lung cancer to HF and examine factors associated with caregiver burden	Quantitative, cross-sectional	Caregiver burden • ZBI-12 • COPE Mood • HADS QOL • SF-36 Symptoms • POS-S • POS-C Performance	• Both HF and lung cancer patients reported high levels of unmet needs, similar between both groups • Caregivers looking after more symptomatic pts reported positive caring experiences • Despite similar levels of symptoms and caregiver burden, HF
	Lung cancer patients		50	70	71								

	Lung cancer caregivers											• PPS	patients had less access to PC services
Herman[141] (2013) Czech Republic	HF outpatients with ICD	Selected population at ICD clinic in tertiary University centre, although consecutive screening at clinic	112	68	84	I (12) II (81) III (7)	32	NA	No	Examine the wishes of HF pts with ICD regarding ICD deactivation	Quantitative, cross-sectional	EOL • Investigator designed questionnaire regarding ICD deactivation	• 46% of patients had never considered ICD deactivation during near- EOL situations • EOL ICD deactivation only discussed with 7% of pts • 40% wanted more information regarding ICD deactivation • 26% refused more information or further discussion regarding ICD deactivation
Evangelista[129] (2014) USA	HF outpatients	Selected population, NYHA II-III, referred to PC services	36	54	72	II (69) III (31)	25	na	na	Describe PC services and levels of symptom burden experienced during initial PC consultation	Quantitative, cross-sectional	Symptoms • ESAS	• 92% of pts reported at least one symptom, 61% reported at least one severely distressful symptom. • Most commonly experienced moderate/ severe distressful symptoms were fatigue (77%), pain (78%), anxiety (50%), depression (39%), dyspnoea (39%), drowsiness (36%), anorexia (36%), nausea (14%), reduced well-being (39%)
Kavalieratos[149] (2014) USA	HF patients attending PC service Cancer patients	Selected population already enrolled in PC service	334 697	84*	41	Na	Na	Na	Na	Describe unresolved symptom and treatment needs in pts with HF and cancer	Retrospective, Quantitative, cross-sectional	Symptoms • McCorkle Symptom Distress Scale Performance • PPS	• Physical symptoms common (fatigue 60%, anorexia 30%, dyspnoea 25%) • 28% of pts with HF had low PPS, with median score of 40 • Cancer pts experienced greater frequencies of anorexia, pain,

	attending PC service												insomnia, anxiety, constipation, and nausea. • Dyspnoea more commonly unresolved in pts with HF.
Janssen[146] (2014) The Netherlands	Outpatients with severe HF	Selected population, NYHA III/IV	80	76	68	III/IV (100)	na	na	na	Explore the profiles of care dependency and compare between different conditions	Quantitative, longitudinal	Care dependency • CDS	• COPD and CHF pts had higher baseline levels of care dependency • COPD pts were more likely to experience increase in care dependency than CHF or CKD pts
	Outpatients with COPD	Selected population, GOLD stage III/IV	105	66	62								
	Outpatients with CKD	Requiring dialysis	80	62	60								
Sidebottom[163] (2014) USA	HF inpatients	Tertiary care setting LVAD, transplant, actively dying pts excluded RCT early PC vs standard care	232	73	53	NA	NA	NA	NA	Compare early inpatient PC use vs standard care in patients with HF, assess change in symptom burden, QOL, service use	RCT Quantitative Longitudinal at baseline, 1 and 3 months	Symptoms • ESAS QOL • KCCQ Mood • PHQ-9	• Greater improvements in symptom burden, mood, and QOL seen in early PC arm • Pts in PC arm 2.87 times more likely to complete a disease specific ACP
Brannstrom[122] (2014) Sweden	HF outpatients • PC arm • Control arm	Selected population RCT early PC vs normal therapy NYHA III/IV + ≥1 HF hospitalization in preceding 6 months	72 36 36	 82 77	 72 69	 III (78) IV (22) III (64) IV (31)	NA	ESC guidelines	No	Evaluate early PC versus normal care in pts with HF with regard to QOL, symptoms, and hospitalizations	RCT Quantitative Longitudinal assessment	Symptoms • ESAS QOL • EQ-5D • KCCQ Resource utilization	• Improved QOL and less symptom burden seen in PC treatment arm vs control arm • Less healthcare utilization in PC arm

ACD= advanced care directives; ADHF= acute decompensated heart failure; BNP= Brain-type natriuretic peptide; BPI= brief pain inventory; CDS= care dependency scale; CHF= chronic heart failure; CKD= chronic kidney disease; COPD= chronic obstructive pulmonary disease; COTE= care of the elderly; CPR= cardio-pulmonary

resuscitation; CPS= Caregiver preparedness scale questionnaire; CPR= cardiopulmonary resuscitation; CRA= caregiver reaction assessment; EF = ejection fraction; EOL= end of life; ESC= European Society of Cardiology; ESSI= ENRICHD Social Support Instrument; FACQ PC= family appraisal of caregiving questionnaire for palliative care; FACIT-Sp= Functional assessment of chronic illness therapy- spiritual well-being; GAD-2= generalized anxiety disorder scale; GDS-5= Geriatric Depression scale; GDS-SG = geriatric depression scale- short form; GOLD= Global initiative for chronic obstructive lung disease; GP= general practitioners; HF = heart failure; HIV= Human immunodeficiency virus; HRQOL = health related quality of life; ICD= implantable cardioverter defibrillator; LVAD= left ventricular assist device; MLHF= Minnesota Living with Heart Failure Questionnaire; MHI-5 = mental health inventory questionnaire; MSAS-SF = memorial symptoms assessment scale-short form; MND= motor neuron disease; NA= not available; NYHA = New York Heart Association; PC= palliative care; PHQ-2= Patient health questionnaire; POS-S= Palliative Care Outcome Scale- symptom; POS-C= Palliative Care Outcome Scale- Core; PPS= palliative performance scale; QLI= quality of life index questionnaire; QOL= quality of life; RCT= randomized controlled trial; TTO= time trade-off; VAD = ventricular assist device; VAS= visual analogue scale; ZBI-12= Zarit burden interview
*= median

Supplementary appendix: Table 1B-Qualitative Studies

Study (year) Country	Cohort description									Aims	Design	Main Findings
	Participants	Recruitment	n	Age (mean)	Male (%)	NYHA (%)	Mean EF (%)	HF diagnosis definition	HF-PEF included			
Lynn[151] (1997) USA	Caregivers of HF inpatients	Selected population, recruited as part of SUPPORT study, NYHA III/IV, expected reduced life expectancy	102	na	na	na	na	na	na	Characterize experience of dying from the perspective of caregiver	Qualitative interview, cross-sectional	• 26% of HF pts died during first hospitalization • 58% died in hospital, 27% died at home, 7% in a nursing home, and 3 % in a hospice • Caregivers reported high levels of severe dyspnoea (~65%), confusion (~15%) and pain (~45%) • ~50% of caregivers felt pt would have preferred comfort care at EOL • ~15% reported feelings that care was at odds with patients' preference • ~40% of pts with HF received at least one of feeding tube, ventilator, or CPR in the last 3 days of life
Krumholz[46] (1998) USA	HF inpatients	Selected population, recruited as part of SUPPORT study, NYHA III/IV, expected reduced life expectancy	936	Na	63	Na	Na	Na	Na	Describe the resuscitation preferences of pts admitted to hospital with HF	Qualitative interview, Longitudinal assessment as inpatient and at 2 months	• 63% viewed their QOL as fair/ poor • Most (67% estimated their 2 month survival at >90%) • 23% reported not wanting CPR • Of 42 pts suffering cardiac arrest s inpatient, 11 stated a wish not to be resuscitated, of these, 6 had resuscitation attempted • 19% of pts changed resuscitation preferences after 2 months, 40% of those expressing wishes DNR changed their mind at 2 months
Rogers[159] (2000) UK	HF outpatients	Outpatient cardiology and care of the elderly clinics Selected population targeting older patients	27	69	74	II (26) III (44) IV (30)	33	na	na	To explore pts understanding of HF, investigate their need for information and issues regarding communication	Qualitative interview, cross-sectional	• Participants often sought further information regarding HF, prognosis and likely mode of death. • Pts described difficulties establishing good communication with doctors such as access to appointments, confusion, memory loss, and belief that doctors did not want to give pts too much information

Murray[153] (2002) UK	HF outpatients and caregivers Lung cancer outpatients and caregivers	Selected population, NYHA IV,	20 20	na na	na na	IV (100)	na	na	na	Compare illness trajectory and needs of pts with HF and lung cancer	Qualitative interview, Longitudinal every 3 months for 1 year	• Illness trajectory is different between lung cancer and HF, with HF affected by periods of acute deterioration, sudden death and no distinct terminal phase • HF pts and carers have less understanding of the condition and prognosis, and fewer opportunities to discuss EOL issues compared to pts with lung cancer • HF pts and carers have less access to support services such as PC, social and health services compared to lung cancer
Formiga[42] (2004) Spain	ADHF inpatients	Largely unselected cohort Recruited by investigator prior to discharge Age > 64	80	79	42	II (10) III (74) IV (16)	NA	NA	NA	Describe EOL and CPR preferences of patients with ADHF	Qualitative, cross-sectional	• 42% did not want CPR • Only 3% had previously discussed CPR preference • 50% would wish EOL care take place at home, 40% in hospital, 10% unsure • 48% expressed a wish for spiritual support
Willems[171] (2004) Holland	HF outpatients	Selected population NYHA >II EF < 25 ≥1 HF hospitalization	31	72	74	I (4) II (19) III (70) IV (7)	na	na	no	Describe and explore the ideas and attitudes of pts with HF to dying	Qualitative interview, Longitudinal every 4-6 months for 1 year	• Most pts only thought about death during exacerbations • Few participants would consider suicide or euthanasia • Aspects considered appropriate dying included usefulness of pt, understanding prognosis, appropriate duration, and mental awareness, • All participants wanted life-prolonging therapy withheld when appropriate
Boyd[121] (2004) UK	HF outpatients/ community HF caregivers Healthcare professionals	Selected population, NYHA IV	20	74	55	IV (100)	na	na	na	Describe pt and caregivers views of health and social care in the last year of life	Qualitative interview , Longitudinal every 3 months	• Pts with HF and their caregivers felt unsupported by services • Pts and their caregivers had little understanding of HF, the treatment options, or prognosis • QOL was impaired primarily by physical limitations and psychological morbidity • Pts and caregivers felt they had poor access to psychosocial care and the communication between primary and secondary care was poor • PC approach was rarely used
Murray[154] (2004)	HF outpatient	Selected population,	20	na	na	IV (100)	na	na	na	Explore spiritual needs, in context	Qualitative interview,	

UK	s + caregivers Lung cancer outpatients + caregivers	NYHA IV Identified by respiratory consultants								of overall needs of pts with HF and compare to pts with inoperable lung cancer	Longitudinal every 3 months	• HF pts experienced isolation, hopelessness and loss of confidence thought the last year of life • Many pts from both groups experienced spiritual needs in the last year of life • Pts were reluctant to raise spiritual needs with professionals, but were willing to discuss issues when prompted
Horne[142] (2004) UK	HF outpatients	Selected population from two teaching hospitals	20	73	70	II (10) III (35) IV (55)	na	na	na	Explore the experiences of pts with advanced HF and identify needs for PC	Qualitative interview, cross-sectional	• Reported problems included difficulty mobilizing, fatigue and difficulties performing activities of daily living • Relying on others, and feelings of burden, loneliness and isolation were identified as themes • Pts discussed dying and fears and frustrations at living with HF • None of the pts involved were referred to PC services
Agard[110] (2004) Sweden	HF outpatients	Selected population, over 60 years University teaching hospital	40	75	63	II (33) III (65) IV (2)	na	na	na	Explore pts with HF's knowledge of their condition and attitude towards prognostic information	Qualitative interview, cross-sectional	• Most pts had a limited understanding of their condition, but were satisfied with their level of understanding • Most did not want prognostic information
Aldred[111] (2005) UK	HF outpatients recently discharged from hospital	Selected population, over 60	10	72	70	II (20) III (60) IV (10)	Na	Na	Na	Explore the impact of HF on the lives of older pts with HF and their caregivers	Qualitative interview, cross-sectional	• HF affect daily lives of pts and caregivers including every day activities • Pts felt concerned regarding the potential burden placed on caregivers • Lack of professional support contributed to social isolation of pts and caregivers • Pts and caregivers had limited understanding of HF and prognosis
Brannstrom[124] (2006) Sweden	House bound HF patients	Selected population, NYHA III/IV plus deemed to be palliative	4	79*	75	III (25) IV (75)	Na	ESC criteria	na	Understand meaning of living with severe HF in palliative advanced home care	Qualitative interview, cross-sectional	• Themes identified included struggling to cope with unpredictability of condition; being aware of terminal condition; isolation; being positively dependent on professional care at home • Other sub themes identified include: dyspnoea; pain; difficulties mobilising; fatigue
Barnes[115] (2006) UK	Community HF patients	Selected population,	44	na	na	na	na	na	na	Explore patient's and professionals attitudes towards communication of	Qualitative interviews and focus group,	• Main issue contributing to poor communication in primary care was diagnostic uncertainty • Terminology avoidance of the word 'failure'

		Subset of population recruited to larger study								diagnosis, prognosis, and symptoms in HF		• Patients had a poor understanding of their condition • Few pts had a discussion regarding prognosis with a healthcare provider
Zapka[172] (2006) USA	Community HF patients	Selected population, expected to be in last year of life	38	na	na	na	na	na	na	Profile communication and recommendations reported by adults with terminal illness	Qualitative interview, cross-sectional	• Pt's with cancer were more likely to receive symptom management at home, be aware of their prognosis, and attend a hospice • Discussions regarding EOL care or ACD was low in both groups of pateints
	Community patients with cancer		52									
Formiga[133] (2007) Spain	CHF inpatients	Selected cohort, case note review of patients who died in hospital	65	81	43	IV (100)	NA	Presence of impaired systolic or diastolic function + NYHA IV	yes	Assess caregiver's opinion of EOL care	Cross-sectional, Qualitative	• 67 % of caregivers satisfied with overall EOL care , remaining thought it could be improved • 45% thought symptoms could be controlled better in last 24 hours of life • 14% thought pain was not controlled • 45% thought dyspnoea was not controlled
	Dementia		37	87	46							
Selman[162] (2007) UK	HF inpatients and outpatients	Selected population, HF-REF, NYHA III/IV	20	69	80	III (80) IV (20)	34	na	no	Generate data on patients' and caregivers' preferences regarding future treatments and EOL care; investigate communication between staff, patients and caregivers regarding EOL	Qualitative interview, cross-sectional	• EOL care preferences varied widely • None of the pts or caregivers had discussed EOL care or ACD with their physician • Patients and caregivers were not aware of different EOL care options such as PC • Pts and caregivers were afraid and anxious regarding the diagnosis of HF, and lacked information regarding the diagnosis • EOL / ACD was rarely raised by staff
Dougherty[127] (2007) USA	HF outpatients contacted via telephone	Selected population, expectancy less than 1 year, AHA stage C/D	24	68	88	na	29	na	na	Describe how patients with advanced HF view and plan for future care including EOL care	Qualitative interview, cross-sectional	• Patients experienced distress from fatigue and reduced functional capacity • Patients did not actively plan for EOL • Patients wanted to discuss EOL care with care providers but initiation of discussions was difficult, leading to frustration • Less than 50% of patients received a life expectancy estimate from healthcare

												providers, although patients did not find estimates of life expectancy helpful • Patients were unaware of ACD including ICD deactivation
Brannstrom[123] (2007) Sweden	Community HF patients Caregivers	Selected population attending PC unit	na 4	na	na	III/IV (100)	na	na	na	Examine the meaning of being a caregiver to someone with severe HF	Qualitative interview, cross-sectional	• Themes identified: caregivers alarmed and aware of the unpredictable nature of HF; caregivers burdened by responsibility; physical burden of caregiving; isolation; struggling to maintain household • Caregivers felt supported by the PC team
Caldwell[125] (2007) Canada	HF outpatients	Selected population attending tertiary care university centre, NYHA III/IV	20	68	70	III (65) IV (35)	28	na	na	Identify preferences of patients with HF regarding communication about EOL and prognosis	Qualitative interview, cross-sectional	Themes identified: • Level of wellness- patients wanted information about prognosis and its implications at a time of good cognitive function • Opportunity to be informed- pts preferred doctors to initiate EOL discussions • Tell the truth- preference from pts for physicians to be honest regarding prognosis, treatments and outcomes • Hope- pts felt a need for truth to be balanced with hope
Cortis[126] (2007) UK	HF outpatients	Selected population attending PC service Age > 80	10	Range 80-90	50	II (20) III (40) IV (40)	na	na	na	Explore experiences of older pts with HF to understand PC and supportive needs	Qualitative interview, cross-sectional	• Common physical symptoms experienced by pts included dyspnoea, falls, anorexia, insomnia, headaches, oedema, palpitations and fatigue • Coping with physical symptoms commonly lead to fear, anxiety and frustration • Pts reported loss of independence • Feelings of low self esteem and low self worth were reported by some pts as well as depression, low mood , and worry • Patients' developed coping mechanisms including stoicism and acceptance • Pts worried about becoming a burden on others, but felt they were getting good standards of care from professionals
Murray[155] (2007) UK	HF outpatients	Selected population, NYHA IV, older	24	77	50	IV (100)	na	na	na	Identify and compare psychological, social, and spiritual needs of people with HF in the last year of	Qualitative interview, Longitudinal every 3 months	• Decline of social, psychological wellbeing tracked decline in physical wellbeing in HF which was characterized by gradual decline punctuated by acute exacerbations with brief recovery

	Lung cancer outpatients			67	58					life and compare to lung cancer		• Spiritual wellbeing fluctuated throughout the last year of patients' lives • Cancer patients had a more gradual and obvious decline in physical wellbeing, tracked by decline in social wellbeing, whereas psychological and spiritual wellbeing fluctuated with diagnosis, discharge after treatment and disease progression
Gott[138] (2008) UK	Community patients with HF	Selected population, sample of larger study with NYHA III/IV	40	77*	52	III/IV (100)	na	na	na	Examine older pts with HF's views on EOL	Qualitative interview, cross-sectional	• Fears about dying included pain and dyspnoea • Many pts did not want open awareness of EOL • Few patients had discussed ACD or prognosis with a physician • Thinking about EOL was anxiety provoking • A sudden death would be preferable for some pts studied • Pts with HF's view of a 'good death' conflicted with conventional views held in PC delivery
Stromberg[166] (2008) Sweden	HF Outpatient	Largely unselected population attending op cardiology clinic following recent HF hospitalization	145	70	70	na	na	ESC 2005 guidelines	na	Explore elderly pts with HF's thoughts regarding EOL in the immediate period following HF hospitalization	Mixed methods: Quantitative QOL: EQ-5D Qualitative interview Cross-sectional	• During acute exacerbations 16% of pts were afraid of dying, and 4% suffered this feeling often • These fears did not change over 6 months following an exacerbation • Fear of death was correlated to higher levels of anxiety and depression, both during deterioration and 6 months later • Common themes regarding EOL were acceptance of death as a relief from suffering, fear of painful death, loss of independence and loss of dignity
Ryan[160] (2009) Ireland	HF outpatients	Selected population attending outpatient clinic NYHA III/IV	9	70	67	III/IV (100)	na	na	na	Describe pts' experiences of living with advanced HF	Qualitative interview, cross-sectional	Themes identified: • Patients lived with fear , particularly of suffering dyspnoea at night or of when the next HF exacerbation would be • Fatigue was a common problem reported • Patients felt hopeless • Frustration at living a restricted life due to HF symptoms • Social isolation commonly reported • Patients expressed frustration at using hospital services multiple times, but also at

												lack of continuity when presenting to secondary care
Thomas[167] (2009) USA	HF inpatients and outpatients	Selected population Age > 60	57	na	70	na	na	na	na	Identify the determinants of doctors' hospice discussions and impact of discussions on hospice referrals	Qualitative interview, cross-sectional	• Common symptoms experienced by pts with HF included pain (29%), decreased activity levels (60%), depression (13%), and dyspnoea (32%). These were similar to levels experienced by cancer and COPD pts, although pts with COPD suffered more dyspnoea • 11% Pts with HF reported QOL as poor – worst ever • 75% pts with HF rate health perception to be fair- poor • 14% of clinicians reported life expectancy to pts with HF • Only 7% of HF pts had a discussion with doctor regarding hospice, common reasons being patient not terminally ill (55%), prognosis too uncertain (34%), or services would not benefit pt (13%)
	Cancer inpatients		79	Na	57							
	COPD inpatients		79	Na	51							
Small[164] (2009) UK	Family members of pts with HF	Selected from larger study	20	Na	Na	Na	Na	Na	Na	Explore carers' views of EOL and bereavement for family members who recently died with HF	Qualitative interview, cross-sectional	• Caregivers found difficulty discussing wishes of relatives for EOL care prior to death, making ACD difficult • Caregivers were generally against futile therapies, with an emphasis on QOL over length of life • Most would opt for a death at home, although not all would have preferred this • The sense that a relative had a 'good death' helped with bereavement, although caregivers were felt to have continuing needs • Deaths at home were considered to be 'good' deaths • Only a small proportion of caregivers took up bereavement counselling
Waterworth[170] (2010) New Zealand	Community patients with HF	Recruited from primary care, or recently discharged from secondary care	25	81	60	II (40) III (44) IV (16)	Na	Na	Na	Explore the experiences of older people with HF and transitions to dependence and EOL	Qualitative interview, Longitudinal every 3-4 months	• Pts expressed fears of becoming a burden as they got older and progressed from independence to dependence to EOL • Pts believed they would receive good care at EOL from healthcare professionals • Pts with HF did not transition from independence – dependence- EOL in a linear fashion

Hupcey[144] (2011) USA	Caregivers of pts with HF	Spouses of pts admitted to hospital with decompensated HF	45	Na	Na	Na	Na	Na	Na	Describe the experiences of spousal caregivers in caring for someone with HF to identify potential PC needs	Qualitative interview, Longitudinal every month for 12-18 months	• Caregivers felt exhausted and stressed and experienced difficulties associated with not having their own health issues addressed • Caregivers often ignored their own health issues during times of exacerbation of their spouse's HF • Psychosocial issues wre present for all spousal caregivers, both during HF exacerbations and at times of stability • Some caregivers experienced financial difficulties, and when present were persistent • All of the spousal caregivers had information needs, from acute treatments to ACD
Bekelman[119] (2011) USA	HF outpatients	Selected population identified from University Hospital outpatient department	33	64	70	II (33) III (39) IV (12)	31	Na	na	Detail pts with HF and their caregivers' needs and explore how PC may be useful to these pts	Qualitative interview Cross-sectional	• Pts and caregivers reported a need to be able to adjust to limitations imposed on them by HF • Pts and caregivers frequently reported physical limitations as a common issue • Caregivers sought information regarding future course of the HF illness • Some pts expressed wishes to know more about prognosis • Pts suffered a number of diverse symptoms , particularly fatigue and dyspnoea. Many pts were pessimistic regarding potential therapies for these symptoms. Other symptoms included pain, dry mouth, and constipation
	caregivers		19	59	5							
Gysels[139] (2011) UK	HF outpatients	Selected population, recruited from clinics NYHA III/IV	10	69*	70	III/IV (100)	Na	Na	Na	Explore and compare patients' experiences of dyspnoea between four conditions	Qualitative interview Cross-sectional	• HF pts described dyspnoea in terms of the physical limitations it placed on their lives • Other common symptoms included oedema , pain, and fatigue • Disability was a common theme identified as a result of dyspnoea • Pts often thought about death
	COPD outpatients		18	69*	30							
	Cancer outpatients		10	69*	50							

	MND outpatients		10	42*	90							
Imes[145] (2011) USA	HF outpatients	Selected population, recruited from outpatient clinic NYHA III/IV Life expectancy < 1 year	14	68	88	III (96) IV (4)	29	Na	na	Describe the experiences of pts living with severe HF as experienced by their partner	Qualitative interview Cross-sectional	• Partners of pts with HF felt the pts' disease affected their lifestyle by causing social isolation • Difficulties were experienced in planning for the future for both pt and caregiver • Caregivers felt under-prepared to manage the disease burden at home • EOL care and ACD was not actively discussed by healthcare providers • Despite having discussion with pts regarding EOL plans, there were frequently no ACD in place
	Partners/ caregiver		14	65	79							
Gerlich[135] (2012) Germany	HF outpatients	Selected population, recruited from two hospitals outpatient department age > 70, patients with reduced life expectancy	12	85	50	Na	Na	Na	na	Explore the needs of older patients with HF	Qualitative interview Cross-sectional	• Pts wanted more information regarding their diagnosis and better communication regarding prognosis • Pts did not recognize HF as a life-limiting condition • Pts had no experience of PC services
Kitko[150] (2013) USA	Caregivers	Selected population, end-stage HF with LVAD	10	62	20				na	Describe the experiences of caregivers of pts with end-stage HF with LVAD	Qualitative interview Cross-sectional	Themes identified: • Adaptation to caregiver role • Caring for a spouse with HF •

Appendix 2- Patient information sheets and consent forms

BHF Glasgow Cardiovascular Research Centre
126 University Place
University of Glasgow
Glasgow
G12 8TA

Enquiries to Dr Ross Campbell
Tel: 0141 330 2237
Fax: 0141 330 6955

STUDY TITLE: Care needs in patients with Heart Failure

PATIENT INFORMATION SHEET- STAGE 1

You are being invited to take part in a research study involving filling in questionnaires about your general health and wellbeing. We would also like to ask your main carer (if applicable) to complete a questionnaire also. Before you decide whether or not to take part it is important you understand why the research is being done and what it involves. Thank you for reading this.

The first part of this study involves having a blood test done and agreeing to the doctors and nurses involved in the study looking at your medical notes and obtaining information about your future progress. This form explains why we want to do this and how it happens.

When you read this you will be in hospital and may have been admitted with shortness of breath or swollen legs. These are symptoms which sometimes indicate a condition called heart failure. Heart failure is a condition where the heart is not pumping blood around the body as well as it should be. As a result, fluid often accumulates in the lungs or the legs. Possible causes include previous heart attacks, high blood pressure or damage to the heart valves.

Some patients with heart failure can experience worsening symptoms, poor quality of life and low mood. Heart failure can also have an effect on carers of some patients with heart failure. Our study aims to provide more information about which patients develop these problems by studying a large group of patients and monitoring their condition over the following years. We also aim to understand patient perspectives on how and where they would like to be treated for heart failure. We will be able to do this by asking a large group of patients with heart failure a series a questionnaires.

The way that we follow a patient's progress in a study like this is by entering their details into a national database, which uses hospital notes to record when you come into hospital. This database is run by the Scottish Health Service and is confidential. Any information gathered is only available to the doctors running this study. It does not require any participation from

you, and no one will contact you or your family as part of this process. If you agree to take part in the study at this stage, we will enter you details into this database.

If you agree to take part, a finger-prick sample of blood will be taken and a blood test for B-type natriuretic peptide (BNP) will be performed. This tests how well the heart is pumping. Having blood taken can be uncomfortable and some people feel faint. If the blood test is positive then either a doctor nurse that is involved in the study will visit you before you are discharged from hospital to discuss whether or not you would like to take part in stage 2 of the research study.

Thank you for taking the time to read this information leaflet. If you have any questions regarding the study please contact the research team on the above number.

Dr Ross Campbell
Clinical Research Fellow
University of Glasgow

Department of Cardiology
Western Infirmary Glasgow, Level 4

Subject number:

NHS Greater Glasgow and Clyde

Care needs of Patients with Heart Failure

Consent Form- Stage 1

Please initial the BOX

I confirm that I have read and understand the information sheet dated 24/09/2012 (version 1.2) for the above study and have had the opportunity to ask questions.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I agree to a finger-prick sample of blood being taken for analysis of B-type Natriuretic Peptide (BNP).	☐
I agree to my details being entered into the database at Information Services Division of NHS Scotland for use during this study and future ethically approved research.	☐
I understand that sections of my medical notes may be looked at by the research team where it is relevant to my taking part in the research. I give my permission for the research team to have access to my records.	☐
I agree to take part in the above study	☐

----------	----------	----------
Name of Participant	Date	Signature
----------	----------	----------
Name of Investigator	Date	Signature

1 copy to the patient, 1 copy to the researcher, 1 Original for the patients' notes

Version 1.3 23/01/2013

BHF Glasgow Cardiovascular Research Centre
126 University Place
University of Glasgow
Glasgow
G12 8TA

Enquiries to Dr Ross Campbell
Tel: 0141 330 2237
Fax: 0141 330 6955

STUDY TITLE: Care Needs in Patients with Heart Failure

PATIENT INFORMATION SHEET- STAGE 2

1. Invitation to take part

You are being invited to take part in a research study involving filling in questionnaires about your general health and wellbeing. We would also like to ask your main carer (if applicable) to complete a questionnaire also. Before you decide whether or not to take part it is important you understand why the research is being done and what it involves. Please read the following information carefully and discuss it with others if you wish. Please ask us if anything is not clear or you would like more information. Take time to decide whether or not you wish to take part. You are not obligated to take part. If you decide to participate in the study you will be given a copy of this information sheet and a signed consent form to keep. Thank you for reading this.

2. What is the purpose of the study?

Heart failure is a condition where the heart is not pumping blood around the body as well as it should be. As a result, fluid often accumulates in the lungs or the legs. Possible causes include previous heart attacks, high blood pressure or damage to the heart valves.

Some patients with heart failure can experience worsening symptoms, poor quality of life and low mood. Heart failure can also have an effect on carers of some patients with heart failure. Our study aims to provide more information about which patients develop these problems by studying a large group of patients and monitoring their condition over the following years. We also aim to understand patient perspectives on how and where they would like to be treated for heart failure. We will be able to do this by asking a large group of patients with heart failure a series a questionnaires.

This study will involve a total of around 500 patients and is expected to last 3 years.

3. Why have I been chosen?

You are being invited to consider taking part in this study as you have been admitted to hospital with heart failure.

4. Do I have to take part?

Taking part in this study is entirely voluntary and your decision. If you take part you will receive this information sheet to keep and be asked to sign a consent form. If you take part you are free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

5. What will happen to me if I take part?

When you read this you will be in hospital and may have been admitted with shortness of breath or swollen legs. You will have been asked in stage 1 of the study whether or not you would be willing to have a special blood test. If this blood test shows your heart is not pumping as well as it should be then you will be asked to complete a series of questionnaires which will ask about your quality of life, symptoms, and mood. These questionnaires will be completed by yourself and will take approximately 20-30 minutes to complete. You will also be asked if you would be willing to talk about any thoughts you have about where you might like to be cared for in the future, both, if you felt reasonably well and in the event of you becoming less well. We are interested in your views – we are not asking for any binding decision and the discussion will not influence your care in the future. We would also like to ask your main carer (if applicable) a questionnaire designed to assess the impact of illness on carers.

In addition to questionnaires, we would like to gather other information which may be useful in helping us understand the needs of patients with heart failure. During your inpatient stay we would like to carry out the following:

- **Medical history**- speaking to a doctor about your symptoms and previous illnesses.
- **Physical examination**- you will be examined and your height and weight will be measured.
- **Echocardiogram**- this is an ultrasound scan of the heart, it is sometimes just called an 'echo'. For this test you will be asked to lie on a bed and a probe will be placed gently on to your chest to allow pictures of the heart to be taken.
- **Blood test**- a blood sample will be taken from a vein in your arm. This blood test is exactly the same as other blood tests that you will have had taken before. Approximately 30 mls (6 teaspoons) of blood will be taken. We are checking the blood for a substance called B-type natriuretic peptide (BNP), which tells us how well the heart is pumping. We will also use this blood sample to check plasma hormones

and proteins, your kidneys and liver and your blood cell counts. A sample of blood will be stored during the course of this study at a secure facility in the British Heart Foundation Glasgow Cardiovascular Research Centre, for future analysis as part of this study but also for future ethically approved research.

- **Electrocardiogram (ECG)**-this is a recording of the electrical activity of the heart. You will probably have had this test before. To take the recording, you will be asked to lie on a bed while stickers are placed on to your chest wall. This test does not involve discomfort.
- **Urine sample**- a sample of urine will be collected and stored for future analysis for proteins that may be raised in patients with heart failure as part of this study, but also for future ethically approved research.
- **Lung ultrasound**- this is an ultrasound of your lungs to ensure that any fluid surrounding your lungs has gone away. This will be done before you go home from hospital, at the bedside, and should take no longer than 5 minutes. This test does not involve any discomfort.

6. **What do I have to do?**

Following discharge from hospital, you will be invited to attend clinic appointments at approximately 4 monthly intervals to see one of the doctors involved in the study. We will try and co-ordinate these appointments with other clinic appointments you may have, and where this is not possible alternative arrangements will be made. You will be asked to attend the British Heart Foundation Glasgow Cardiovascular Research Centre, in the University of Glasgow. If you are unable to attend the hospital it may be possible for a member of the study team to visit your residence. At these clinic visits you will be reviewed by one of the doctors and nurses involved in the study. This will allow us to chart any changes over time in how your condition is affecting your life. At these clinic appointments we will repeat the blood and urine samples, medical history and examination, and repeat questionnaires. Again the questionnaires will ask about your quality of life, symptoms, mood, and you will be asked to consider your preference for where you would like to be cared for in the future. These questionnaires will be completed by yourself and will take 20-30 minutes to complete. We would also like to ask your main carer (if applicable) a questionnaire designed to assess the impact of illness on carers.

7. **What are the possible disadvantages and risk of taking part?**

Having your blood taken is occasionally uncomfortable and some people may feel faint. There is a small risk of bleeding, bruising or infection at the puncture site following the blood test.

8. **What are the possible benefits of taking part?**

You may not benefit directly from taking part in the study, however, the information we get from this study may help us to give better treatment to patients with heart failure in the future.

If the research doctor discovers during the study that you have another medical condition of which you were previously unaware you will be referred to the appropriate doctor for treatment of this condition.

9. **What if new information becomes available?**

If any new information becomes available that is relevant to your care we will inform you.

10. **What if something goes wrong?**

There are no special compensation arrangements if taking part in this research project harms you. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. The normal National Health Service complaints mechanisms are available if you wish to complain or have any concerns.

11. **Will my taking part in this study be kept confidential?**

If you consent to take part in the study, the research doctor may inspect your medical records for purposes of analysing the results. Only government regulatory authorities and the research doctor will have access to your medical notes.

All information collected about you during the course of the research will be kept strictly confidential. Any information about you, which leaves the hospital, will have your name and address removed so that you cannot be recognised from it. Reports or publication resulting from the study will not contain any personal details.

12. **Will my GP be informed that I am taking part?**

Yes, your General Practitioner will be informed that you are participating in this study. We would like to contact your General Practitioner (GP) and ask permission to access your GP's medical records. This would be done at the end of the study and will provide us with valuable information regarding how often patients with Heart Failure are seen by their GP.

13. **What will happen to the results of the research study?**

The results of the research study will be stored on a computer database and are likely to be published in cardiology journals. Reports or publications resulting from the study will not contain any personal details. The research doctor will provide a copy of the results on request.

14. Who is organising and funding the research?

The University of Glasgow is performing the study and the British Heart Foundation is funding the research.

15. Who has reviewed the study?

This study has been reviewed and approved by one of the West of Scotland Research Ethics Service (WoSRES) Committees, which is an independent panel.

16. Contact for further information

You are encouraged to ask questions at any time during the study.

Please contact:-

Study Doctor:	Dr Ross T Campbell	0141 330 2237
Supervisor:	Professor John J McMurray	0141 330 2000
Independent Doctor:	Dr Niko Tzemos	0141 330 2000

Thank you for taking the time to read this patient information leaflet.

Department of Cardiology
Western Infirmary Glasgow, Level 4

Subject number:

Care needs of Patients with Heart Failure

Consent Form- Stage 2

Please initial the BOX

I confirm that I have read and understand the information sheet dated 30/01/2013 (version 1.4) for the above study and have had the opportunity to ask questions.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I agree to give permission to store samples of my blood and urine for a period of 10 years so that any new tests, relating to chronic heart failure, can be evaluated as part of this study and future ethically approved studies.	☐
I agree to my next of kin/ carer being contacted by the study team and invited to participate in the study.	☐
I understand that sections of my general practitioner medical notes may be looked at by the research team where it is relevant to my taking part in the research. I give my permission for the research team to contact my general practitioner and to have access to my records.	☐
I agree to take part in the above study.	☐

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Name of Participant	Date	Signature
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Name of Investigator	Date	Signature

1 copy to the patient, 1 copy to the researcher, 1 Original for the patients' notes

Version 1.4 30/01/2013

BHF Glasgow Cardiovascular Research Centre
126 University Place
University of Glasgow
Glasgow
G12 8TA

Enquiries to Dr Ross Campbell
Tel: 0141 330 2237
Fax: 0141 330 6955

STUDY TITLE: Care needs in patients with Heart Failure

CARER INFORMATION SHEET

1. Introduction

You are being invited to take part in a research study involving filling in questionnaires about your general health and wellbeing. You have been identified as the main caregiver for your relative/ friend who has been admitted to hospital with a condition called heart failure. They have given us permission to ask you if you would like to participate in this study. Before you decide whether or not to take part it is important you understand why the research is being done and what it involves. Thank you for reading this.

2. What is the purpose of the research?

When you read this your relative or friend will be in hospital and may have been admitted with shortness of breath or swollen legs. These are symptoms which sometimes indicate a condition called heart failure. Heart failure is a condition where the heart is not pumping blood around the body as well as it should be. As a result, fluid often accumulates in the lungs or the legs. Possible causes include previous heart attacks, high blood pressure or damage to the heart valves.

Some patients with heart failure can experience worsening symptoms, poor quality of life and low mood. Heart failure can also have an effect on carers of some patients with heart failure. Our study aims to provide more information about which patients develop these problems by studying a large group of patients and monitoring their condition over the following years. We also aim to understand patient perspectives on how and where they would like to be treated for heart failure. We will be able to do this by asking a large group of patients with heart failure a series a questionnaires. We also aim to understand how heart failure affects the lives of carers of patients with heart failure.

3. What will happen if I agree to take part?

If you agree to take part we will ask you to complete a questionnaire which will assess caregiver strain. This will take approximately 10-15 minutes to complete. We would also like to invite you to complete the same questionnaire following your relative/ friend's discharge from hospital. This will help us to understand how heart failure affects the lives of

carers over time. Specifically, we would like to post a questionnaire to you, or ask you to attend a clinic appoint with your relative/carer, at approximately 4 monthly intervals until the completion of the study. We anticipate completion of the study in March 2015.

4. Will the care of my friend/ relative be affected?

The care of your friend/relative will not be affected by you participating in this study. All information will be kept confidential.

5. Do I have to take part?

Taking part in this study is entirely voluntary and your decision. If you take part you will receive this information sheet to keep and be asked to sign a consent form. If you take part you are free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care your relative or friend will receive.

6. Will my taking part in the study be kept private?

All information collected about you during the course of the research will be kept strictly confidential. Any information about you, which leaves the hospital, will have your name and address removed so that you cannot be recognised from it. Reports or publication resulting from the study will not contain any personal details.

7. Who is funding the Research?

We have applied to the British Heart Foundation for funding.

8. **Who has reviewed the study**

This study has been reviewed and approved by one of the West of Scotland Research Ethics Service (WoSRES) Committees, which is an independent panel.

9. **What if I want to make a complaint?**

If you have any questions or comments regarding the study, please contact a member of the study team on the above telephone number. If you will to make a complaint regarding this study then please utilise the normal National Health Service complaints mechanisms, which are available.

10. **What do I do now?**

If you are happy to participate in the study please sign the consent form attached and complete the questionnaire entitled Zarit Burden Interview. This can then be returned to a member of the study team.

11. What will happen to the results of the study?

The results of the research study will be stored on a computer database and are likely to be published in cardiology journals. Reports or publications resulting from the study will not

contain any personal details. The research doctor will provide a copy of the results on request.

12. Can I find out more?

If you have any questions regarding this study please feel free to contact the study team on 0141 330 2237.

Thank you for taking the time to read this information leaflet.

Dr Ross Campbell
Clinical Research Fellow
University of Glasgow

Department of Cardiology
Western Infirmary Glasgow, Level 4

Subject number:

Care Needs of Patients with Heart Failure

Consent Form- Carer

Please initial the BOX

I confirm that I have read and understand the information sheet dated 24/09/2012 (version 1.3) for the above study and have had the opportunity to ask questions. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care or legal rights of my relative/ friend being affected. ☐

I agree to take part in the above study ☐

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Name of Participant	Date	Signature
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Name of Investigator	Date	Signature

1 copy to the patient, 1 copy to the researcher, 1 Original for the patients' notes

Version 1.3 23/01/2013

Appendix 3- Case Report form

PCHF Study

Patient Identification and Contact Information

Version 2.1 (27 Aug 2013)

Patient ID. ___ - ___ 01 | Initials ___ 02 | Date of Completion D D M M Y Y Y Y 03

*** *PLEASE FILE - do NOT send to Data Centre* ***

1. Hospital GRI ☐ 1 WIG ☐ 2 04
2. Gender Male ☐ 1 Female ☐ 2 05
3. Date of Recruitment D D M M Y Y Y Y 06
4. Surname ___ 07
5. Forename(s) ___ 08
6. Hospital Number ___ 09
7. CHI Number ___ 10
8. Date of Birth D D M M Y Y Y Y 11
9. Address ___ 12
   Postcode ___ 13
10. Home phone Number ___ 14
11. Mobile phone Number ___ 15
12. Work phone Number ___ 16
13. Holiday home phone No. ___ 17
14. Next of kin (or friend /carer) ___ 18
15. Relationship ___ 19
16. Next of kin phone number ___ 20
17. Next of kin address ___ 21
    Postcode ___ 22

18. GP Name ___ 23
19. GP Address ___ 24
    Postcode ___ 25
20. GP phone number ___ 26

Checklist

- Old casenotes reviewed ☐
- Letter to GP sent ☐
- Date of Study Visit issued to patient ☐
- Next of Kin/Carer Contacted ☐
- Consent Yes ☐ No ☐
- ZARIT Yes ☐ No ☐

If Yes,

- Prefer Postal Yes ☐ No ☐

Other useful info

Produced by Robertson Centre for Biostatistics, University of Glasgow

Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊____⌋ 02 Date of Completion ⌊D D M M Y Y Y Y⌋ 03

A. CONSENT

	Yes	No
1. Has the patient provided written, informed consent for participation in the Study? 04	☐1	☐2

If Yes, date consent was given ⌊D D M M Y Y Y Y⌋ 05

If No, the patient is not eligible to continue in the study

B. INCLUSION CRITERIA

	Yes	No
1. Age 18 or over 06	☐1	☐2
2. Admitted to hospital with suspected heart failure (according to ESC guidelines) 07	☐1	☐2
3. BNP ≥ 100 pg/ml 08	☐1	☐2

PATIENTS MUST FULFIL ALL CRITERIA TO CONTINUE

C. EXCLUSION CRITERIA

	Yes	No
1. Cognitive Impairment 09	☐1	☐2
2. Unable to participate for geographical or social reasons 10	☐1	☐2
3. BNP < 100 pg/ml 11	☐1	☐2
4. Acute coronary syndrome with pulmonary oedema 12	☐1	☐2
5. Patient already in this study 13	☐1	☐2

PATIENTS MUST ANSWER NO TO ALL EXCLUSION CRITERIA ABOVE TO CONTINUE

Version 2.1 (27 Aug 2013)

Patient ID. ___-___ (01) Initials ___ (02) Date of Completion D D M M Y Y Y Y (03)

A. DEMOGRAPHICS

1. Date of Birth D D M M Y Y Y Y (04)

2. Gender Male ☐1 Female ☐2 (05)

3. Race

- White ☐1
- Black ☐2 (Caribean / African)
- South Asian ☐3 (India, Pakistan, Sri Lanka, Nepal, Bangladesh, Maldives)
- Arab/Middle East ☐4 (Bahrain, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Palestinian territories, Oman, Qatar, Saudi Arabia, Sudan, Syrian Arab Republic, United Arab Emirates and Yemen)
- Oriental ☐5 (Japanese, Chinese)
- Malay ☐6 (Malaysia, Philippines, Indonesia)
- Other ☐7 (06)

If Other, specify _____ (07)

4. Date of Admission D D M M Y Y Y Y (08)

5. Date of Recruitment D D M M Y Y Y Y (09)

6. Date of Discharge D D M M Y Y Y Y (10)

OR

7. Date of Death D D M M Y Y Y Y (11)

B. SCREENING CHECK

	Yes	No	
1. Has screening sheet been completed?	☐1	☐2	(12)
2. Has patient fulfilled all inclusion/exclusion criteria and is eligible to take part in the study?	☐1	☐2	(13)
3. Has patient signed informed consent?	☐1	☐2	(14)

Answers must all be YES for inclusion in study.

C. HEART FAILURE SYMPTOM STATUS PRIOR TO ADMISSION

1. NYHA I ☐1 II ☐2 III ☐3 IV ☐4 (15)

I = No limitation of daily activities
II = mild limitation of activity
III = marked limitation of activity
IV = symptoms at rest

2. Orthopnea	Yes ☐1	No ☐2 (16)
3. Paroxysmal Nocturnal Dyspnoea	Yes ☐1	No ☐2 (17)
4. Ankle swelling	Yes ☐1	No ☐2 (18)
5. Wheeze	Yes ☐1	No ☐2 (19)
6. Palpitations	Yes ☐1	No ☐2 (20)

D. CHF

1. Diagnosed Chronic Heart Failure before this admission — Yes ☐1 No ☐ (21)

If Yes,

a) Diagnosis over 2 years ago — Yes ☐1 No ☐2 (22)

b) Which healthcare professionals are involved:

	Yes	No	
i. GP only	☐1	☐2	(23)
ii. General physician	☐1	☐2	(24)
iii. Cardiologist	☐1	☐2	(25)
iv. HF specialist	☐1	☐2	(26)
v. HF liaison nurse	☐1	☐2	(27)

c) Previous admission with decompensated heart failure — Yes ☐1 No ☐2 (28)

2. Previous admission in past 6 months with a diagnosis of HF? — Yes ☐1 No ☐2 (29)

If Yes, Number of admissions ___ (30)

Produced by Robertson Centre for Biostatistics, University of Glasgow

Version 2.1 (27 Aug 2013)

Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊___⌋ 02 Date of Completion ⌊D D M M Y Y Y Y⌋ 03

A. MEDICAL HISTORY

	Yes	No
1. Myocardial Infarction	1	2 (04)
2. History of Angina	1	2 (05)
If Yes, current	Yes 1	No 2 (06)
If Current, stable	Yes 1	No 2 (07)
3. Coronary Angiography	1	2 (08)

If Yes,

Year of procedure ⌊Y Y Y Y⌋ 09

Result

- Normal 1
- Plaque only 2
- Significant CHD (>50% Stenosis in > 1 vessel) 3 → No. of vessels involved ⌊__⌋ 11
- Unknown 4 (10)

	Yes	No
4. Percutaneous Coronary Intervention (PCI)	1	2 (12)
5. Coronary Artery Bypass Graft (CABG)	1	2 (13)
6. Treated Hypertension	1	2 (14)
7. Hypercholesterolaemia	1	2 (15)
8. Cerebrovascular disease (CVA/TIA)	1	2 (16)
9. Atrial Fibrillation/Flutter	1	2 (17)

If Yes,

- a. past 1
- b. paroxysmal 2
- c. persistent (potential restoration SR) 3
- d. permanent 4 (18)

	Yes	No
10. Valvular Heart Disease	1	2 (19)

If Yes,

	Yes	No
a. AS	1	2 (20)
b. AR	1	2 (21)
c. MS	1	2 (22)
d. MR	1	2 (23)
e. TR	1	2 (24)

	Yes	No
11. Rheumatic Valvular Heart Disease	1	2 (25)
12. Rheumatic Fever	1	2 (26)
13 Valve replacement	1	2 (27)
14. Pacemaker	1	2 (28)

If Yes,

	Yes	No
a. Conventional	1	2 (29)
b. CRT-P	1	2 (30)
c. CRT-D	1	2 (31)

	Yes	No
15. Primary Prevention ICD	1	2 (32)
16. Syncope (brief loss of consciousness)	1	2 (33)
17. Prior arrythmia	1	2 (34)

If Yes,

	Yes	No
a. SVT	1	2 (35)
b. Ventricular tachycardia	1	2 (36)

- 1. Sustained 1
- 2. Nonsustained 2 (37)

	Yes	No
c. SSS	1	2 (38)
d. AV block	1	2 (39)

- 1. 1st degree 1
- 2. 2nd degree 2
- 3. 3rd degree 3 (40)

Produced by Robertson Centre for Biostatistics, University of Glasgow

Version 2.1 (27 Aug 2013)

Patient ID. ___-___ (01) Initials ___ (02) Date of Completion D D M M Y Y Y Y (03)

18. Diabetes Mellitus — Yes 1 No 2 (04)
- **If Yes,**
  - a. Diet Controlled — Yes 1 No 2 (05)
  - b. Oral Hypoglycaemic — Yes 1 No 2 (06)
  - c. Insulin — Yes 1 No 2 (07)

19. Involuntary weight loss (>5% in 6 months) — Yes 1 No 2 (08)

20. Depression — Yes 1 No 2 (09)
- **If Yes,** Current — Yes 1 No 2 (10)

21. Cancer — Yes 1 No 2 (11)
- **If Yes, specify**

	Metastatic Yes	Metastatic No	Current Yes	Current No
a. _____ (12)	1 (13)	2 (13)	1 (14)	2 (14)
b. _____ (15)	1 (16)	2 (16)	1 (17)	2 (17)
c. _____ (18)	1 (19)	2 (19)	1 (20)	2 (20)
d. _____ (21)	1 (22)	2 (22)	1 (23)	2 (23)
e. _____ (24)	1 (25)	2 (25)	1 (26)	2 (26)

22. COPD — Yes 1 No 2 (27)

23. Peripheral Vascular Disease — Yes 1 No 2 (28)

24. Asthma — Yes 1 No 2 (29)

25. Neuropathy — Yes 1 No 2 (30)

26. Hypothyroidism — Yes 1 No 2 (31)

27. Hyperthyroidism — Yes 1 No 2 (32)

28. Rheumatoid Arthritis — Yes 1 No 2 (33)

29. Connective tissue disease — Yes 1 No 2 (34)

30. Osteoarthritis — Yes 1 No 2 (35)

31. Anaemia — Yes 1 No 2 (36)

32. Urinary incontinence — Yes 1 No 2 (37)

33. Smoker — Yes 1 No 2 (38)
- **If Yes,**
  - a. Current — Yes 1 No 2 (39)
  - b. Ex (<12 months) — Yes 1 No 2 (40)
  - c. Ex (≥12 months) — Yes 1 No 2 (41)

34. Alcohol — Yes 1 No 2 (42)
- **If Yes,**
  (Excess: Male > 21units Female > 14 units)
  - a. Excess — Yes 1 No 2 (43)
  - b. Previous Excess — Yes 1 No 2 (44)
  - c. Within recommended limits — Yes 1 No 2 (45)

35. Family history heart disease — Yes 1 No 2 (46)
- **If Yes,**
  - a. Coronary heart disease — Yes 1 No 2 (47)
  - b. Cardiomyopathy — Yes 1 No 2 (48)
  - c. Unknown — Yes 1 No 2 (49)
  - d. Other — Yes 1 No 2 (50)

  (specify) _____ (51)

36. Any other significant medical history — Yes 1 No 2 (52)
- **If Yes, specify**

1. _____ (53)
2. _____ (54)
3. _____ (55)
4. _____ (56)
5. _____ (57)
6. _____ (58)
7. _____ (59)
8. _____ (60)
9. _____ (61)
10. _____ (62)

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Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊____⌋ 02 Date of Completion ⌊D D M M Y Y Y Y⌋ 03

A. CARDIOVASCULAR MEDICATION

1. ACE-Inhibitor Yes ☐1 No ☐2 04

(i) **If Yes**, specify type and dose

	Yes	No		
a. Captopril	☐1 05	☐2	06	mg
b. Enalapril	☐1 07	☐2	08	mg
c. Fosinopril	☐1 09	☐2	10	mg
d. Lisinopril	☐1 11	☐2	12	mg
e. Perindopril	☐1 13	☐2	14	mg
f. Quinapril	☐1 15	☐2	16	mg
g. Ramipril	☐1 17	☐2	18	mg
h. Trandolapril	☐1 19	☐2	20	mg
i. Other	☐1 21	☐2		
Specify 22			23	mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 24
(iii) Intolerant of higher dose than current	☐1	☐2 25
(iv) Patient on optimal dose	☐1	☐2 26
(v) If No, Patient on optimal tolerated dose	☐1	☐2 27

2. Hydralazine Yes ☐1 No ☐2 28

If Yes, specify dose ____ 29 mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 30
(iii) Intolerant of higher dose than current	☐1	☐2 31
(iv) Patient on optimal dose	☐1	☐2 32
(v) If No, Patient on optimal tolerated dose	☐1	☐2 33

3. Beta-blocker Yes ☐1 No ☐2 34

(i) **If Yes**, specify type and dose

	Yes	No		
a. Atenolol	☐1 35	☐2	36	mg
b. Bisoprolol	☐1 37	☐2	38	mg
c. Carvedilol	☐1 39	☐2	40	mg
d. Metoprolol	☐1 41	☐2	42	mg
e. Nebivolol	☐1 43	☐2	44	mg
f. Propanolol	☐1 45	☐2	46	mg
g. Other	☐1 47	☐2		
Specify 48			49	mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 50
(iii) Intolerant of higher dose than current	☐1	☐2 51
(iv) Patient on optimal dose	☐1	☐2 52
(v) If No, Patient on optimal tolerated dose	☐1	☐2 53

4. Aldosterone Blocker Yes ☐1 No ☐2 54

(i) **If Yes**, specify type and dose

	Yes	No		
a. Spironolactone	☐1 55	☐2	56	mg
b. Eplerenone	☐1 57	☐2	58	mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 59
(iii) Intolerant of higher dose than current	☐1	☐2 60
(iv) Patient on optimal dose	☐1	☐2 61
(v) If No, Patient on optimal tolerated dose	☐1	☐2 62

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5. ARB — Yes ☐1 No ☐2 (04)

(i) **If Yes**, specify type and dose

	Yes	No		
a. Candesartan	☐1	☐2 (05)	____ (06)	mg
b. Irbesartan	☐1	☐2 (07)	____ (08)	mg
c. Losartan	☐1	☐2 (09)	____ (10)	mg
d. Olmesartan	☐1	☐2 (11)	____ (12)	mg
e. Telmisartan	☐1	☐2 (13)	____ (14)	mg
f. Valsartan	☐1	☐2 (15)	____ (16)	mg
g. Other	☐1	☐2 (17)		
Specify ____ (18)			____ (19)	mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 (20)
(iii) Intolerant of higher dose than current	☐1	☐2 (21)
(iv) Patient on optimal dose	☐1	☐2 (22)
(v) If No, Patient on optimal tolerated dose	☐1	☐2 (23)

6. Ivabradine — Yes ☐1 No ☐2 (24)

If Yes, specify dose ____ (25) mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 (26)
(iii) Intolerant of higher dose than current	☐1	☐2 (27)
(iv) Patient on optimal dose	☐1	☐2 (28)
(v) If No, Patient on optimal tolerated dose	☐1	☐2 (29)

7. Anti-arrhythmic — Yes ☐1 No ☐2 (30)

If Yes, specify type

	Yes	No
a. Amiodarone	☐1	☐2 (31)
b. Other	☐1	☐2 (32)

Specify ____ (33)

8. Calcium channel-blocker — Yes ☐1 No ☐2 (34)

If Yes, specify type

	Yes	No
a. Amlodipine	☐1	☐2 (35)
b. Diltiazem	☐1	☐2 (36)
c. Felodipine	☐1	☐2 (37)
d. Nifedipine	☐1	☐2 (38)
e. Verapamil	☐1	☐2 (39)
f. Other	☐1	☐2 (40)

Specify ____ (41)

9. Long-acting nitrates (not s/c or short acting GTN) — Yes ☐1 No ☐2 (42)

If Yes, specify type

	Yes	No
a. ISDN	☐1	☐2 (43)
b. ISMN	☐1	☐2 (44)
c. GTN patch	☐1	☐2 (45)
d. Other	☐1	☐2 (46)

Specify ____ (47)

10. Statin — Yes ☐1 No ☐2 (48)

If Yes, specify type

	Yes	No
a. Atorvastatin	☐1	☐2 (49)
b. Pravastatin	☐1	☐2 (50)
c. Rosuvastatin	☐1	☐2 (51)
d. Simvastatin	☐1	☐2 (52)
e. Other	☐1	☐2 (53)

Specify ____ (54)

11. Other lipid-lowering drug — Yes ☐1 No ☐2 (55)

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12. Diabetic Meds — Yes ☐1 No ☐2 04

If Yes, specify type

	Yes	No
a. Insulin	☐1	☐2 05
b. Sulphonylurea (eg gliclazide)	☐1	☐2 06
c. Biguanide (eg metformin)	☐1	☐2 07
d. Glitazone	☐1	☐2 08
e. Other	☐1	☐2 09

Specify _____ 10

13. Diuretics — Yes ☐1 No ☐2 11

If Yes, specify type and dose where relevant

	Yes	No		
a. Furosemide	☐1	☐2 12	_____ 13	mg
b. Other loop	☐1	☐2 14		
c. Spironolactone	☐1	☐2 15		
d. Other K+ sparing	☐1	☐2 16		
e. Thiazide	☐1	☐2 17		
f. Bumetanide	☐1	☐ 18	_____ 19	mg
g. Other	☐1	☐2 20		

Specify _____ 21

	Yes	No
14. Digoxin	☐1	☐2 22
15. Aspirin	☐1	☐2 23
16. Clopidogrel	☐1	☐2 24
17. Warfarin	☐1	☐2 25
18. Nicorandil	☐1	☐2 26

19. List Other Cardiovascular medications in addition to above prior to admission (state indication)

a. Name _____ 27
Indication _____ 28

b. Name _____ 29
Indication _____ 30

c. Name _____ 31
Indication _____ 32

d. Name _____ 33
Indication _____ 34

e. Name _____ 35
Indication _____ 36

f. Name _____ 37
Indication _____ 38

B. ASSESSMENT OF THERAPY

1.	Optimally tolerated HF therapy	☐1 ☐2 39
2.	Optimal HF therapy	☐1 ☐2 40

Patient ID. ___-___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

C. NON-CARDIOVASCULAR MEDICATION

	Yes	No	
1. Bronchodilator	1	2	04
If Yes, specify type			
a. Beta-agonist tablets	1	2	05
b. Steroid tablets	1	2	06
c. Beta-agonist inhalers	1	2	07
d. Anti-cholinergic inhalers	1	2	08
e. Steroid inhalers	1	2	09
2. Antidepressants	1	2	10
If Yes, specify type			
a. SSRI	1	2	11
b. TCA	1	2	12
c. MAOI	1	2	13
d. Other	1	2	14
Specify ___			15
3. NSAIDs	1	2	16
4. Vitamins	1	2	17
5. Incontinence meds	1	2	18
6. Antihistamines	1	2	19

7. List any prescribed medications in addition to above prior to admission (state indication

a. Name ___ 20
Indication ___ 21

b. Name ___ 22
Indication ___ 23

c. Name ___ 24
Indication ___ 25

d. Name ___ 26
Indication ___ 27

e. Name ___ 28
Indication ___ 29

f. Name ___ 30
Indication ___ 31

g. Name ___ 32
Indication ___ 33

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Continued Regular Cardiovascular Medications

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Patient ID. ___ - ___ (01) Initials ___ (02) Date of Completion ___ (03) D D M M Y Y Y Y

1. Furosemide (04) Yes ☐1 No ☐2

If Yes, specify type and dose

	Yes	No		
a. Intravenous once-off	☐1 (05)	☐2	___ (06)	mg
b. Intravenous regular	☐1 (07)	☐2	___ (08)	mg
c. Oral once-off	☐1 (09)	☐2	___ (10)	mg
d. Oral regular	☐1 (11)	☐2	___ (12)	mg

	Yes	No	
2. IV nitrate	☐1	☐2 (13)	
3. IV dobutamine	☐1	☐2 (14)	
4. IV dopamine	☐1	☐2 (15)	
5. IV other specify ___ (17)	☐1	☐2 (16)	

6. Digoxin (18) Yes ☐1 No ☐2

If Yes, specify type

	Yes	No
a. Intravenous once-off	☐1	☐2 (19)
b. Intravenous regular	☐1	☐2 (20)
c. Oral once-off	☐1	☐2 (21)
d. Oral regular	☐1	☐2 (22)

7. Other Diuretics (23) Yes ☐1 No ☐2

If Yes, specify type and dose where relevant

	Yes	No		
a. Other loop	☐1	☐2 (24)		
Specify ___ (25)				
b. Spironolactone	☐1	☐2 (26)		
c. Other K^+ sparing	☐1	☐2 (27)		
d. Thiazide	☐1	☐2 (28)		
e. Bumetanide	☐1	☐2 (29)	___ (30)	mg
f. Other	☐1	☐2 (31)		
Specify ___ (32)				

8. ACE-Inhibitor (33) Yes ☐1 No ☐2

(i) **If Yes**, specify type and dose

	Yes	No		
a. Captopril	☐1	☐2 (34)	___ (35)	mg
b. Enalapril	☐1	☐2 (36)	___ (37)	mg
c. Fosinopril	☐1	☐2 (38)	___ (39)	mg
d. Lisinopril	☐1	☐2 (40)	___ (41)	mg
e. Perindopril	☐1	☐2 (42)	___ (43)	mg
f. Quinapril	☐1	☐2 (44)	___ (45)	mg
g. Ramipril	☐1	☐2 (46)	___ (47)	mg
h. Trandolapril	☐1	☐2 (48)	___ (49)	mg
i. Other	☐1	☐2 (50)		
Specify ___ (51)			___ (52)	mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 (53)
(iii) Intolerant of higher dose than current	☐1	☐2 (54)
(iv) Patient on optimal dose	☐1	☐2 (55)
(v) If No, Patient on optimal tolerated dose	☐1	☐2 (56)

9. Hydralazine (57) Yes ☐1 No ☐2

If Yes, specify dose ___ (58) mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 (59)
(iii) Intolerant of higher dose than current	☐1	☐2 (60)
(iv) Patient on optimal dose	☐1	☐2 (61)
(v) If No, Patient on optimal tolerated dose	☐1	☐2 (62)

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10. Beta-blocker — Yes ☐1 No ☐2 04

(i) **If Yes**, specify type and dose

	Yes	No		
a. Atenolol	☐1	☐2 05	06	mg
b. Bisoprolol	☐1	☐2 07	08	mg
c. Carvedilol	☐1	☐2 09	10	mg
d. Metoprolol	☐1	☐2 11	12	mg
e. Nebivolol	☐1	☐2 13	14	mg
f. Propanolol	☐1	☐2 15	16	mg
g. Other	☐1	☐2 17		
Specify 18			19	mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 20
(iii) Intolerant of higher dose than current	☐1	☐2 21
(iv) Patient on optimal dose	☐1	☐2 22
(v) If No, Patient on optimal tolerated dose	☐1	☐2 23

11. Aldosterone Blocker — Yes ☐1 No ☐2 24

(i) **If Yes**, specify type and dose

	Yes	No		
a. Spironolactone	☐1	☐2 25	26	mg
b. Eplerenone	☐1	☐2 27	28	mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 29
(iii) Intolerant of higher dose than current	☐1	☐2 30
(iv) Patient on optimal dose	☐1	☐2 31
(v) If No, Patient on optimal tolerated dose	☐1	☐2 32

12. ARB — Yes ☐1 No ☐2 33

(i) **If Yes**, specify type and dose

	Yes	No		
a. Candesartan	☐1	☐2 34	35	mg
b. Irbesartan	☐1	☐2 36	37	mg
c. Losartan	☐1	☐2 38	39	mg
d. Olmesartan	☐1	☐2 40	41	mg
e. Telmisartan	☐1	☐2 42	43	mg
f. Valsartan	☐1	☐2 44	45	mg
g. Other	☐1	☐2 46		
Specify 47			48	mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 49
(iii) Intolerant of higher dose than current	☐1	☐2 50
(iv) Patient on optimal dose	☐1	☐2 51
(v) If No, Patient on optimal tolerated dose	☐1	☐2 52

13. Ivabradine — Yes ☐1 No ☐2 53

If Yes, specify dose ___ 54 mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 55
(iii) Intolerant of higher dose than current	☐1	☐2 56
(iv) Patient on optimal dose	☐1	☐2 57
(v) If No, Patient on optimal tolerated dose	☐1	☐2 58

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14. Calcium channel-blocker — Yes 1 No 2 (04)

If Yes, specify type

	Yes	No
a. Amlodipine	1	2 (05)
b. Diltiazem	1	2 (06)
c. Felodipine	1	2 (07)
d. Nifedipine	1	2 (08)
e. Verapamil	1	2 (09)
f. Other	1	2 (10)

Specify _____ (11)

15. Anti-arrhythmic — Yes 1 No 2 (12)

If Yes, specify type

	Yes	No
a. Amiodarone	1	2 (13)
b. Other	1	2 (14)

Specify _____ (15)

	Yes	No
16. Aspirin	1	2 (16)
17. Clopidogrel	1	2 (17)
18. Warfarin	1	2 (18)
19. Nicorandil	1	2 (19)

20. Long-acting nitrates (not s/c or short acting GTN) — Yes 1 No 2 (20)

If Yes, specify type

	Yes	No
a. ISDN	1	2 (21)
b. ISMN	1	2 (22)
c. GTN patch	1	2 (23)
d. Other	1	2 (24)

Specify _____ (25)

21 Statin — Yes 1 No 2 (26)

If Yes, specify type

	Yes	No
a. Atorvastatin	1	2 (27)
b. Pravastatin	1	2 (28)
c. Rosuvastatin	1	2 (29)
d. Simvastatin	1	2 (30)
e. Other	1	2 (31)

Specify _____ (32)

22. List any other relevant Non-Cardiovascular medications started since admission (state indication)

a. Name _____ (33)
Indication _____ (34)

b. Name _____ (35)
Indication _____ (36)

c. Name _____ (37)
Indication _____ (38)

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A. VITAL SIGNS

1. Height ⌊_____⌋ cm 04
2. Weight ⌊_____.__⌋ kg 05
3. SpO2 ⌊_____⌋ % 06 Air ⌊__⌋ or O_2 ⌊__⌋ 07
4. Blood pressure ⌊_____⌋ / ⌊_____⌋ mmHg 08
5. Heart rate ⌊_____⌋ bpm 09
6. Temperature ⌊_____.__⌋ °C 10
7. Respiratory rate ⌊_____⌋ bpm 11

B. CARDIOVASCULAR EXAMINATION

	Yes	No	Not Seen
1. Elevated JVP (>4cm)	☐1	☐2	☐3 12
2. Palpable Apex	☐1	☐2 13	
If Yes, Displaced Apex	☐1	☐2 14	
3. Third Heart Sound	☐1	☐2 15	
4. Murmur	☐1	☐2 16	
If Yes, a. AS	☐1	☐2 17	
b. AR	☐1	☐2 18	
c. MR	☐1	☐2 19	
d. MS	☐1	☐2 20	
e. TR	☐1	☐2 21	
5. Pulmonary crackles	☐1	☐2 22	
If Yes, a. Basal	☐1	☐2 23	
b. Middle	☐1	☐2 24	
c. Apex	☐1	☐2 25	
6. Pleural effusion	☐1	☐2 26	
If Yes, a. Right	☐1	☐2 27	
b. Left	☐1	☐2 28	
c. Bilateral	☐1	☐2 29	

	Yes	No
7. Peripheral Oedema	☐1	☐2 30
If Yes, a. Ankle	☐1	☐2 31
b. Knee	☐1	☐2 32
c. Thigh	☐1	☐2 33
d. Sacrum	☐1	☐2 34
e. Abdomen	☐1	☐2 35
8. Ascites	☐1	☐2 36
9. Carotid Bruit	☐1	☐2 37

If Yes, specify — Right ☐1 Left ☐2 Bilateral ☐3 38

10. Killip Class I ☐1 II ☐2 III ☐3 IV ☐4 39

I = No clinical signs heart failure
II = lung crackles / gallop rhythm / S3
III = frank pulmonary oedema
IV = cardiogenic shock

C GRIP STRENGTH

1. ⌊___⌋ kg 40
2. ⌊___⌋ kg 41
3. ⌊___⌋ kg 42

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Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊____⌋ 02 Date of Completion ⌊D D M M Y Y Y Y⌋ 03

A. ECG

1. Was an ECG performed? Yes ☐1 No ☐2 04

If Yes,

a. Hard copy obtained for study Yes ☐1 No ☐2 05

b. ECG Analysis

	Yes	No	
a. SR	☐1	☐2	06
b. AF/flutter	☐1	☐2	07
c. BBB	☐1	☐2	08
specify... Right ☐1 Left ☐2			09
d. Paced	☐1	☐2	10
e. Pathological Q waves	☐1	☐2	11
f. LVH	☐1	☐2	12
g. Ischaemic ST depression	☐1	☐2	13

h. QRS duration ⌊____⌋ ms 14

i. QTc duration ⌊____⌋ ms 15

j. Other ☐1 ☐2 16

specify _____ 17

B. CXR

1. Performed Yes ☐1 No ☐2 18

If Yes,

	Yes	No	
a. Cardiomegaly (CTR>0.5)	☐1	☐2	19
b. Upper lobe venous diversion	☐1	☐2	20
c. Interstitial oedema (kerley B lines)	☐1	☐2	21
d. Alveolar oedema (patchy consolidation)	☐1	☐2	22
e. Pleural effusions	☐1	☐2	23

Specify... Right ☐1 Left ☐2 Bilateral ☐3 24

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Patient ID. ___-___ (01) Initials ___ (02) Date of Completion D D M M Y Y Y Y (03)

A. ECHO - PRIOR TO CURRENT ADMISSION

1. Previous ECHO — Yes ☐1 No ☐2 (04)

If Yes,

a. Performed in last year — Yes ☐1 No ☐2 (05)

b. Year of most recent — Y Y Y Y (06)

2. Analysis of most recent ECHO:

a. LVEDD ___.___ cm (07)

b. Dilated left ventricle — Yes ☐1 No ☐2 (08)

c. LVH — ☐1 ☐2 (09)

d. Left ventricular systolic dysfunction — Yes ☐1 No ☐2 (10)

If Yes,

Mild ☐1 Mild-Mod ☐2 Moderate ☐3 Mod-Severe ☐4 Severe ☐5 (11)

e. Valvular heart disease — ☐1 ☐2 (12)

If Yes,

		Mild	Mild-Mod	Moderate	Mod-Severe	Severe
a. AS	☐ severity.. (13)	☐1	☐2	☐3	☐4	☐5 (14)
b. AR	☐ severity.. (15)	☐1	☐2	☐3	☐4	☐5 (16)
c. MS	☐ severity.. (17)	☐1	☐2	☐3	☐4	☐5 (18)
d. MR	☐ severity.. (19)	☐1	☐2	☐3	☐4	☐5 (20)
e. TR	☐ severity.. (21)	☐1	☐2	☐3	☐4	☐5 (22)
f. Other	☐ severity.. (23)	☐1	☐2	☐3	☐4	☐5 (24)

specify _____ (25)

f. Other relevant ECHO findings

i. _____ (26)

ii. _____ (27)

iii. _____ (28)

iv. _____ (29)

B. ECHO DURING ADMISSION

1. Was admission ECHO performed — Yes ☐1 No ☐2 (30)

If Yes date, D D M M Y Y Y Y (31)

C. ADMISSION LUNG ULTRASOUND

1. Was admission LUS performed — Yes ☐1 No ☐2 (32)

If No, specify why _____ (33)

If Yes,

a. Pleural effusion: Right — Yes ☐1 No ☐2 (34)

If No, specify why _____ (35)

b. Pleural effusion: Left — Yes ☐1 No ☐2 (36)

If No, specify why _____ (37)

2. Date of admission LUS: D D M M Y Y Y Y (38)

3. Time difference between treatment start of ADHF and LUS: ___ hours (39)

4. Does the patient have any of the following?

	Yes	No
a) Left ventricular assist device	☐1	☐2 (40)
b) Current unilateral or bilateral chest drains	☐1	☐2 (41)
c) Current pneumothorax	☐1	☐2 (42)
d) Current pulmonary contusions	☐1	☐2 (43)
e) Current pneumonia/ARDS	☐1	☐2 (44)
f) Current lung cancer	☐1	☐2 (45)
g) Known pulmonary fibrosis	☐1	☐2 (46)
h) Currently on hemodialysis or peritoneal dialysis	☐1	☐2 (47)
i) Advanced hepatic failure	☐1	☐2 (48)

C. PRE-DISCHARGE LUNG ULTRASOUND

1. Was pre-discharge LUS performed — Yes ☐1 No ☐2 (49)

If No, specify why _____ (50)

If Yes,

a. Pleural effusion: Right — Yes ☐1 No ☐2 (51)

If No, specify why _____ (52)

b. Pleural effusion: Left — Yes ☐1 No ☐2 (53)

If No, specify why _____ (54)

2. Date of pre-discharge LUS: D D M M Y Y Y Y (55)

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Version 2.1 (27 Aug 2013)

Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊____⌋ 02 Date of Completion ⌊_____⌋ 03 (D D M M Y Y Y Y)

ADMISSION BLOOD RESULTS
(1st available result during admission)

A: Biochemistry

1. BNP level ⌊____⌋ 04 pg/ml
2. TnI ⌊__.__⌋ 05 µg/l
3. Sodium ⌊____⌋ 06 mmol/l
4. Potassium ⌊__.__⌋ 07 mmol/l
5. Chloride ⌊____⌋ 08 mmol/l
6. Urea ⌊__.__⌋ 09 mmol/l
7. Creatinine ⌊____⌋ 10 µmol/l
8. eGFR ⌊__⌋ 11 ml/min
9. Bilirubin ⌊____⌋ 12 mmol/l
10. AST ⌊____⌋ 13 mmol/l
11. ALT ⌊____⌋ 14 mmol/l
12. Alk Phos ⌊____⌋ 15 mmol/l
13. Albumin ⌊__⌋ 16 mmol/l
14. TSH ⌊__.__⌋ 17 mUI/l
15. T4 ⌊__.__⌋ 18 pmol/L
16. Urate ⌊__.__⌋ 19 mmol/l
17. Phosphate ⌊__.__⌋ 20 mmol/l
18. Glucose ⌊__.__⌋ 21 mmol/l

B: Lipid Profile

Fasting ☐ 1 Non-Fasting ☐ 2 22

1. Chol (total) ⌊__.__⌋ 23 mmol/l
2. C/HDL ⌊__.__⌋ 24 mmol/l
3. LDL ⌊__.__⌋ 25 mmol/l
4. HDL ⌊__.__⌋ 26 mmol/l
5. Triglycerides ⌊__.__⌋ 27 mmol/l

C: Haematology

1. WCC ⌊__.__⌋ 28 x10 9/l
2. Haemoglobin ⌊____⌋ 29 g/L
3. HbA1c ⌊____⌋ 30 mmol/mol
4. MCV ⌊____.__⌋ 31 fl
5. RDW ⌊____.__⌋ 32 %
6. Platelets ⌊_____⌋ 33 $x10^9$
7. Lymphocytes ⌊__.__⌋ 34 x10 9/l

Version 2.1 (27 Aug 2013)

Patient ID. ___-___ (01) Initials ___ (02) Date of Completion ___ (03) D D M M Y Y Y Y

A. Primary Aetiology

	Yes	No	Unknown	
1. Ischaemic	☐1	☐2	☐3	04

If Yes, must have:

	Yes	No	
a. Definite previous MI	☐1	☐2	05
OR			
b. Angio. CHD (>50% stenosis in ≥1 vessel)	☐1	☐2	06

If No (and all other causes excluded)

	Yes	No	
a. Idiopathic DCM	☐1	☐2	07
b. Hypertension	☐1	☐2	08
c. Alcohol Cardiomyopathy	☐1	☐2	09
d. Valvular	☐1	☐2	10
e. Other	☐1	☐2	11

If other, specify _____ (12)

	Yes	No	
2. Unknown Aetiology	☐1	☐2	13

B. Contributing Aetiologies

	Yes	No	
1. Valvular Heart Disease	☐1	☐2	14

If Yes,

	Yes	No	
a. AS	☐1	☐2	15
b. AR	☐1	☐2	16
c. MS	☐1	☐2	17
d. MR	☐1	☐2	18
e. TR	☐1	☐2	19

	Yes	No	
2. Diabetes Mellitus	☐1	☐2	20
3. Atrial Fibrillation	☐1	☐2	21
4. Hypertension	☐1	☐2	22
5. Alcohol Cardiomyopathy	☐1	☐2	23
6. Other	☐1	☐2	24

If Other, specify _____ (25)

Version 2.1 (27 Aug 2013)

Patient ID. ___-___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

1. Preferred place of care
   - a. Home ☐1
   - b. Hospital ☐2
   - c. Care facility/nursing Home ☐3
   - d. Other _____ 05 ☐4
   - e. Undecided ☐5 04

2. Preferred place of death
   - a. Home ☐1
   - b. Hospital ☐2
   - c. Care facility/Nursing home ☐3
   - d. Other _____ 07 ☐4
   - e. Undecided ☐5 06

3. Patient preference resuscitation
   - a. DNACPR ☐1
   - b. For CPR ☐2
   - c. Undecided ☐3 08

4. Physician assessment prognosis
   - a. Expected life expectance
     - i. Greater than 1 year ☐1
     - ii. Less than 1 year ☐2 09
   - b. Should patient be resuscitated?
     - i. Yes ☐1
     - ii. No ☐2
     - iii. Unsure ☐3 10
   - c. Does the patient have PC needs?
     - i. Yes ☐1
     - ii. No ☐2
     - iii. Unsure ☐3 11

   - d. Grade of physician
     - i. Consultant ☐1
     - ii. SpR ☐2
     - iii. Staff grade ☐3
     - iv. SHO ☐3 12
   - e. Speciality of physician
     - i. Cardiology ☐1
     - ii. General Medicine ☐2
     - iii. COTE ☐3
     - iv. Other _____ 14 ☐3 13

The Australia-modified Karnofsky Performance Scale (AKPS)

Version 2.1 (27 Aug 2013)

Patient ID. _ - _ 01 Initials _ _ 02 Date of Completion _ _ _ _ _ _ _ _ D D M M Y Y Y Y 03

Record the rating as assessed by entering ONE number (scores in increments of 10) selected from the table below. In between scores such as 45, 55 or scores such as 50-60 are invalid.

SCORE _ _ _ 04

AKPS ASSESSMENT CRITERIA	SCORE
Normal; no complaints; no evidence of disease	100
Able to carry on normal activity; minor sign of symptoms of disease	90
Normal activity with effort; some signs or symptoms of disease	80
Cares for self; unable to carry on normal activity or to do active work	70
Able to care for most needs; but requires occasional assistance	60
Considerable assistance and frequent medical care required	50
In bed more than 50% of the time	40
Almost completely bedfast	30
Totally bedfast and requiring extensive nursing care by professionals and/or family	20
Comatose or barely rousable	10
Dead	0

Version 2.1 (27 Aug 2013)

Patient ID. ___-___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

Section 1: Priority Referral for Further Assessment

	Yes	No
1. Does the patient have a caregiver readily available if required?	☐1	☐2 04
2. Has the patient or caregiver requested a referral to a specialist palliative care service (SPCS)?	☐1	☐2 05
3. Do you require assistance in managing the care of this patient and/or family?	☐1	☐2 06

Section 2: Patient Wellbeing	Level of Concern		
	None	**Some/ Potential**	**Significant**
1. Is the patient experiencing unresolved physical symptoms (including problems with breathlessness, pain, fatigue, nausea, oedema, insomnia or cough)?	☐1	☐2	☐3 07
2. Does the patient have problems with daily living activities?	☐1	☐2	☐3 08
3. Does the patient have psychological symptoms that are interfering with wellbeing or relationships?	☐1	☐2	☐3 09
4. Does the patient have concerns about how to manage his/her medication and treatment regimes?	☐1	☐2	☐3 10
5. Does the patient have concerns about spiritual or existential issues?	☐1	☐2	☐3 11
6. Does the patient have financial or legal concerns that are causing distress or require assistance?	☐1	☐2	☐3 12
7. From the health delivery point of view, are there health beliefs, cultural or social factors involving the patient or family that are making care more complex?	☐1	☐2	☐3 13

8. Does the patient require information about: (tick any options that are relevant)
☐1 14 The prognosis ☐1 15 Treatment options ☐1 16 Advance directive/resuscitation preferences
☐1 17 Financial/legal issues ☐1 18 Heart disease ☐1 19 Medical/health/support services ☐1 20 Social/emotional issues

Section 3: Ability of Caregiver or Family to care for patient	Level of Concern		
a) Who provided this information? (please tick one) Patient ☐1 Caregiver ☐2 Both ☐3 21	**None**	**Some/ Potential**	**Significant**
1. Is the caregiver or family distressed about the patient's physical symptoms?	☐1	☐2	☐3 22
2. Is the caregiver or family having difficulty providing physical care?	☐1	☐2	☐3 23
3. Is the caregiver or family having difficulty coping?	☐1	☐2	☐3 24
4. Does the caregiver have difficulty managing the patient's medication and treatment regimes?	☐1	☐2	☐3 25
5. Does the caregiver or family have financial or legal concerns that are causing distress or require assistance?	☐1	☐2	☐3 26
6. Is the family currently experiencing problems that are interfering with their functioning or inter-personal relationships, or is there a history of such problems?	☐1	☐2	☐3 27

7. Does the caregiver require information: (tick any options that are relevant)
☐1 28 The prognosis ☐1 29 Advance directive/resuscitation preferences ☐1 30 Medical/health/support services
☐1 31 Heart disease ☐1 32 Treatment options ☐1 33 What to do in event of patient's death
☐1 34 Social/emotional issues ☐1 35 Financial/legal issues

Section 4: Caregiver Wellbeing	Level of Concern		
a) Who provided this information? (please tick one) Patient ☐1 Caregiver ☐2 Both ☐3 36	**None**	**Some/ Potential**	**Significant**
1. Is the caregiver or family experiencing physical,spiritual, existential or psychological problems that are interfering with their wellbeing or funtioning?	☐1	☐2	☐3 37
2. Is the caregiver or family experiencing grief over the impending or recent death of the patient that is interfering with their wellbeing or functioning?	☐1	☐2	☐3 38

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Appendix 4- Patient reported outcome measures

PCHF Study

In Hospital Visit, Page 1
Hospital, Anxiety and Depression Scale (HADS)

Version 2.0 (08 April 2013)

Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊____⌋ 02 Date of Completion ⌊_____⌋ D D M M Y Y Y Y 03

This questionnaire helps your physician to know how you are feeling. Read every sentence. Place an "X" in the box that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer. In this questionnaire, spontaneous answers are more important.

I feel tense or 'wound up': A
- Most of the time ☐ 3
- A lot of the time ☐ 2
- From time to time, occasionally ☐ 1
- Not at all ☐ 0

04

I still enjoy the things I used to enjoy: D
- Definitely as much ☐ 0
- Not quite so much ☐ 1
- Only a little ☐ 2
- Not at all ☐ 3

05

I get a sort of frightened feeling as if something awful is about to happen: A
- Very definitely and quite badly ☐ 3
- Yes, but not too badly ☐ 2
- A little, but it doesn't worry me ☐ 1
- Not at all ☐ 0

06

I can laugh and see the funny side of things: D
- As much as I always could ☐ 0
- Not quite so much now ☐ 1
- Definately not so much now ☐ 2
- Not at all ☐ 3

07

Worrying thoughts go through my mind: A
- A great deal of the time ☐ 3
- A lot of the time ☐ 2
- From time to time but not too often ☐ 1
- Only occasionally ☐ 0

08

I feel cheerful: D
- Not at all ☐ 3
- Not often ☐ 2
- Sometimes ☐ 1
- Most of the time ☐ 0

09

I can sit at ease and feel relaxed: A
- Definitely ☐ 0
- Usually ☐ 1
- Not often ☐ 2
- Not at all ☐ 3

10

I feel as if I am slowed down: D
- Nearly all of the time ☐ 3
- Very often ☐ 2
- Sometimes ☐ 1
- Not at all ☐ 0

11

I get a sort of frightened feeling like 'butterflies in the stomach': A
- Not at all ☐ 0
- Occasionally ☐ 1
- Quite often ☐ 2
- Very often ☐ 3

12

I have lost interest in my appearance: D
- Definitely ☐ 3
- I don't take as much care as I should ☐ 2
- I may not take quite as much care ☐ 1
- I take just as much care as ever ☐ 0

13

I feel restless as if I have to be on the move: A
- Very much indeed ☐ 3
- Quite a lot ☐ 2
- Not very much ☐ 1
- Not at all ☐ 0

14

I look forward with enjoyment to things: D
- As much as I ever did ☐ 0
- Rather less than I used to ☐ 1
- Definitely less than I used to ☐ 2
- Hardly at all ☐ 3

15

I get sudden feelings of panic: A
- Very often indeed ☐ 3
- Quite often ☐ 2
- Not very often ☐ 1
- Not at all ☐ 0

16

I can enjoy a good book or radio or TV programme: D
- Often ☐ 0
- Sometimes ☐ 1
- Not often ☐ 2
- Very seldom ☐ 3

17

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Version 2.0 (08 April 2013)

Patient ID. ☐☐-☐☐☐☐ 01 Initials ☐☐☐ 02 Date of Completion ☐☐ ☐☐ ☐☐ ☐☐☐☐ 03
D D M M Y Y Y Y

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some may mainly feel shortness of breath while others mainly fatigue. Please indicate how limited you have been by heart failure (for example, shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Please put an X in one box on each line

Activity	Extremely limited	Quite a bit limited	Moderately limited	Slightly limited	Not at all limited	Limited for other reasons or did not do the activity
1. Dressing yourself	☐0	☐1	☐2	☐3	☐4	☐5 04
2. Showering or having a bath	☐0	☐1	☐2	☐3	☐4	☐5 05
3. Walking 100 yards on level ground	☐0	☐1	☐2	☐3	☐4	☐5 06
4. Doing gardening, housework or carrying groceries	☐0	☐1	☐2	☐3	☐4	☐5 07
5. Climbing a flight of stairs without stopping ..	☐0	☐1	☐2	☐3	☐4	☐5 08
6. Jogging or hurrying (as if to catch a bus).....	☐0	☐1	☐2	☐3	☐4	☐5 09

2. Compared with 2 weeks ago, have your symptoms of heart failure (for example, shortness of breath, fatigue, or ankle swelling) changed?

	Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
My symptoms of heart failure are now....	☐0	☐1	☐2	☐3	☐4	☐5 10

3. Over the past 2 weeks, how many times have you had swelling in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐0	☐1	☐2	☐3	☐4 11

4. Over the past 2 weeks, how much has swelling in your feet, ankles or legs bothered you?

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no swelling
☐0	☐1	☐2	☐3	☐4	☐5 12

5. Over the past 2 weeks, on average, how many times has fatigue limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐0	☐1	☐2	☐3	☐4	☐5	☐6 13

Version 2.0 (08 April 2013)

Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊____⌋ 02 Date of Completion ⌊_____⌋ D D M M Y Y Y Y 03

6. Over the past 2 weeks, how much has your fatigue bothered you?

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no fatigue
☐0	☐1	☐2	☐3	☐4	☐5 04

7. Over the past 2 weeks, on average, how many times has shortness of breath limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐0	☐1	☐2	☐3	☐4	☐5	☐6 05

8. Over the past 2 weeks, how much has your shortness of breath bothered you?

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no shortness of breath
☐0	☐1	☐2	☐3	☐4	☐5 06

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of shortness of breath?

Every night	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐0	☐1	☐2	☐3	☐4 07

10. Heart failure symptoms can worsen for a number of reasons. How sure are you Ihat you know what to do, or whom to call, if your heart failure gets worse?

Not at all sure	Not very sure	Somewhat sure	Mostly sure	Completely sure
☐0	☐1	☐2	☐3	☐4 08

11. How well do you understand what things you are able to do to keep your heart failure symptoms from getting worse (for example, regularly weighing yourself, eating a low salt diet etc.)?

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
☐0	☐1	☐2	☐3	☐4 09

12. Over the past 2 weeks, how much has your heart failure limited your enjoyment of life?

It has extremely limited my enjoyment of life	It has limited my enjoyment of life	It has moderately limited my enjoyment of life	It has slighty limited my enjoyment of life	It has not limited my enjoyment of life
☐0	☐1	☐2	☐3	☐4 10

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Version 2.0 (08 April 2013)

Patient ID. ☐☐-☐☐☐☐☐ 01 Initials ☐☐☐ 02 Date of Completion ☐☐☐☐☐☐☐☐ D D M M Y Y Y Y 03

13. If you had to spend the rest of your life with your heart failure the way it is right now, how would you feel about this?

Completely dissatisfied	Mostly dissatisfied	Somewhat dissatisfied	Mostly satisfied	Completely satisfied
☐0	☐1	☐2	☐3	☐4 04

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your heart failure?

I have felt that way all of the time	I have felt that way most of the time	I have occasionall felt that way	I have rarely felt that way	I have never felt that way
☐0	☐1	☐2	☐3	☐4 05

15. How much does your heart failure affect your lifestyle? Please indicate how your heart failure may have limited your participation in the following activities <u>over the past 2 weeks</u>.

Please put an **X** in one box on each line.

Activity	Extremely limited	Quite a bit limited	Moderately limited	Slightly limited	Not at all limited	Limited for other reasons or did not do the activity
1. Hobbies, recreational activities	☐0	☐1	☐2	☐3	☐4	☐5 06
2. Working or doing household chores	☐0	☐1	☐2	☐3	☐4	☐5 07
3. Visiting family or friends	☐0	☐1	☐2	☐3	☐4	☐5 08
4. Intimate or sexual relationships	☐0	☐1	☐2	☐3	☐4	☐5 09

Edmonton Symptom Assessment System (revised version) (ESAS-R)

Version 2.0 (08 April 2013)

Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊____⌋ 02 Date of Completion ⌊_____⌋ D D M M Y Y Y Y 03

Please circle the number that best describeshow you feel NOW:

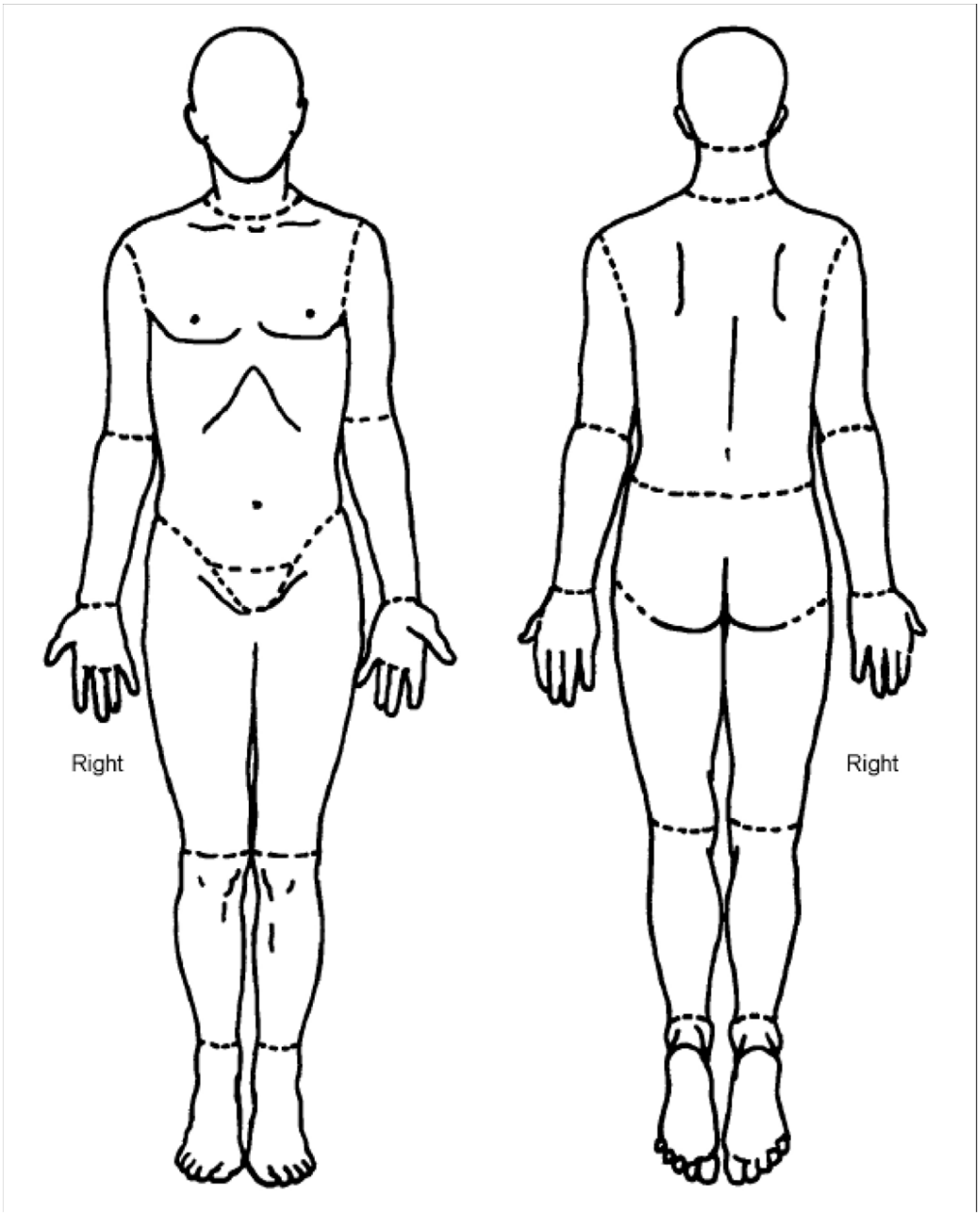
No Pain	0 1 2 3 4 5 6 7 8 9 10 04	**Worst Possible Pain**
No Tiredness *(Tiredness= lack of energy)*	0 1 2 3 4 5 6 7 8 9 10 05	**Worst Possible Tiredness**
No Drowsiness *(Drowsiness = feeling sleepy)*	0 1 2 3 4 5 6 7 8 9 10 06	**Worst Possible Drowsiness**
No Nausea	0 1 2 3 4 5 6 7 8 9 10 07	**Worst Possible Nausea**
No Lack of Appetite	0 1 2 3 4 5 6 7 8 9 10 08	**Worst Possible Lack of Appetite**
No Shortness of Breath	0 1 2 3 4 5 6 7 8 9 10 09	**Worst Possible Shortness of Breath**
No Depression *(Depression = feeling sad)*	0 1 2 3 4 5 6 7 8 9 10 10	**Worst Possible Depression**
No Anxiety *(Anxiety = feeling nervous)*	0 1 2 3 4 5 6 7 8 9 10 11	**Worst Possible Anxiety**
Best Wellbeing *(Wellbeing = how you feel overall)*	0 1 2 3 4 5 6 7 8 9 10 12	**Worst Possible Wellbeing**
No _____ 13 **Other Problem** *(for example constipation)*	0 1 2 3 4 5 6 7 8 9 10 14	**Worst Possible** _____ 15

BODY DIAGRAM ON REVERSE SIDE

Version 2.0 (08 April 2013)

Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊_____⌋ 02 Date of Completion ⌊_____⌋ D D M M Y Y Y Y 03

Please mark on these pictures where it is you hurt.



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Version 2.0 (08 April 2013)

Patient ID. ☐-☐ 01 Initials ☐ 02 Date of Completion ☐ D D M M Y Y Y Y 03

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Thank you for completing this survey!

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very Good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5 04

2. The following two questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a Little	No, not limited at all
a. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1.....	☐2.....	☐3 05
b. Climbing <u>several</u> flights of stairs	☐1.....	☐2.....	☐3 06

Version 2.0 (08 April 2013)

Patient ID. ☐☐-☐☐☐☐☐☐ 01 Initials ☐☐☐ 02 Date of Completion ☐☐☐☐☐☐☐☐ D D M M Y Y Y Y 03

3. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A Little of the time	None of the time
a. <u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5 04
b. Were limited in the <u>kind</u> of work or other activities	☐1	☐2	☐3	☐4	☐5 05

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A Little of the time	None of the time
a. <u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5 06
b. Did work or other activities <u>less carefully than usual</u>	☐1	☐2	☐3	☐4	☐5 07

5. During the <u>past 4 weeks</u>, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5 08

United Kingdom (English) Standard

Produced by Robertson Centre for Biostatistics, University of Glasgow

Version 2.0 (08 April 2013)

Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊____⌋ 02 Date of Completion ⌊_____⌋ D D M M Y Y Y Y 03

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A Little of the time	None of the time
a. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5 04
b. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5 05
c. Have you felt downhearted and low?	☐1	☐2	☐3	☐4	☐5 06

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A Little of the time	None of the time
☐1	☐2	☐3	☐4	☐5 07

8. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A Little of the time	None of the time
a. Have you been very nervousl?	☐1	☐2	☐3	☐4	☐5 04
b. Have your felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5 05
c. Have you been happy?	☐1	☐2	☐3	☐4	☐5 06

Thank you for completing these questions!

Appendix 5- KCCQ scoring instructions

The Kansas City Cardiomyopathy Questionnaire
Scoring Instructions

There are 10 summary scores within the KCCQ, which are calculated as follows:

1. **Physical Limitation**

   - Code responses to each of Questions 1a-f as follows:

     Extremely limited = 1
     Quite a bit limited = 2
     Moderately limited = 3
     Slightly limited = 4
     Not at all limited = 5
     Limited for other reasons or did not do = <*missing value*>

   - If at least three of Questions 1a-f are not missing, then compute

     Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered) – 1]/4

     (see footnote at end of this document for explanation of meaning of "actually answered")

2. **Symptom Stability**

   - Code the response to Question 2 as follows:

     Much worse = 1
     Slightly worse = 2
     Not changed = 3
     Slightly better = 4
     Much better = 5
     I've had no symptoms over the last 2 weeks = 3

   - If Question 2 is not missing, then compute

     Symptom Stability Score = 100*[(Question 2) – 1]/4

3. **Symptom Frequency**

   - Code responses to Questions 3, 5, 7 and 9 as follows:

     <u>Question 3</u>
     Every morning = 1
     3 or more times a week but not every day = 2
     1-2 times a week = 3
     Less than once a week = 4
     Never over the past 2 weeks = 5

3. Symptom Frequency (cont.)

Questions 5 and 7
All of the time = 1
Several times a day = 2
At least once a day = 3
3 or more times a week but not every day = 4
1-2 times a week = 5
Less than once a week = 6
Never over the past 2 weeks = 7

Question 9
Every night = 1
3 or more times a week but not every day = 2
1-2 times a week = 3
Less than once a week = 4
Never over the past 2 weeks = 5

- If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

S3 = [(Question 3) – 1]/4
S5 = [(Question 5) – 1]/6
S7 = [(Question 7) – 1]/6
S9 = [(Question 9) – 1]/4

Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. Symptom Burden

- Code responses to each of Questions 4, 6 and 8 as follows:

Extremely bothersome = 1
Quite a bit bothersome = 2
Moderately bothersome = 3
Slightly bothersome = 4
Not at all bothersome = 5
I've had no swelling/fatigue/shortness of breath = 5

- If at least one of Questions 4, 6 and 8 is not missing, then compute

Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. Total Symptom Score

= mean of the following available summary scores:
Symptom Frequency Score
Symptom Burden Score

6. Self-Efficacy

- Code responses to Questions 10 and 11 as follows:

  Question 10
  Not at all sure = 1
  Not very sure = 2
  Somewhat sure = 3
  Mostly sure = 4
  Completely sure = 5

  Question 11
  Do not understand at all = 1
  Do not understand very well = 2
  Somewhat understand = 3
  Mostly understand = 4
  Completely understand = 5

- If at least one of Questions 10 and 11 is not missing, then compute

  Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. Quality of Life

- Code responses to Questions 12, 13 and 14 as follows:

  Question 12
  It has extremely limited my enjoyment of life = 1
  It has limited my enjoyment of life quite a bit = 2
  It has moderately limited my enjoyment of life = 3
  It has slightly limited my enjoyment of life = 4
  It has not limited my enjoyment of life at all = 5

  Question 13
  Not at all satisfied = 1
  Mostly dissatisfied = 2
  Somewhat satisfied = 3
  Mostly satisfied = 4
  Completely satisfied = 5

  Question 14
  I felt that way all of the time = 1
  I felt that way most of the time = 2
  I occasionally felt that way = 3
  I rarely felt that way = 4
  I never felt that way = 5

7. Quality of Life (cont.)

- If at least one of Questions 12, 13 and 14 is not missing, then compute

  Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. Social Limitation

- Code responses to each of Questions 15a-d as follows:

  Severely limited = 1
  Limited quite a bit = 2
  Moderately limited = 3
  Slightly limited = 4
  Did not limit at all = 5
  Does not apply or did not do for other reasons = <*missing value*>

- If at least two of Questions 15a-d are not missing, then compute

  Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

9. Overall Summary Score

= mean of the following available summary scores:
  Physical Limitation Score
  Total Symptom Score
  Quality of Life Score
  Social Limitation Score

10. Clinical Summary Score

= mean of the following available summary scores:
  Physical Limitation Score
  Total Symptom Score

Note: references to "**means of questions actually answered**" imply the following.

- If there are *n* questions in a scale, and the subject must answer *m* to score the scale, but the subject answers only *n-i*, where *n-i* >= *m*, calculate the **mean of those questions** as
  (sum of the responses to those *n-i* questions) / (*n-i*)
  not
  (sum of the responses to those *n-i* questions) / *n*

If doing these calculations seems like too much trouble, consider using one of our tools – available at www.cvoutcomes.org:

- SAS or SPSS code
- Excel spreadsheets
- Web data services

Appendix 6- Physician prognosis questionnaire

Cardiology Research Study: Palliative Care needs of patients admitted to hospital with Heart Failure

Patient ID

Name:
DOB:
Hospital/ CHI no:

This patient has kindly agreed to participate in a cardiology research study. The first stage involves taking a blood test for B-type natriuretic peptide (BNP) in patients with signs and symptoms of heart failure to screen for the presence of heart failure. This was taken on :……..

The result of this test is :……...

This would make the diagnosis of heart failure possible / unlikely.

Patients with a positive BNP will be included in this study. As part of the study they will be asked to complete a series of questionnaires and have an echocardiogram performed. Their main carer (if applicable) will be asked to complete a questionnaire assessing caregiver burden. As part of the study they will be invited to attend the Cardiology Department of the Western Infirmary for follow up visits at 4 month intervals for up to 2 years.

As part of the study we plan to determine how clinical acumen compares to prognostic scores in identifying patients with heart failure who are in the last year of life as well as identifying those patients who have palliative care needs. We would be grateful if you could fill in the tick box questionnaire attached to this information sheet. Completion of this questionnaire is entirely voluntary.

If the BNP test is negative then there will be no further contact with the patient.

Further information: Dr Ross Campbell 0141 330 2237

Project Supervision: Prof J McMurray, Dr K Hogg, Dr M Petrie

Patient study number:

Physician questionnaire.

Please tick box for answer that you feel to be most representative.

1. Do you anticipate this patients life expectancy to be:	> 1 year	☐
	< 1 Year	☐
	Unknown	☐
2. Do you think this patient has palliative care needs?	Yes	☐
	No	☐
3. Do you think this patient should be resuscitated in the event of a cardiac arrest?	Yes	☐
	No	☐
4. Please state your specialty:	Cardiology	☐
	Acute Medicine	☐
	COTE	☐
	General Medicine	☐
5. Please state your grade:	Consultant	☐
	SpR/StR	☐
	SHO	☐
	Staff grade	☐

Thank you for taking the time to complete this questionnaire.

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