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Patient-reported outcomes in patients with heart failure

PhD dissertation

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Faculty of Health Sciences
Aarhus University
Department of Cardiology
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Preface

This Ph.D. thesis is based on studies carried out during my employment at the Department of Cardiology, Aarhus University Hospital from 2016-2019.

I feel very privileged that this work was made possible and that I was given the opportunity to work with leading experts within epidemiology, biostatistics and cardiology.

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Anne Ankerstjerne Rasmussen, November 2019

This PhD thesis is based on the following three papers:

This dissertation is based on the following three papers and is referred to as study I-III in the thesis

Paper I

Predictors of Patient-Reported Outcomes at Discharge in Patients with Heart Failure

Rasmussen AA, Johnsen SP, Berg SK, Rasmussen TB, Borregaard B, Thrysoee L, Thorup CB, Mols RE, Wiggers H, Larsen SH

(Submitted)

Paper II

Patient-Reported Outcomes and Medication Adherence in Patients With Heart Failure

Rasmussen, AA, Wiggers H, Jensen M, Berg SK, Rasmussen TB, Borregaard B, Thrysoee L, Thorup CB, Mols RE, Larsen SH, Johnsen SP

(Submitted)

Paper III

Prognostic Impact of Self-Reported Health on Clinical Outcomes in Patients with Heart Failure

Rasmussen AA, Larsen SH, Jensen M, Berg SK, Rasmussen TB, Borregaard B, Thrysoee L, Thorup CB, Mols RE, Wiggers H, Johnsen SP

(Submitted)

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
β-blocker	Beta blocker
B-IPQ	The Brief Illness Perception Questionnaire
95% CI	95% confidence interval
CCI	Charlson Comorbidity Index
CRS	Civil Registration System
CV	Cardiovascular
DNPR	Danish National Patient Registry
ESAS	The Edmonton Symptom Assessment Scale
ESC	European Society of Cardiology
EQ-5D-5L	The EuroQol five-dimensional, five-level Questionnaire
HF	Heart failure
HADS	The Hospital Anxiety and Depression Scale
HADS-A	The Hospital Anxiety and Depression Scale, anxiety subscale
HADS-D	The Hospital Anxiety and Depression Scale, depression subscale
HFmEF	Heart failure with mid-range left ventricular ejection fraction
HFpEF	Heart failure with preserved left ventricular ejection fraction
HFrEF	Heart failure with reduced left ventricular ejection fraction
HRQoL	Health-Related Quality of Life
ICD	Implantable Cardioverter Defibrillator
ICD-10	The International Classification of Diseases, 10th Revision
LVEF	Left ventricular ejection fraction
MAR	Missing at random
MDD	Mean daily dose
MI	Multiple imputation
MRAs	Mineralocorticoid receptor antagonists
NYHA	The New York Heart Association Functional Classification
RCT	Randomised controlled trial

RMPS	Register of Medicinal Products Statistics
PICO model	Patient-Intervention-Comparison-Outcome model
PDC	Proportion of days covered
PRO	Patient-reported outcomes
PROMs	Patient-reported outcome measures
RCD	The Registry of Causes of Death
SF-12	The Short Form-12
SD	Standard deviation
SBP	Systolic blood pressure
US	United States
WHO	The World Health Organization

Contents

1. Introduction

Heart failure (HF) is a serious condition with a poor prognosis and a high risk of adverse outcomes, affecting more than 37 million people worldwide [1-3]. The prevalence of HF in the developed countries is between 1% and 2% of the population, increasing with advanced age [2]. Accordingly, due to an ageing population, an increasing comorbidity burden, improved treatment strategies and survival of HF, the prevalence of HF is expected to increase over the next decades [1, 4-6].

The incidence of HF is estimated to be on a constant level or slightly decreasing. A cohort study from the UK found a seven percent decrease over a 12-year period in age and sex standardised models [7]. A Danish nationwide register-based study of trends in the incidence of HF in the past two decades found the incidence of HF declining in individuals >50 years of age, but increasing in patients below the age of 50 years, together with an increasing trend in cardiovascular comorbid conditions [8].

HF is a growing burden to the healthcare system and related costs, and initiatives to identify risk factors for a poor prognosis and to enhance quality of life is therefore warranted [5, 9]

1.1 Definition of heart failure

HF is defined as a clinical syndrome, and the diagnosis is established by diagnostic tests following criteria issued by the European Society of Cardiology (ESC) [2]. Establishing the underlying cause of the HF is essential to target treatment, including pharmaceutical treatment and potentially surgical interventions [2]. HF can present acutely in relation to, e.g., acute coronary syndrome or as a chronic condition, with increasing symptoms over time, as in dilatated cardiomyopathy, or secondary to another disease, e.g., in patients with pulmonary or renal disease. The HF diagnosis is based on symptoms, signs and structural and/or functional cardiac abnormalities [2].

Symptoms of HF include typical symptoms of orthopnoea, nocturnal dyspnoea, fatigue and ankle swelling and signs include e.g. pulmonary crackles, peripheral oedema and jugular venous pressure due to a structural or functional cardiac abnormality, leading to a reduced cardiac output [2].

The left ventricular ejection fraction (LVEF) is most often determined by echocardiography and is a measure of cardiac function. It is essential to differentiate the patients by the LVEF because of choice of treatment strategy. A patient with HF can have a normal LVEF ≥50%, and in this case has HF with preserved LVEF (HFpEF). Patients with an LVEF of 40-49% is defined as a mid-range LVEF (HFmEF), and patients with an LVEF <40% are referred to as patients with reduced LVEF (HFrEF) [2].

To be diagnosed with HFrEF the patient must fulfil the criteria of having an LVEF <40% together with symptoms or signs of HF. To be diagnosed with HFmEF or HFpEF the patient must present symptoms or signs of HF, elevated level of natriuretic peptides together with either relevant structural heart disease and/or diastolic dysfunction. HFmEF is then distinguished from HFpEF by the additional LVEF [2]. However, in randomised controlled trials of HF medication a cut-off for the LVEF of ≤40% was used[10-12].

1.2 Patient-reported outcome measures

Patient-reported outcome measures (PROMs) are measurements of subjective health, reported by the patient. In general, it assesses mental and physical health, symptom burden, health-related quality of life and illness perception and quantifies the impact a disease has on every-day life and leisure activities [13-17]. The US Food and Drug Administration has more explicitly defined PROMs as: "A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" [18].
PROMs have been developed to use in research, but are also broadly used for many other purposes: surveillance of population health, to measure individual health to target treatment and care, to evaluate quality of care and as indicators for evaluating new interventions [14, 15].
The interest in PROMs has increased during the past decades, as the use of PROMs has emerged, not only for assessment of patient outcomes in research studies and in routine clinical settings, but also as a tool for healthcare stakeholders to evaluate whether healthcare costs are reflected in better healthcare [19].

1.2.1 Patient-reported outcome measures in heart failure

An increasing understanding of PROMs in cardiovascular research and HF care has emerged. This is underlined in a 2019 editorial in J AmColl Cardiol HF, where the potential for using PROMs in HF is emphasised [20]. Here it is argued that using PROMs adds information on severity of HF and that PROMs can be used as quality indicators in HF treatment and to improve care [20].
The American Heart Association has stated that improvement of cardiovascular care, is a strategic goal to enhance cardiovascular health [13]. One important factor is patient-reported health, since it is associated with subsequent course of the disease. Measuring health status potentially enables targeted care and optimise resources in healthcare [13].

Likewise, the ESC has recently stated that there is a need to use PROMs in cardiovascular research [19]. According to this statement the purpose is multifaceted and can be used to measure health status and as a quality indicator, but also in clinical trials as an end point of adverse outcomes. Further, the ESC positions that the ESC can facilitate this by encouraging to implement PROMs in all cardiovascular trials and registries [19].

1.3 Heart failure and course of disease

HF is associated with a high risk of mortality, and 5-year mortality rates can be compared with mortality rates for many cancers [21]. Knowledge regarding morbidity and mortality can guide in the decision-making of care and is often estimated in different studies and settings.

The economic burden of HF is growing and despite improved treatment and subsequent better survival, the mortality of HF remains high. Worldwide, 17-45% of patients with HF die within one year and between 50-80% die within five years after an HF hospitalisation [9].

The ESC-HF pilot study, an observational, multicentre study including 5,118 patients with HF in 12 European countries, found a 12-month all-cause mortality rate of 17% for hospitalised patients and a hospitalisation rate of 44%. In the stable/ambulatory patients, the 12-months mortality rate was 7% and the hospitalisation rate was 32%. The study also demonstrated that cardiovascular causes of death accounted for the majority of deaths [22].

One Danish population-based nationwide register-based study of 30-year trends in mortality, including slightly more than 300,000 patients with a first-time hospital HF diagnosis, found a one-year mortality in the period of 2008-2012 of 33% and a five-year mortality of 43%. Over the entire period from 1983-2012, the five-year mortality-rate decreased by >40% and standardised hospitalisation rates decreased in the period, with the lowest rate for individuals below 60 years of age and in women [23].

1.4 Heart failure and HF medication

Pharmacological treatment is essential to reduce mortality and HF hospitalisation and to enhance functional ability in patients with HF with reduced LVEF according to the Guidelines for HF medication issued by the ESC [2]. The evidence-based key HF medications include angiotensin-converting enzyme inhibitors (ACEI), β-blockers and mineralocorticoid receptor antagonists (MRAs) [2]. In several double-blind, randomised clinical trials (RCT), these drugs have been validated and recommended as cornerstones in HF treatment.

ACEI are recommended as standard therapy in HF and reduce mortality in patients with HFrEF [2]. In patients intolerant to the ACEI, the angiotensin II receptor blocker (ARB) is recommended based on findings in the CHARM-alternative trial of CV mortality supported by another large trial, demonstrating lower incident mortality and HF hospitalisations [2, 10, 24]. In 2016 the Angiotensin receptor neprilysin inhibitor was introduced as a substitute to ACEI/ARB in patients with symptomatic HF despite full up-titration of these drugs, and is now recommended by the ESC [2, 12]. β-blockers are also the ESC recommended standard HF medication. β-blockers have been shown to significantly reduce all-cause mortality and risk of sudden death and CV hospitalisations in placebo-controlled clinical trials [2].

Finally, to reduce mortality and HF hospitalisations, MRAs are recommended by the ESC as standard HF medication therapy in patients with symptomatic HF with an LVEF ≤ 35%, despite optimal treatment with ACEI and β-blockers. The recommendations of eplerenone and spironolactone are based on results from two large placebo-controlled trials [2, 25, 26].

1.4.1 Heart failure and medication adherence

According to numerous trials, it is evident that the ACEI, the β-blocker and the MRAs are associated with lower risk of death and hospitalisation in patients with HF [10-12, 24-33]. They are recommended as standard HF medication including target dosages in clinical guidelines issued by the ESC [34]. It is evident that adherence to HF medication is essential to improve the course of the disease. In recent years, there has been an increased attention towards factors related to medication adherence in HF, particularly modifiable factors with impact on the course of the disease and the economic healthcare burden [35].

The World Health Organization (WHO) proposes five dimensions for which to account in the assessment and interventions of adherence to long-term therapies: social- and economic-related factors, health system/health care team-related factors, therapy-related factors, condition-related factors and patient-related factors [36]. In HF research, these dimensions are also overall depicted as important in patients with HF [35, 37]. Medication adherence was operationalised according to these dimensions. Inspired by the framework provided by the WHO, Table 1 provides an illustration of factors potentially affecting medication adherence in HF [36].

The term medication *adherence* is used in contrast to *compliance*. Adherence refers to the level of concordance of the agreements between the patient and physician using shared decision-making. In adherence is imbedded an active involvement of the patient and decision-making by the patient to

adhere to the medication agreed. Compliance refers to a more passive role of the patient and expresses the degree of concordance to recommended medication without patient agreement [38]. Medication adherence in patients with HF has been examined in several studies, using different cut-off values for measuring adherence, data sources, type of HF medicine, setting and follow-up time. The literature demonstrates that adherence typically ranges from approximately 65%-89% [39-41].
A study from the United States of regional variance in adherence to HF medication in a random sample of Medicare beneficiaries found that patients using either an ACEI, ARB or diuretics were classified with good adherence in 52%, ranging from 37%-71% depending on regional area [42]. A Danish cohort study from 2007 investigated maintenance doses with HF medication after first-time hospitalisation for HF during a five-year observation period the authors found that on average 43.1% of the patients redeemed at least one prescription for ACEI, in β-blockers 27.2%, and in MRAs every fifth patient redeemed at least one prescription [43]. However in the last year of the observation period, the percentage of patients redeeming at least one prescription after discharge were 49.1% in ACEI, 42.7% in β-blockers and 24.9% in MRAs [43]. A recent Danish cohort study of patients with systolic HF initiating HF medication in an HF clinic found a high three-year adherence in ACEI of 90%, β-blockers of 88% and MRAs of 74%, using register-based follow-up data on redeemed prescriptions [44].
The consequences of non-adherence are reflected in the course of the disease and have been found associated with risk of CV events, emergency department visits, hospitalisation and mortality in several studies, using different assessment methods, statistical analyses, population sizes and follow-up time [45-47].

Table 1. Overview of factors associated with medication adherence, inspired by the dimensions provided by the World Health Organization [36]				
Patient-related factors	**Condition-related factors**	**Therapy-related factors**	**Healthcare team/ system-related factors**	**Social and socioeconomic factors**
• Age [48, 49] • Sex [50, 51] • Patient education [48, 52] • Reading ability [46] • Beliefs [53] • Patient routine [54] • Patient knowledge [53, 55]	• Comorbidity [50] • Dialysis [56] • Depression [57] • Progression and severity [43] • Cognitive dysfunction [58] • Excessive daytime sleepiness [59]	• Frequency of pill regimens [54, 58, 60] • Difficulty in lifestyle changes [48] • Side-effects [60]	• Patient-physician relationship [60] • Reimbursement costs [61] • Accessibility of treatment [55] • Type of contact [48]	• Social support [62] • Marital status [63] • Educational level [64] • Ethnicity [56, 62] • Financial situation [62] • Drug co-payment [61] • Health literacy [65] • Health insurance [66] • Income [67]

1.5 Literature review

The aim was to study the association between patient-related predictors and PROMs, and the association between PROMs and subsequent medication adherence, CV events and mortality in patients with HF. A literature search on the three studies was conducted to assess the existing research in each of the three studies.

PubMed and Scopus were searched, using both a free-text search and the PICO (Patient-Intervention-Comparison-Outcome) model to structure the search. Mail notifications with new potentially relevant literature were used from August 2016. The literature search was performed during January-February 2016, repeated in January-February 2017 and May-June 2018. Further, a search was performed for the substudy II and III in July 2019. Because the free-text search resulted in too many hits, a Medical Subject Headings search was used. The PICO model was followed to ensure a systematic search strategy. Studies published before 1995 were excluded and studies in languages other than English, Swedish, Norwegian and Danish. The search was restricted to observational studies, clinical studies and trials, meta-analyses, literature reviews, government reports and public health reports. Finally, statements and clinical reports from societies in cardiology were included. All relevant papers were selected by title and abstracts. A summary of the literature is presented in Tables 2 and 4.

1.5.1 Study I

A total of seven studies were identified in relation to patient-related predictors of PROMs in patients with HF (Table 2). Research in this area was to a large extent characterised by findings in relation to other research questions, though one Spanish study, by Comín-Colet et al, investigated a range of patient characteristics in relation to health-related quality of life [68]. The remaining six studies were from Sweden and Denmark, and all studies except one focused on patients with HF and included in- and outpatients in study populations between 349-10,575 patients with HF [69-73]. One large study by Hansen et al, on supportive relatives in relation to symptoms of anxiety and depression in 2,496 patients, including both patients with ischemic heart disease, atrial fibrillation, heart valve disease and HF [74].

According to Table 2, the literature on PROMs in HF research has indicated that patient-related predictors such as age, sex, LVEF and comorbid diseases, are associated with mental and physical health. However, the research has to a limited extent addressed patient-related predictors of PROMs in patients with HF in relation to discharge from a cardiac hospitalisation. Due to lack of knowledge

on patient-related predictors of PROMs in patients with HF, the evidence on how PROMs can be utilised and incorporated in clinical care is also lacking.

The aim of study I was to identify patient-related predictors associated with PROMS reflecting mental and physical health, health-related quality of life, burden of symptoms and illness perception in a cohort of patients with HF at discharge from a cardiac hospitalisation.

Table 2. Summary of the literature in study I			
Study I – Patient-related predictors of PROMs			
Author, journal, year	**Design, setting, registries, observation period**	**Population, exposure, outcome**	**Results**
Comín-Colet et al. [68] - Rev Esp Cardiol - 2016	- Cross-sectional - Spain (multicenter) - 2011-2012	- HF outpatients (n=1,037) - Health-related quality of life (EQ-5D) - Clinical factors associated with HRQoL	Poor EQ-5D in adjusted analyses (being older, β = -0.2) (female, β = -10.3) (having worse functional class, = -20.4) (CCI, β = -1.2) (recent hospitalisation for HF, β = 6.28)
Berg et al. [69] - Value Health - 2015	- Cohort study - Sweden (multicenter) - 2008-2010	- HF inpatient or outpatient (n=5,334) - Health-related quality of life (EQ-5D) - Determinants of utility in HF and drivers of change	Determinants of utility at inclusion was affected by (p-value <0.05): sex (female), age (categorised), NYHA (in classes), LVEF (categorised), haemoglobin, SBP, lung disease, diabetes, ACEI/ARB, nitrates, antiplatelets, and diuretics
Franzén et al. [70] Eur J Cardiovasc Nurs 2007	- Cross sectional survey - Sweden (one county council) - 1999-2001	- HF patients (n=357) - Health-related quality of life (SF-12) - Patient demographics as predictors of HRQoL	In adjusted linear regression analysis: Age, ≥80 years: (β -1.837, 95% CI: -3.459 − -0.215) Sex, women: (β -2.016 95% CI: -3.622 − -0.410) Diabetes: (β -2.495, 95% CI: -4.421− -0.570) Respiratory diseases: (β 2.877, 95% CI: -4.784 − -0.969)
Lawson et al. [71] PLoS Med 2018	- Cross sectional survey (multicenter) - Sweden - 2008-2013	- HF patients (n= 10,575) - Health-related quality of life EQ-5D and EQ-VAS - Impact of symptoms, functional limitations and comorbidity on health-related quality of life	In adjusted sequences of regression analyses: Associations between CV-comorbidities and patient-rated health were explained by their associations with anxiety, depression or pain. Associations between non-CV comorbidity and patient-rated health were explained by SOB and fatigue. Affecting patient-rated health: increased age, being single, duration of HF, higher heart rate, use of diuretic, inpatient, DM, having symptoms and functional limitations
Hansen et al. [74] Eur J Cardiovasc Nurs 2017	- Cross-sectional study (multicenter) - Denmark - 2014	- IHD, AF, HF and heart valve patients (n=2,496) - Supportive relatives (high vs. low and some) - Anxiety and depression (HADS) (anxiety/depression = ≥8 points)	In multiple logistic regression analyses: Odds of anxiety in low or some degree of supportive relatives: (OR 2.20, 95% CI: 1.28–2.37 and OR 1.75, 95% CI: 1.57–3.08, respectively).

			Odds of depression in low or some degree of supportive relatives (OR 1.96, 95% CI: 1.40–2.66 and OR 1.93, 95% CI: 1.37–2.60, respectively)
Årestedt et al. [72] Eur J Cardiovasc Nurs 2013	- Cross-sectional study (one county council) - Sweden	- HF patients (n=349) - Different aspects of social support - Patient demographics and health-related quality of life (SF-12)	Demographics negatively associated with social support in adjusted analyses: Being male, living alone, perception of problematic situation, high disease severity (NYHA class) SF-12 MCS in adjusted analysis: Availability of Social Integration: (β 1.50 (0.32)) Adequacy of Social Integration: (β 1.42 (0.29)) Adequacy of Attachment: (β 1.02 (0.23)) Availability of Attachment: (β 1.19 (0.40))
Chamberlain et al. [73] J Am Heart Assoc. 2014	-Cohort study - US (one community) -2007-2010	Community HF patients (n=417) -Health-related quality of life (SF-12) (PCS score ≤25) - Patient-centered factors associated with prognosis	In adjusted logistic regression analyses: Low self-rated physical functioning and risk of hospitalisation (HR: 1.52, 95% CI:1.17 to 1.99) Low self-rated physical functioning and risk of ED visits (HR: 1.48, 95% CI: 1.04 to 2.11) Analyses of difference in baseline chracteristics between low and moderate/high physical functioning (unadjusted): Low self-reported physical functioning associated with higher comorbidity (CCI) (p <0.0001), diabetes (p=0.005), estimated GFR, mL/min per 1.73 m2 (p=0.04) and Body mass index, kg/m2 (p=0.033)

Abbreviations: EuroQoL-Five-Dimensional Questionnaire, EQ-5D; HRQoL, Health-Related Quality of Life; β, Beta-Coefficient; CI, Confidence Interval; CCI, Charlson Comorbidity Index; p-value, significance level; HF, Hazard Ratio; NYHA, New York Heart Association; LVEF, Left Ventricular Ejection Fraction; SBP, Systolic Blood Pressure; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; EQ-VAS, EuroQol visual analogue scale; CV, Cardiovascular; SOB, Shortness of Breath; DM, diabetes mellitus; IHD, Ischemic Heart Disease; AF, Atrial Fibrillation; HADS, the Hospital Anxiety and Depression Scale; OR, Odds Ratio; SF-12 MCS, the Short Form-12 mental component score; PDC, Proportion of Days Covered; KCCQ, The Kansas City Cardiomyopathy Questionnaire; BAAS, Basel Assessment of Adherence Scale; MEMS, Medication Event Monitoring System; PHQ-9, Patient Health Questionnaire; CHARM, the Candesartan in Heart Failure Assessment of Mortality and Morbidity Programme; ACS, Acute Coronary Syndrome; HADS-A, the Hospital Anxiety and Depression Scale, anxiety subscale; PROMs, Patient-Reported Outcome Measures; I^2, Heterogeneity; HADS-D, the Hospital Anxiety and Depression Scale, Depression Subscale; CVD, Cardiovascular Disease; COACH, Coordinating study evaluating Outcomes of Advising and Counselling in HF patients; CES, the Centre for Epidemiological Studies Depression Scale; ASCEND-HF, The global Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure; MI, Myocardial Infarction; IHF, Ischemic Heart Disease; AP, Angina Pectoris

Search-query:

Study I: "heart failure"[MeSH Terms] OR "heart patient*" OR "congestive heart failure" OR "cardiac insufficiency" AND "patient-related predictors" OR "patient characteristics" OR "demographic*" OR "patient factors" AND (combined with all PROMs stepwise using the following terms): "SF-12" OR "short form-12"; "BIPQ"OR "brief IPQ" OR "Brief Illness Perception Questionnaires"; "Hospital Anxiety and Depression Scale" OR "HADS"; "HeartQoL" OR "health-related quality of life [limits adults +19 years]"; "Edmonton Symptom Assessment Scale" OR "ESAS"; "euroqol eq-5d" OR "eq-5d" OR "euroqol". Additional search included the following terms: "cardiac patients", "health-related quality of life", "depression" [MeSH Terms].

1.5.2 Study II

In all, eight studies were identified in relation to medication adherence in HF. The studies were based on either multinational populations, US or Danish populations (Table 3). Three of these were included based on methods of assessing medication adherence or factors associated with medication adherence in populations ranging from 557-107,092 patients with HF [43, 50, 75]. The remaining five studies investigated health status, anxiety or depression in relation to medication adherence in patients with HF. One study was a systematic review of 11 studies on medication adherence, where three studies assessed depression in relation to medication adherence and one was a meta-analysis of 38 studies of anxiety and mediation adherence [48, 76]. Finally, three cohort studies on PROMs and medication adherence were identified in populations ranging from 134-522 in- or outpatients with HF or cardiac disease in general [77-79].

There is substantial evidence that adherence to evidence-based HF medication is associated with lower risk of adverse events and improved survival in patients with HF [34]. In contrast, medication non-adherence leads to decline in physical capacity, exacerbation of HF, hospitalisation, death and increased healthcare expenses [43, 75, 80]. Research has shown several factors associated with HF medication non-adherence and includes age, sex, side-affects, comprehension regarding medication-regime and patients health status [48, 77].

According to Table 3, only a few studies have demonstrated anxiety and depression associated with medication non-adherence, though often in smaller populations, but PROMs have not been investigated thoroughly in HF using different domains of physical and mental health [78, 81]. The aim of study II was to address whether mental and physical health is associated with subsequent risk of HF medication non-adherence, since this would be valuable information and increase the potential for offering individualised targeted healthcare.

Table 3. Summary of the literature in study II			
Study II – PROMs and risk of HF medication non-adherence			
Fitzgerald et al. [75] J Card Fail 2011	- Cohort study - US - 2001-2006	- HF patients (n=557) - HF medication non-adherence (<80% PDC in ACEI/ARB/β-blockers/MRAs) - All-cause mortality, CV hospitalisations, HF hospitalisations	In adjusted Cox regression: All-cause mortality (HR 2.99, 95% CI: 2.09 - 4.29) CV hospitalisation (HR 1.86, 95% CI: 1.22 - 2.83) HF hospitalisation (HR 1.81, 95% CI: 1.26 - 2.60)
Gislason et al. [43] Circulation 2007	- Cohort study - Denmark (multicenter) - 1995-2004	- HF patients (n=107,092) - HF medication adherence (Break in Treatment >90 Days) - Mortality	Mortality in adjusted Cox regression: ACEI/ARB: (HR 1.37, 95% CI: 1.31 to 1.42) B-blocker: (HR 1.25, 95% CI: 1.19 to 1.32) Statins (HR 1.88, 95% CI: 1.67 to 2.12)
Morgan et al. [77] J Card Fail 2006	- Cross sectional Study - US (multicenter) - 2001-2002	- HF outpatients (n= 522) - Patient-reported difficulty taking medications as directed (5-level Likert-scale question) - Health status (KCCQ)	In adjusted analysis: Lower health status associated to difficulty in medication (8.0 ± 3.2 point lower KCCQ scores)
Oosterom-Calo et al. [48] Heart Fail Rev 2013	- Systematic review	- Refer to individual studies (n=11 studies) - Best evidence synthesis to give directions for future HF medication adherence interventions	Three studies on depression
Tang et al. [78] Clin Nurs Res 2014	-Cohort study - US (3 centres) - 2007-2010	- HF outpatients (n=244) - Self-reported adherence (BAAS) - medication adherence (MEMS, non-adherence <80%) - PHQ-9 ≥ 5	In adjusted analysis: Difference between patients being depressed and nondepressed in self-reported medication nonadherence (p = 0.008) Self-reported medication non-adherence in depressed patients (OR 2.26, 95% CI: 1.26-4.07)
Granger et al. [50] Eur J Heart Fail 2009	- Cohort study - Multinational - 1999-2001	- HF patients (n=7,599) from the CHARM - Percentage of blinded study pills taken as prescribed (adherence > 80%) - Patient demographics associated with adherence - Mortality	Adherence: females (87.9%): men (89.8%) In adjusted analysis: All-cause mortality in women (HR 0.77, 95% CI: 0.69–0.86) Not associated with adherence: Age, smoking status, severity of HF, number prescribed medications
Bauer et al. [79] Am J Cardiol 2012	- Cohort study (secondary analyses of RCT data)	- Cardiac patients (ACS, decompensated HF, arrhythmia) (n=134) - Depression (PHQ-9 score) - Anxiety (HADS-A)	In adjusted regression analysis: Association between improved anxiety and adherence after 6 weeks (β 0.16. 95% CI: 0.04–0.30)

	- US (singlecenter) - 2007-2009	- Self-reported adherence to health behaviours (including medication)	No associations after 6 weeks.
Easton et al. [76] J Cardiovasc Nurs 2016	- Meta-analysis of 38 studies	- HF in- and outpatients - Anxiety (PROMs include also HADS) - Pooled prevalence	Overall random effects pooled prevalence of 32% (95% CI: 26.5%-37.6%) High heterogeneity (I^2 >0.80)

Abbreviations: EuroQoL-Five-Dimensional Questionnaire, EQ-5D; HRQoL, Health-Related Quality of Life; β, Beta-Coefficient; CI, Confidence Interval; CCI, Charlson Comorbidity Index; p-value, significance level; HF, Hazard Ratio; NYHA, New York Heart Association; LVEF, Left Ventricular Ejection Fraction; SBP, Systolic Blood Pressure; ACEI/ARB, angiotensin-converting enzyme inhibitor /angiotensin II receptor blocker; EQ-VAS, EuroQol visual analogue scale; CV, Cardiovascular; SOB, Shortness of Breath; IHD, Ischemic Heart Disease; AF, Atrial Fibrillation; HADS, the Hospital Anxiety and Depression Scale; OR, Odds Ratio; SF-12 MCS, the Short Form-12 mental component score; PDC, Proportion of Days Covered; KCCQ, The Kansas City Cardiomyopathy Questionnaire; BAAS, Basel Assessment of Adherence Scale; MEMS, Medication Event Monitoring System; PHQ-9, Patient Health Questionnaire; CHARM, the Candesartan in Heart Failure Assessment of Mortality and Morbidity Programme; ACS, Acute Coronary Syndrome; HADS-A, the Hospital Anxiety and Depression Scale, anxiety subscale; PROMs, Patient-Reported Outcome Measures; I^2, Heterogeneity; HADS-D, the Hospital Anxiety and Depression Scale, Depression Subscale; CVD, Cardiovascular Disease; COACH, Coordinating study evaluating Outcomes of Advising and Counselling in HF patients; CES, the Centre for Epidemiological Studies Depression Scale; ASCEND-HF, The global Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure; MI, Myocardial Infarction; IHF, Ischemic Heart Disease; AP, Angina Pectoris

Search-query:

Study II: "heart failure"[MeSH Terms] OR "heart patient*" OR "congestive heart failure" OR "cardiac insufficiency" AND (combined with the three PROMs stepwise using the following terms): "Hospital Anxiety and Depression Scale" OR "HADS"; "HeartQoL" OR "health-related quality of life [limits adults +19 years]"; "euroqol eq-5d" OR "eq-5d" OR "euroqol" AND "Medication Adherence" [MeSH Terms], "Drug Therapy" [MeSH Terms], "adherence", "medication". Additional search included the following terms: "cardiac patients", "health-related quality of life", "depression" [MeSH Terms], "compliance".

1.5.3 Study III

The literature research in relation to study III resulted in ten identified studies investigating the association between PROMs and risk of adverse clinical events (Table 4).

A total of seven of these studies studied depression or health-related quality of life and risk of all-cause mortality in both minor and larger populations of HF patients or patients with cardiac disease, ranging from 111 patients to one study including 6,943 patients with HF in a post hoc analysis [82-88]. Research on the association between PROMs and risk of adverse clinical outcomes indicates that lower health-related quality of life, mental and physical health, is associated with increased risk of adverse cardiac events and mortality. Thus, comorbid depression has been found to be associated with higher mortality and lower health-related quality of life is found to be associated with risk of readmission [82-84, 87, 89]. However, research has often been carried out in mixed populations of patients with heart disease, in older populations or in small populations, where control for potential confounding factors is insufficient [83, 84, 87]. To use PROMs as an integrated tool in health service delivery in patients with HF, it is imperative to understand the relation between PROMs and clinical outcomes and the interplay between PROMs and severity of HF. Thus, to assess the potential of using PROMs, study III aimed to investigate the association between PROMs and risk of adverse outcomes in patients with HF. Addressing this in a large population of patients with well-defined HF at discharge from a cardiac hospitalisation and combining self-reported, register-based and clinical data, offers potential for incorporating PROMs as a screening tool and in risk-assessment with the purpose of offering differentiated treatment and care.

Table 4. Summary of the literature in study III			
Study III – PROMs and risk mortality and CV events			
Sokoreli et al. [82] In J Cardiol 2016	-Cohort study -UK (2 centres) -2012-2015	- HF patients (n=242) - HADS-D (≥8 points points) - All-cause mortality	In adjusted analyses: Moderate/severe depression (HR 2.97, 95% CI:1.26-6.99)
Junger et al. [83] - Eur J Heart Fail - 2005	- Cohort study - Germany (singlecenter) - 1996-1999	- HF outpatients (n=209) - Depression (HADS) - Mortality	All-cause mortality in adjusted analysis (HR 1.08. 95% CI: 1.01-1.15)
Volz et al. [84] J Behav Med 2011	- Cohort study -Switzerland (singlecenter) - 2004-2008	- HF outpatients (n=111) - Depression (HADS) (depression: ≤7 vs. >7) (moderate: ≤10 vs. >10) - Anxiety (HADS) (anxiety: ≤7 vs. >7) (moderate anxiety: ≤10 vs. >10). - Mortality - Readmission	Mortality: (depression: HR 0.89, 95% CI: 0.23-4.40) (moderate depression: HR 0.65, 95% CI: 0.08–5.17) (anxiety: HR 0.92, 95% CI: 0.24–3.57) (moderate anxiety: HR, 1.75, 95% CI: 0.37–8.21) Readmission: (depression: HR 1.37, 95% CI: 0.55–3.37) (moderate depression: HR 1.64, 95% CI: 0.48–5.56) (anxiety: HR 1.06, 95% CI: 0.41–2.75) (moderate anxiety: HR, 3.21, 95% CI: 1.04–9.93)
Watkins et al. [87] J Am Heart Assoc 2013	-Cohort study -US (singlecenter)	- CVD in- and outpatients (n=934) - HADS (≥8 points) - All-cause mortality	Anxiety and all-cause mortality in adjusted analysis (HR, 2.27, 95% CI: 1.55 to 3.33) Depression and all-cause mortality in adjusted analysis (HR, 2.18; 95% CI, 1.47 to 3.22) Anxiety and depression in model: All-cause mortality (anxiety, HR, 1.83, 95% CI: 1.18 to 2.83) (depression, HR, 1.66, 95% CI: 1.06 to 2.58) Anxiety and depression vs no disorder and all-cause mortality: (HR, 3.10, 95% CI: 1.95 to 4.94)
Johansson et al. [85] Eur J Heart Fail 2011	- cohort study -Dutch (multicenter) -2002-2005	- HF patients (n= 958) from the COACH - Depressive symptoms (CES-D ≥ 16) - Duration of delay between onset of symptoms of worsening HF and hospitalisation	Delay in adjusted analysis (OR 1.45, 95% CI: 1.1-1.9)
Sokoreli et al. - Heart Fail Rev - 2016	- Meta-analysis of 26 studies	- Report from individual studies on anxiety and depression in HF - Pooled estimates (random effect meta-analysis)	Depression and adjusted all-cause mortality (HR 1.40, 955 CI:1.22-1.60)

Rutlegde et al. - JACC - 2006	- Meta-analysis of 8 studies	- Report from individual studies on depression in HF - Pooled estimates	Depression and mortality and cardiac events (HR 2.1, 95% CI: 1.71-2.58)
Fan et al. - Prev Med - 2014	- Meta-analysis of 9 studies	- Report from individual studies on depression in HF - Pooled estimates	Adjusted all-cause mortality (HR 1.51, 95% CI: 1.19-1.91) Adjusted all-cause mortality (severe depression, HR 1.98, 95% CI: 1.23-3.19) Adjusted CV mortality (HR 2.19, 95% CI: 1.46-3.29)
Ambrosy et al. [86] Eur J Heart Fail 2016	- Cohort study - Multinational - 2007-2010	- HF patients (n=6943) from ASCEND-HF (posthoc analysis) - Health-related quality of life (EuroQoL-5D) (baseline and discharge) - All-cause death or HF rehospitalisation	Adjusted all-cause death/HF rehospitalisation: (by baseline EQ-5D score: OR 1.04, 95% CI: 1.01-1.07) (by discharge EQ-5D score: OR 1.10, 95% CI: 1.05–1.15) Adjusted cardiac death or cardiac rehospitalisation: (by baseline EQ-5D score: OR 1.03, 95% CI: 1.00–1.06) Adjusted mortality: By discharge EQ-5D score: HR 1.13, 95% CI: 1.09–1.18)
Hansen et al. [88] Eur J Prev Cardiol 2015	-Cohort study - Denmark (2 centres) - 2005	- Cardiac patients (n= 662) (MI, IHD, AP) - health-related quality of life - HeartQoL (global, physical, emotional) - All-cause mortality and cardiac readmissions	Adjusted all-cause mortality: (global hql: HR 1.67, 95% CI: 1.26–2.23) and (physical hql HR 1.71, 1.33–2.21) Adjusted readmission: (global hql HR 1.73, 1.41– 2.12) and (physical hql HR 1.63, 1.35–1.96)

Abbreviations: EuroQoL-Five-Dimensional Questionnaire, EQ-5D; HRQoL, Health-Related Quality of Life; β, Beta-Coefficient; CI, Confidence Interval; CCI, Charlson Comorbidity Index; p-value, significance level; HF, Hazard Ratio; NYHA, New York Heart Association; LVEF, Left Ventricular Ejection Fraction; SBP, Systolic Blood Pressure; ACEI/ARB, angiotensin-converting enzyme inhibitor /angiotensin II receptor blocker; EQ-VAS, EuroQol visual analogue scale; CV, Cardiovascular; SOB, Shortness of Breath; IHD, Ischemic Heart Disease; AF, Atrial Fibrillation; HADS, the Hospital Anxiety and Depression Scale; OR, Odds Ratio; SF-12 MCS, the Short Form-12 mental component score; PDC, Proportion of Days Covered; KCCQ, The Kansas City Cardiomyopathy Questionnaire; BAAS, Basel Assessment of Adherence Scale; MEMS, Medication Event Monitoring System; PHQ-9, Patient Health Questionnaire; CHARM, the Candesartan in Heart Failure Assessment of Mortality and Morbidity Programme; ACS, Acute Coronary Syndrome; HADS-A, the Hospital Anxiety and Depression Scale, anxiety subscale; PROMs, Patient-Reported Outcome Measures; I^2, Heterogeneity; HADS-D, the Hospital Anxiety and Depression Scale, Depression Subscale; CVD, Cardiovascular Disease; COACH, Coordinating study evaluating Outcomes of Advising and Counselling in HF patients; CES, the Centre for Epidemiological Studies Depression Scale; ASCEND-HF, The global Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure; MI, Myocardial Infarction; IHF, Ischemic Heart Disease; AP, Angina Pectoris

Search-query:

Study III: "heart failure"[MeSH Terms] OR "heart patient*" OR "congestive heart failure" OR "cardiac insufficiency" AND (combined with the three PROMs stepwise using the following terms): "Hospital Anxiety and Depression Scale" OR "HADS"; "HeartQoL" OR "health-related quality of life [limits adults +19 years]"; "euroqol eq-5d" OR "eq-5d" OR "euroqol" AND "Hospital mortality" [MeSH Terms] OR "Mortality" [MeSH Terms], "cardiovascular" OR "Cardiovascular event" OR "Patient readmission" [MeSH Terms], OR "Hospitalization" [MeSH Terms] OR "hospital readmission", "adverse events". Additional search included the following terms: "cardiac patients", "health-related quality of life", "depression" [MeSH Terms].

1.6 Aim of the thesis

PROMs have been used widely in research, in quality improvement projects and as a screening tool in different healthcare settings across patient groups and settings. However, in-depth studies on the association between PROMs assessed at the time of hospital discharge and the subsequent course of disease in patients with HF are warranted in order to evaluate the applicability of PROMs in clinical practice.

The aims of this thesis were:

- To identify patient-related predictors of PROMs reflecting both mental and physical health, symptom burden and illness perception in patients with HF.
- To study whether health-related quality of life and symptoms of anxiety and depression are associated with one- and three years HF medication adherence in patients with HF.
- To study whether health-related quality of life and symptoms of anxiety and depression are associated with one- and three years mortality, CV events and HF hospitalisation in patients with HF.

2. Methods

2.1 Setting

In Denmark healthcare is tax-financed and free and equal access to care at hospitals and general practitioners is ensured [90]. At birth each Danish citizen is assigned a unique and lifelong civil registration number to keep lifelong record of vital status and habitation [90]. This also enables individual-level linkage to all public registries using the civil registration number as key identifier [91].

Individuals having symptoms or signs of HF in primary care must be referred to a cardiology hospital setting to be diagnosed with relevant echocardiography, x-ray and blood samples. Patients admitted with incident HF are referred to follow-up in visits in outpatient HF clinics for up-titration in HF medication together with psychosocial and physical rehabilitation.

2.2 Data sources

Data on PROMs were used in combination with data from nationwide population-based public registries and medical records. The data sources are described below.

The DenHeart Survey

In 2013-2014, all patients discharged from a department of cardiology in one of the five tertiary heart centres in Denmark were invited to answer a questionnaire on PROMs and supplemental questions on lifestyle habits outside hospital at discharge. The DenHeart Survey included five generic and one disease-specific PROMs questionnaire on mental and physical health, health-related quality of life, symptom burden and illness perception [92].

Danish Civil Registration System

Since 1968, the Danish Civil Registration System (CRS) has kept records on vital status and other demographic key information such as name, date of birth, address and emigration on all Danish citizens using the civil registration number. Data in the registry is updated on a daily basis, and the civil registration number is recorded in every contact with the healthcare system and all other public authorities. This enables linkage to all public registries [90].

Danish National Patient Registry

In the Danish National Patient Registry (DNPR) each Danish somatic healthcare contact has been recorded since 1977 on inpatients and since 1995 on outpatients. In each contact information in relation to admission are recorded including: Date of hospitalisation and discharge, type of admission (acute/elective), procedures and surgical interventions. At discharge, all patients are given one primary discharge diagnosis and one or several secondary discharge diagnoses, indicating a primary cause of hospitalisation and one or more secondary reasons, e.g. secondary conditions or significant comorbidity. All diagnoses are classified according to the International Classification of Diseases, 10th Revision (ICD-10) codes [91]. Codes in relation to surgery are in accordance with the NOMESCO surgical codes [93].

Statistics Denmark registry on education, income and labour affiliation

Since 1980, Statistics Denmark has offered access to information regarding income, highest educational level and attachment to labour market on an individual level in annual updated registries [94-96].

Register of Medicinal Products Statistics

The Register of Medicinal Products Statistics (RMPS) has kept information on every redeemed prescribed drug at Danish pharmacies since 1994, including date of dispensing, Anatomical Therapeutic Chemical (ATC) code, strength and package size [97].

The Registry of Causes of Death

In the Registry of Causes of Death (RCD), all immediate and underlying causes of death have been collected for more than 100 years. Since 1994, the World Health Organization (WHO) International Classification 10th revision (ICD-10) codes were used to classify causes of death [98].

Medical records

In Denmark, all medical and nurse charts have been available for electronical use since the start of the 21st century and have replaced all records on paper. Each region in Denmark use different software providers and operator systems, but the purpose and applicability is the same. Here, all information from each hospitalisation or outpatient visit, including blood samples and medication,

is recorded and shared between departments and healthcare sectors within the region, though general practitioners have their own system.

2.3 Study designs

One cross-sectional study and two cohort studies were conducted. An overview of the three studies is provided in Table 5.

Table 5. Overview of aims, setting and methods

	Study I	Study II	Study III
Aim	Identify patient-related predictors of PROMs reflecting self-reported mental and physical health, health-related quality of life, symptoms of anxiety and depression, symptom burden and illness perception in patients with HF	To investigate the association between health-related quality of life, symptoms of anxiety and depression and medication adherence in patients with HF	To investigate the association between health-related quality of life, symptoms of anxiety and depression and subsequent risk of mortality, CV events and HF hospitalisations in patients with HF
Setting and study period	Nationwide: April 15, 2013 and April 15, 2014	Similar to study I	Similar to study I
Design	Cross-sectional study	Cohort study with one and three-year follow-up	Cohort study with one and three-year follow-up
Data sources	The DenHeart Survey, CRS, DNPR, Statistics Denmark on income and labour affiliation, medical records	The DenHeart Survey, CRS, DNPR, Statistics Denmark on income and labour affiliation, medical records, RMPS	The DenHeart Survey, CRS, DNPR, Statistics Denmark on income and labour affiliation, medical records, RMPS, RCD
Study population	Patients with HF at discharge in the study period	Similar to study I	Similar to study I
Exposure	Patient-related predictors: Age, sex, length of hospital stay, acute admission, incident HF, CCI, LVEF, SBP, BMI, smoking, alcohol intake, ≥ three HF drugs, device-related procedures, living alone, social support, educational level, household income and attachment to labour market	PROMs: The HADS, the EQ-5D and HeartQoL	Similar to substudy II
Outcome	PROMs: The SF-12, the HADS, the EQ-5D, the HeartQoL, the B-IPQ and the ESAS	Adherence to HF medication: ACEI/ARB/ARNI, β-blockers MRAs.	All-cause mortality, CV mortality, CV events and HF hospitalisation
Potential confounding factors	None	Age, sex, length of hospital stay, incident HF, CCI, LVEF, social support and SBP	Similar to substudy II
Statistics	Multivariable linear and logistic regression analyses Multiple chained imputations	Multivariable logistic regression analyses Multinomial regression analyses Multiple chained imputations	Cox proportional hazard regression analyses Cumulative incidence Multiple chained imputations
Stratified analysis	HF primary/secondary discharge diagnosis Non-responders/responders ANOVA to test mean PROM scores across hospitals	None	None
Sensitivity analysis	Regression analyses on non-imputed compared to imputed dataset to compare results using both strategies	Applying 14 grace days compared to 30 grace days between redeemed prescriptions to test robustness Regression analyses on non-imputed compared to imputed dataset to compare results using both strategies	Regression analyses on non-imputed compared to imputed dataset to compare results using both strategies

Abbreviations: CV, cardiovascular; CRS, the Civil Registration System; DNPR, the Danish National Patient Registry; RMPS, the Register of Medicinal Product Statistics; RCD, the Registry of Causes of Death; CCI, the Charlson Comorbidity Index; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; BMI, body mass index; HADS, the Hospital Anxiety and Depression Scale; EQ-5D, the EuroQol five-dimensional questionnaire; SF-12, Short Form-12, ESAS, the Edmonton Symptom Assessment Scale, B-IPQ, the Brief Illness Perception Questionnaire; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker, ARNI, angiotensin receptor neprilysin inhibitor

2.4 Study population

The study population in all three sub-studies consisted of patients with HF identified through the DenHeart Survey. Patients discharged from one of the five tertiary heart centres in Denmark in the study period were eligible for inclusion in the DenHeart Survey of PROMs [92]. Patients fulfilling one of the following criteria were excluded: age < 18 years, not having a Danish civil registration number, not being able to read or understand Danish language or patients suffering from severe illness, e.g. terminally ill or unconsciousness patients. All patients answering the PROMs at discharge from index hospitalisation, with incident or prevalent HF and HF as a primary or secondary discharge diagnoses (ICD-10 codes: I110, I13.0, I13.2, I42, I43, I50, I517 and R570), were eligible for inclusion in this study.

2.5 Exposures

In study I, patient-related predictors were considered the exposure of interest and PROMs the outcome (although the study was cross-sectional) and in study II and III PROMs were the exposures of interest.

2.5.1 Patient-related predictors

Patient-related predictors is a collective name of factors related to the patient and cover organisational/administrative information, patient demographics, socioeconomic factors and clinical factors. The understanding of the term patient-related predictors is used equally to the term patient-related characteristics. The organisational/administrative predictors include; length of hospital stay, type of hospital and procedures during hospitalisation; patient demographics cover age, sex, comorbidity, sociodemographic data and clinical factors; clinical disease-related factors LVEF, systolic blood pressure and body mass index.

A panel of potential patient-related predictors were chosen a priory. Information on age, length of stay in hospital, type of admission, incident/prevalent HF, device-related procedures and comorbidity was retrieved from the DNPR. Age was categorised in three categories: < 65 years (likely active workforce), 65-74 years (retired or early pensioners) and ≥ 75 years (old age pensioners) [99]. Length of stay in hospital included days in one of the five Heart Centres and CCI covered all recorded primary and secondary discharge diagnoses at any Danish hospital within the last ten years before the index hospitalisation. The Charlson Comorbidity Index (CCI) score was calculated as a weighted index based on all primary and secondary discharge diagnoses in- and

outpatients the past ten years leading up to index hospitalisation and categorised: no co-morbidity, moderate co-morbidity level and high co-morbidity level [100, 101]. Having a device-related procedure covered a pacemaker or an Implantable Cardioverter Defibrillator (ICD) – implantation or replacement during index hospitalisation.

From medical records, information on LVEF, systolic blood pressure (SBP) and pharmacological therapy at discharge was obtained from the index hospitalisation. In each heart centre, one person was assigned to collect data from medical records according to standardised data collection forms. All persons were peer to peer trained by the researcher to collect data and all persons had unlimited access to guidance by regular telephone conference meetings or by mail when in doubt about how to classify or interpret data from the medical records. In two of the three heart centres, the researcher participated in the entire data collection, by typing data in the electronical data collection instrument.

Information on LVEF was recorded as the last measured value and categorised in three categories (>40%, ≤40% - 26% and ≤25%). An LVEF >40% was chosen as reference, and ≤25% defined the group with most severe illness [28]. If echocardiography was not performed during the index hospitalisation, the last value was noted as valid if referred to as at a steady state from previous measures. SBP was the last measured SBP prior to discharge, and information on pharmacological therapy was retrieved from the medical records at the day of discharge from the index hospitalisation.

Use of HF medication was dichotomised into ≥ three drugs related to anticongestive treatment: ACEI/ARB, β-blockers-blockers, MRAs and diuretics.

From the DenHeart Survey, information on lifestyle habits and one single question to cover social support outside hospital was used: “Do you have somebody to talk to when you have problems or are in need of support?” and dichotomised the four response options into: “yes, often or mostly” versus “sometimes, almost never or never”. Smoking habits among active smokers were dichotomised at heavy smoker status (≥15 cigarettes per day) and alcohol intake at high risk intake (14 and 21 units in females and males per week, respectively), according to guidelines issued by The Danish Health Authority [102, 103]. Body mass index (BMI) was categorised according to issued guidelines from the World Health Organization [104]. Finally, data on education, income and labour market affiliation were retrieved from Statistics Denmark and covered the index year or previous years, depending on the availability of data.

2.5.2 Patient-reported outcome measures

In study II and III, three PROMs were used as exposures to study mental and physical health and symptoms of anxiety and depression in relation to subsequent medication adherence and course of disease, using both generic and disease-specific PROMs. Since the six PROMs were used as outcomes in study I, a comprehensive overview of all six PROMs is given in this section (Table 6).

In study I, the outcomes were PRO data from the following six PROMs: The Short Form-12 (SF-12), the HADS, the EQ-5D, the HeartQoL, the Brief Illness Perception Questionnaire (B-IPQ) and the Edmonton Symptom Assessment Scale (ESAS). The SF-12 is a generic instrument, validated to measure mental and physical health in medical patients in the past four weeks. A representative US norm population with a mean score of 50 (SD:10) were used as the reference value in the development of the Questionnaire [105].

The B-IPQ is a generic questionnaire assessing emotional and cognitive representations of illness. The ninth item is an open-ended question and left out of this study, resulting in a range of scores from 0-80. In three items, a reverse score is calculated, giving a higher score, reflecting a better illness perception in all eight items [106, 107]. The instrument is validated in a single study of patients with HF having an implantable cardioverter defibrillator unit (ICD) [108].

The ESAS is also a generic questionnaire, rating current physical and psychological symptoms on a visual scale. The scores range from 0-10 in each item, but the tenth item was left out in this study [109].

In study II and study III, the following three questionnaires were used as exposures: The Hospital Anxiety and Depression Scale (HADS), the EuroQol five-dimensional questionnaire (EQ-5D) and the HeartQoL (Table 6).

The HADS is a generic questionnaire, validated to assess symptoms of anxiety and depression within the last week in non-psychiatric medical patients [110-112]. One UK study from 2015 of normative data in patients from a general practitioner (n=6,198) reported median value scores for symptoms of anxiety of 6.0 in females and 5.0 in males and a median score of 3.0 for symptoms of depression in both males and females [113]. Also, a study using a representative population from the German population (n=4,410) from 2011 reported a mean anxiety score of 5.0 and 4.4 in females and males, respectively, and a mean depression score of 4.7 and 4.8 in females and males, respectively [114].

The generic EuroQol five-dimensional, five-level questionnaire (EQ-5D-5L) consists of a visual analogue scale (VAS) of self-rated current general health and five dimensions of health-related

quality of life (EQ-5D-5L). The EQ-5D is a validated questionnaire, often used in economic evaluations to inform politicians, using quality adjusted life year. The five-level version, where ceiling effect has been shown to be reduced compared to the three-level version, was used in this study [115-117]. According to the official webpage of the EuroQol Group, no normative data are yet published for the EQ-5D-5L [118].

The HeartQoL instrument is a validated, disease-specific measure of emotional and physical health-related quality of life in patients with heart disease covering the past four weeks. These scores can generate a global score, which was operationalised in this study [119, 120]. The HeartQoL has been developed based on three PROMs questionnaires, among these three, the Minnesota Living with Heart failure Questionnaire [119].

Table 6. Overview of included PROMs*

	Cover	Subscales	Range, points	Interpretation
The Short Form-12 (SF-12) [105]	Eight domains of self-reported mental and physical health within the past four weeks	Mental component score (MCS) Physical component score (PCS)	0-100	Higher score indicates better health
The Hospital and Depression Scale (HADS) [110-112]	14-item covers symptoms of anxiety and depression within one week	Anxiety subscale (HADS-A) Depression subscale (HADS-D)	0-21	Higher scores indicate symptoms of anxiety and depression
The EuroQol five-dimensional questionnaire (EQ-5D-5L) [115-117]	Five dimensions of current health-related quality of life.	None		Higher scores indicate better health Scores <0 indicate states worse than death
The HeartQoL [119, 120]	14-item, assesses health-related quality of life in patients with heart disease within the past four weeks	Emotional score (HeartQoL emotional, 4 items) Physical score (HeartQoL physical, 10 items) Global score (HeartQoL global)	0-3	Higher scores indicate better health
The Brief Illness Perception Questionnaire (B-IPQ) [106, 107]	9-item instrument, assesses current emotional and cognitive representations of illness (ninth item left out in this study)	None	0-80	Higher score represents lower illness perception (reverse score in three items)
The Edmonton Symptom Assessment Scale (ESAS) [109]	10-item instrument rating current physical and psychological symptoms on a visual numeric scale (tenth item left out in this study)	None	0-90	higher sum score indicates a higher symptom burden.

*All instruments are generic, except for the disease-specific HeartQoL

2.6 Outcomes

In study I, a panel of PRO data was the outcome, in study II the outcome was medication adherence, and in study III mortality and CV events were the outcomes.

2.6.1 Patient-reported outcomes

In study I, the outcomes was PRO data from the following six PROMs: The Short Form-12 (SF-12), the HADS, the EQ-5D, the HeartQoL, the Brief Illness Perception Questionnaire (B-IPQ) and the Edmonton Symptom Assessment Scale (ESAS). All six questionnaires regarding PROMs as exposure variables are covered in Table 6 for a complete overview.

2.6.2 Medication adherence

In study II, the outcome was medication adherence. Data on HF medication after discharge was retrieved from the RMPS [97]. All redeemed prescriptions were traced for ACEI/ARB/ARNI, β-blockers and MRAs using the ATC coding system. Substitution of pharmaceutical agent within group was allowed, but combination therapy (≥ two active drugs) was excluded. Medication adherence was assessed using two strategies: I) <80% of proportion of days covered (PDC) according to a gold standard and II) dispensing of HF medication across three periods. Having <80% of PDC defined non-adherence [47]. The gold standard for each patient was defined as follows: In patients alive ninety days after discharge from index hospitalisation, every first and second redeemed prescription was traced and the mean daily dose (MDD) estimated. A blanking period of 90 days after discharge from index hospitalisation was chosen, to allow breaks in medication, change of drug or up-titration in patients with incident HF. The MDD was calculated as the number of dispensed pills at redemption one, divided by number of days between redemption one and two and multiplied it with the strength of the dispensed pills.

2.6.3 Mortality, CV events and HF hospitalisations

In study III, the two primary outcomes were all-cause mortality and CV mortality, and secondary outcomes were CV events and HF hospitalisation.

Information on all-cause mortality was obtained from the CRS, and information on CV mortality was obtained from the RCD. Information on CV events and HF hospitalisations was retrieved from the DNPR. To identify all outcomes of interest, the primary and secondary discharge diagnoses were used. Only in HF hospitalisations the outcome was identified by primary discharge diagnoses

(appendix II). A first-time event following index hospitalisation defined the CV events of interest: Stroke, arrythmia, acute coronary syndrome, cardiac revascularisation, heart transplantation and HF hospitalisation.

2.7 Statistical analyses

Table 5 summarises the statistical analyses, and appendices (paper I-III) describe the statistical analyses in detail.

All PROMs were analysed using the continuous response scale and dichotomised, where a score in the worst quartile and in HADS ≥ 8 points defined the group of interest [110]. All domain scores of the PROMs were presented with mean (standard deviation (SD)).

In the cross-sectional study of patient-related predictors in PROMs (study I), index hospitalisation was hospital days in one of the five heart centres. In this study, a multivariable linear and logistic regression analyses was performed to examine the association between patient-related predictors and PROMs.

The medication adherence study and the mortality study (study II and III) were cohort studies with one- and three years of follow-up. Baseline was the day of discharge from index hospitalisation which also included any hospital days in patients transferred from a heart centre to another department or hospital.

In study II, a blanking period of 90 days was applied to the baseline date, to allow fluctuation in the use of HF medication. Patients dying during this period were excluded from further analyses. After this blanking period, all prescriptions were traced, and index day was the date of the second redeemed prescription. The PDC was estimated between every two redeemed prescriptions and applied thirty grace days between every two redeemed prescriptions, to account for short medication breaks. In the primary analyses of medication adherence, having <80% of PDC defined HF medication non-adherence [50, 56]. In the second analyses, the number of dispensed drugs was estimated (zero-three drugs). A multivariable logistic regression of the association between PROMs and having <80% of PDC (defining non-adherence) in one and three years was performed. Multinomial regression analyses of the association between PROMs and number of dispensed HF medication in three periods, each consisting of three months were also performed.

In study III, the Cox proportional hazard model was applied to analyse the association between mortality and CV events and PROMs in one and three-year follow-up. The patients were followed

until event, emigration or end of observation period. Patients were censored in the event of emigration or mortality in the analyses of CV events and HF hospitalisation.
To avoid immortal time bias, follow-up started at the day of discharge from the subsequent hospitalisation for patients with a new hospitalisation on the day of discharge from index hospitalisation.
Cumulative incidence hazards, using the Aalen-Johansen estimator, were computed in one- and three years of follow-up. In the analyses of CV events and HF hospitalisation, emigration and mortality were treated as competing events.
In regression analyses in study II and III, the EQ-5D and the HeartQoL scores were reversed, and a higher score indicated the worst state of self-reported health across all three PROMs.
In all regression models in study II and III, a panel of potential confounding factors were adjusted for. These factors were patient-related predictors, identified as associated with the PROMs in study I.
Multiple chained imputations were applied (Markow Chain Method), due to missing data. Assuming data to being missing at random (MAR), 50 datasets were imputed, using Rubins Rule [121-124]. All assumptions behind statistical tests in the three studies were tested before analysis.
All data from medical records were typed in the electronical data collection form Redcap. All statistical analyses were performed using Stata version 14.0 (StataCorp) on a server hosted by Statistics Denmark.

2.8 Sensitivity analyses

In study II, a sensitivity analysis was performed, applying 14 grace days compared to the 30 grace days in the main analysis, to assess robustness of the analysis.
In all three studies, sensitivity analyses of the imputed compared to the non-imputed datasets were performed to check the robustness of the analyses.

2.9 Ethics

The study was permitted by the DenHeart Steering Committee (DenHeart registered at ClinicalTrials.gov: NCT01926145). Using human study objects is in accordance with the 1964 Helsinki declaration or comparable ethical standards [125].
Observational studies do not require approval from an ethic committee according to Danish law. Approval was obtained from the Danish Data Protection Agency (no: 2012-58-006).

Patients gave written informed consent, and in addition access to medical records was authorised by the Danish Patient Safety Authority (no: 3-3013-1691).

3. Results

The main results of study I-III are presented in this section and in detail in appendices I-III.

3.1 Patient-related predictors of patient-reported outcomes in patients with HF (study I)

A total of 1,506 patients with an HF diagnosis were included in study I, and table 7 provides an overview of the study population and the potential confounding factors included in regression analyses with the purpose of identifying patient-related predictors of PROMs.

The main findings in study I were a consistent pattern between patient-related predictors and PROM scores across the six PROMs. Patients with a high comorbidity level and hospitalisation longer than two days were more likely to report a worse score in all PROMs in adjusted linear regression analyses. Only a lower illness perception was not associated with duration of hospitalisation. Patients reporting low social support had a lower mental health (SF-12 MCS), a lower health-related quality of life (EQ-5D), symptoms of anxiety and depression (HADS), higher burden of symptoms (ESAS) and a lower illness perception (B-IPQ) in adjusted analyses.

In contrast, male patients and patients undergoing a device-related procedure during index hospitalisation were associated with the reporting of a better score across all PROMs in adjusted linear regression analyses. However no association between being male and reporting less symptoms of depression was found. Further, increasing age and having incident HF was associated with a higher health-related quality of life (EQ-5D), a higher illness perception (B-IPQ) and a lower symptom burden (ESAS) in the adjusted analyses. Increasing age was also associated with the reporting of higher mental health (SF-12 MCS) and fewer symptoms of anxiety (HADS-A) and incident HF associated with higher physical health (SF-12 PCS) and fewer symptoms of depression (HADS-D). Finally, in linear adjusted regression analyses, patients with a higher SBP were more likely to report a better score across all PROMs except in the mental health component score of the SF-12 or symptoms of anxiety in the HADS.

Overall, this pattern of findings across PROM scores was overall confirmed in a supplemental logistic regression analysis, where all PROM scores were dichotomised, and a score in the worst quartile and in HADS a score ≥8 points defined the outcome of interest.

Table 7. Patient characteristics of the 1,506 patients[a]

Demographics, n (%)	
Age	
< 65 years	582 (38.7)
65-74 years	511 (33.9)
≥ 75 years	413 (27.4)
Males	1,117 (74.2)
Hospital-related, n (%)	
Length of hospital stay > 2 days	509 (33.8)
Acutely admitted	553 (36.7)
Undisclosed	45 (3.0)
Incident heart failure	552 (36.7)
Comorbidity, n (%)	
Charlson co-morbidity index (CCI)[b]	
No co-morbidity	569 (37.8)
Moderate co-morbidity level	652 (43.3)
High co-morbidity level	285 (18.9)
Clinical characteristics	
Left ventricular ejection fraction, n (%)	
> 40	266 (17.7)
26 - 40	577 (37.0)
≤ 25	622 (41.3)
Undisclosed	61 (4.1)
Systolic blood pressure, mean (SD)	125 (20.6)
Undisclosed	50 (3.3)
Body mass index, n (%)	
Underweight	25 (1.7)
Normal weight	480 (31.9)
Overweight	553 (36.7)
Obese	401 (26.6)
Undisclosed	47 (3.1)
Heavy smokers, n (%)	74 (5.1)
Undisclosed	52 (3.5)
High risk alcohol intake, n (%)	105 (7.0)
Undisclosed	150 (10.0)
Procedures, n (%)	
Device-related procedure	403 (26.8)
HF medication, n (%)[c]	
≥ 3 pharmaceutics, n (%)	899 (59.7)
Undisclosed	23 (1.5)
Sociodemographics, n (%)	
Living alone[d]	462 (30.7)
Undisclosed	6 (0.4)
Low social support	184 (12.2)
Undisclosed	32 (2.1)
Highest completed education[e]	
Basic school	518 (34.4)
Upper secondary or vocational school	666 (44.2)
Higher education	287 (19.1)
Undisclosed	35 (2.3)
Household income[f]	
Low	369 (24.5)
Intermediary high	377 (25.0)
High	371 (24.6)
Very high	378 (25.1)
Undisclosed	11 (0.7)
Attachment to labour market[e]	
Employed	430 (28.6)

Unemployed	32 (2.1)
Outside the workforce	1,041 (69.3)
Undisclosed	3 (0.2)

[a]If nothing stated, the descriptive characteristics are from the index hospitalisation
[b]CCI is calculated as a 10-year index
[c]Missing information on pharmacological treatment in 3 patients and not allowed access to the medical records in 20 patients (1.5%)
[d]Based on data one year prior to index hospitalisation
[e]Based on 2013 data for the entire cohort
[f]Calculated as a 5-year index one year prior to index hospitalisation and five years back
Adapted from *Rasmussen et al.* (*Appendix I*)

3.2 Patient-reported outcomes and medication adherence in patients with HF (study II)

In study II, a total of 1,464 patients with HF, discharged from a cardiac-related hospitalisation, were included.

In adjusted logistic regression analyses, patients reporting a lower health-related quality of life (EQ-5D), when analysed on a continuous scale, were more likely to be non-adherent in the use of MRAs (adjusted OR 3.49, 95% CI: 1.10-11.1) after one year of follow-up (Table 8). After three years, lower health-related quality of life (EQ-5D) was associated with higher odds being non-adherent in the use of ACEI/ARB/ARNI (adjusted ORs 2.78, 95% CI: 1.19-6.49) and β-blockers (adjusted ORs 2.35, 95% CI: 1.04-5.29, respectively). Accordingly, the association remained for the use of β-blockers after three years in the dichotomised analysis (Table 9).

Analysing HeartQoL on a continuous scale, a lower cardiac health-related quality of life (HeartQoL) was associated with HF medication non-adherence in β-blockers after one year (adjusted OR 1.26, 95% CI: 1.06-1.49) and again after three-year follow-up, when the HeartQoL was dichotomising (adjusted OR 1.37, 95% CI: 1.01-1.87) (Table 8 and 9).

Finally, symptoms of depression were associated with HF medication non-adherence: ACEI/ARB/ARNI (adjusted OR 1.04, 95% CI: 1.01-1.07), β-blockers (adjusted OR 1.05, 95% CI: 1.02-1.09) and MRAs (adjusted OR 1.06, 95% CI; 1.01-1.11) after one year of follow-up (Table 8). After three years of follow-up, the association remained for patients using ACEI/ARB/ARNI (adjusted OR 1.07, 95% CI: 1.03-1.11) and β-blockers (adjusted OR 1.06, 95% CI: 1.02-1.10) (Table 9).

The result of the multinomial regression analyses did not reveal any consistent pattern of dispensing HF medication when analysing the PRO data on a continuous scale. Patients with symptoms of anxiety (HADS-A) were more likely to dispense one drug compared to three drugs (adjusted RRR 1.06, 95% CI: 1.01-1.10) three to six months after discharge in continuous analysis

and associated with the dispensing of HF medication in two out of three time periods in the dichotomised analysis (Appendix II).

Reporting a lower cardiac health-related quality of life (HeartQoL) score was associated with dispensing of one drug compared to three drugs (adjusted RRR 1.32, 95% CI: 1.05-1.65) nine to twelve months after discharge, and symptoms of depression (HADS-D) were associated with the dispensing of one or zero drugs compared to three drugs (adjusted RRRs 1.05, 95% CI: 1.01-1.10 and 1.08, 95% CI: 1.03-1.14, respectively) nine to twelve months after discharge. Finally, respondents reporting health-related quality of life (EQ-5D) in the worst quartile of the scale were more likely to dispense one drug compared to three drugs, nine to twelve months after discharge (Appendix II).

Table 8. Health-related quality of life, symptoms of anxiety and depression at discharge and one-year non-adherence to HF medication[a]

	Continuous PRO data			**Dichotomised PRO data**	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**[b]		**Crude OR (95% CI)**	**Adjusted OR (95% CI)**[b]
ACEI/ARB/ARNI, n=1,118			**ACEI/ARB/ARNI, n=1,118**		
EQ-5D-5L	1.02 (0.48-2.17)	1.20 (0.53-2.70)	EQ-5D-5L	1.06 (0.79-1.42)	1.10 (0.81-1.50)
HeartQoL global	1.07 (0.91-1.26)	1.08 (0.91-1.28)	HeartQoL global	1.06 (0.79-1.42)	1.10 (0.81-1.49)
HADS-A	0.98 (0.96-1.01)	0.99 (0.96-1.02)	HADS-A	0.81 (0.62-1.06)	0.84 (0.63-1.11)
HADS-D	1.03 (0.99-1.06)	1.04 (1.01-1.07)	HADS-D	1.21 (0.90-1.60)	1.24 (0.92-1.66)
β -blockers, n=1,248			**β -blockers, n=1,248**		
EQ-5D-5L	2.47 (1.18-5.16)	2.11 (0.97-4.61)	EQ-5D-5L	1.38 (1.04-1.83)	1.31 (0.98-1.77)
HeartQoL global	1.31 (1.11-1.54)	1.26 (1.06-1.49)	HeartQoL global	1.33 (0.99-1.77)	1.25 (0.93-1.68)
HADS-A	1.01 (0.98-1.04)	1.01 (0.98-1.04)	HADS-A	1.13 (0.87-1.46)	1.10 (0.84-1.45)
HADS-D	1.06 (1.02-1.09)	1.05 (1.02-1.09)	HADS-D	1.52 (1.15-2.00)	1.47 (1.10-1.97)
MRAs, n=686			**MRAs, n=686**		
EQ-5D-5L	3.50 (1.17-10.4)	3.49 (1.10-11.1)	EQ-5D-5L	1.47 (0.97-2.24)	1.48 (0.96-2.29)
HeartQoL global	1.10 (0.87-1.40)	1.10 (0.86-1.42)	HeartQoL global	0.88 (0.57-1.35)	0.86 (0.55-1.34)
HADS-A	1.02 (0.98-1.06)	1.02 (0.98-1.07)	HADS-A	1.13 (0.78-1.65)	1.12 (0.75-1.67)
HADS-D	1.06 (1.01-1.11)	1.06 (1.01-1.11)	HADS-D	1.63 (1.09-2.44)	1.62 (1.06-2.48)

[a]Multivariable logistic regression; OR, indicates odds ratio; CI, confidence interval

[b]OR were adjusted for the following: age, sex, length of hospital stay, Charlson Comorbidity Index score, left ventricular ejection fraction, social support, device-related procedure, incident HF and systolic blood pressure (mmHg)

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; EQ-5D-5L, the EuroQoL five-dimensional, five-level questionnaire; HADS-A and HADS-D, the Hospital Anxiety and Depression Scale, anxiety (HADS-A) and depression (HADS-D) subscale, respectively; HeartQoL global, the HeartQoL global score; MRAs; mineralocorticoid receptor antagonists. Adapted from *Rasmussen et al.* (*Appendix II*)

Table 9. Health-related quality of life, symptoms of anxiety and depression at discharge and three-year non-adherence to HF medication[a]

	Continuous PRO data			Dichotomised PRO data	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**[b]		**Crude OR (95% CI)**	**Adjusted OR (95% CI)**[b]
ACEI/ARB/ARNI, n=1,118			**ACEI/ARB/ARNI, n=1,118**		
EQ-5D-5L	3.18 (1.42-7.09)	2.78 (1.19-6.49)	EQ-5D-5L	1.33 (0.97-1.82)	1.30 (0.94-1.79)
HeartQoL global	1.17 (0.99-1.37)	1.12 (0.94-1.33)	HeartQoL global	1.01 (0.75-1.36)	0.96 (0.71-1.31)
HADS-A	1.03 (0.99-1.06)	1.03 (0.99-1.06)	HADS-A	1.11 (0.85-1.45)	1.12 (0.84-1.48)
HADS-D	1.08 (1.04-1.12)	1.07 (1.03-1.11)	HADS-D	1.64 (1.20-2.23)	1.55 (1.12-2.14)
β -blockers, n=1,248			**β -blockers, n=1,248**		
EQ-5D-5L	3.51 (1.62-7.60)	2.35 (1.04-5.29)	EQ-5D-5L	1.55 (1.15-2.09)	1.38 (1.01-1.89)
HeartQoL global	1.27 (1.09-1.49)	1.17 (0.99-1.37)	HeartQoL global	1.54 (1.14-2.07)	1.37 (1.01-1.87)
HADS-A	1.02 (0.99-1.05)	1.01 (0.98-1.04)	HADS-A	1.11 (0.86-1.43)	1.03 (0.79-1.35)
HADS-D	1.07 (1.04-1.11)	1.06 (1.02-1.10)	HADS-D	1.70 (1.26-2.29)	1.53 (1.13-2.08)
MRAs, n=686			**MRAs, n=686**		
EQ-5D-5L	0.94 (0.34-2.55)	0.87 (0.30-2.53)	EQ-5D-5L	0.72 (0.49-1.05)	0.71 (0.47-1.06)
HeartQoL global	1.07 (0.87-1.33)	1.06 (0.85-1.33)	HeartQoL global	0.87 (0.60-1.27)	0.85 (0.57-1.26)
HADS-A	0.97 (0.94-1.01)	0.98 (0.94-1.02)	HADS-A	0.77 (0.55-1.08)	0.77 (0.54-1.10)
HADS-D	1.01 (0.96-1.05)	1.01 (0.96-1.05)	HADS-D	0.94 (0.64-1.38)	0.97 (0.64-1.46)

[a]Multivariable logistic regression; OR, indicates odds ratio; CI, confidence interval

[b]OR were adjusted for the following: age, sex, length of hospital stay, Charlson Comorbidity Index score, left ventricular ejection fraction, social support, device-related procedure, incident HF and systolic blood pressure (mmHg)

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; EQ-5D-5L, the EuroQoL five-dimensional, five-level questionnaire; HADS-A and HADS-D, the Hospital Anxiety and Depression Scale, anxiety (HADS-A) and depression (HADS-D) subscale, respectively; HeartQoL global, the HeartQoL global score; MRAs; mineralocorticoid receptor antagonists. Adapted from *Rasmussen et al.* (*Appendix II*)

3.3 Patient-reported outcomes and mortality, CV events and HF hospitalisations in patients with HF (study III)

In study III, a total of 1,499 patients with HF were included.

In adjusted Cox regression analyses treating the PRO data on a continuous scale, an association between a worse PROM score at discharge from index hospitalisation and higher mortality after one- and three years of follow-up was demonstrated (Tables 10 and 11). An approximately two-fold increase was demonstrated for lower cardiac health-related quality of life (HeartQoL) and increased risk of all-cause mortality (adjusted HR 1.91, 95% CI: 1.42-2.57) and CV mortality (adjusted HR 2.17, 95% CI: 1.50-3.15) after one year (Table 10). Lower health-related quality of life (HeartQoL and EQ-5D) remained associated with the highest risk of mortality after three years, thus a 1.5-fold increased risk of all-cause mortality in patient reporting lower cardiac health-related quality of life (HeartQoL) (adjusted HR 1.46, 95% CI: 1.22-1.74) and CV mortality (adjusted HR 1.60, 95% CI: 1.26-2.03) after three years of follow-up (Table 11). When analysing the PROM scores dichotomised, defining the worst quartile as outcome of interest, the same pattern was demonstrated (Tables 10 and 11).

In the Cox regression analyses of the association of PROMs and risk of non-fatal events, analysing the PROM scores on a continuous scale, a worse score, except symptoms of anxiety, was associated with higher risk of CV events and HF hospitalisation. The strongest association was demonstrated for lower cardiac health-related quality of life (HeartQoL) and risk of HF hospitalisations after one and three years (adjusted HRs 1.47, 95% CI: 1.29-1.68 and 1.43, 95% CI: 1.28-1.61, respectively) and risk of CV events after three years (adjusted HR 1.33, 95 % CI: 1.20-1.42) (Tables 10 and 11). In the dichotomised analyses, a 40%-60% increased risk of experiencing a CV event or an HF hospitalisation during follow-up was observed for patients reporting lower cardiac health-related quality of life (HeartQoL) (Tables 10 and 11).

Table 10. Health-related quality of life, symptoms of anxiety and depression and mortality, cardiovascular events and HF hospitalisation after one year (n=1,499)[a]

	PRO data, continuous scale			PRO data, dichotomised	
	Crude HR (95% CI)	Adjusted HR (95% CI) [b]		Crude HR (95% CI)	Adjusted HR (95% CI) [b]
All-cause mortality			**All-cause mortality**		
HeartQoL global	2.32 (1.76-3.06)	1.91 (1.42-2.57)	HeartQoL global	2.41 (1.66-3.52)	1.90 (1.29-2.80)
EQ-5D-5L	1.35 (1.24-1.46)	1.26 (1.15-1.38)	EQ-5D-5L	3.08 (2.10-4.50)	2.43 (1.68-3.66)
HADS-A	1.08 (1.04-1.13)	1.08 (1.03-1.13)	HADS-A	1.80 (1.24-2.61)	1.74 (1.17-2.58)
HADS-D	1.15 (1.10-1.19)	1.12 (1.07-1.17)	HADS-D	2.18 (1.49-3.19)	1.86 (1.25-2.77)
Cardiovascular mortality			**Cardiovascular mortality**		
HeartQoL global	2.52 (1.79-3.55)	2.17 (1.50-3.15)	HeartQoL global	2.59 (1.64-4.07)	2.07 (1.30-3.30)
EQ-5D-5L	1.34 (1.21-1.48)	1.27 (1.13-1.42)	EQ-5D-5L	2.95 (1.87-4.65)	2.44 (1.53-3.90)
HADS-A	1.08 (1.03-1.14)	1.09 (1.04-1.15)	HADS-A	1.80 (1.14-2.83)	1.90 (1.19-3.04)
HADS-D	1.13 (1.07-1.19)	1.11 (1.05-1.17)	HADS-D	1.85 (1.16-2.96)	1.63 (1.01-2.64)
Cardiovascular events			**Cardiovascular events**		
HeartQoL global	1.46 (1.29-1.64)	1.17 (1.18-1.49)	HeartQoL global	1.62 (1.35-1.95)	1.41 (1.17-1.70)
EQ-5D-5L	1.14 (1.08-1.20)	1.10 (1.04-1.16)	EQ-5D-5L	1.32 (1.09-1.59)	1.10 (0.91-1.34)
HADS-A	1.03 (1.01-1.05)	1.01 (0.99-1.04)	HADS-A	1.27 (1.06-1.52)	1.11 (0.92-1.35)
HADS-D	1.05 (1.02-1.07)	1.03 (1.01-1.06)	HADS-D	1.25 (1.03-1.51)	1.12 (0.91-1.36)
HF hospitalisation			**HF hospitalisation**		
HeartQoL global	1.60 (1.40-1.83)	1.47 (1.29-1.68)	HeartQoL global	1.81 (1.48-2.22)	1.60 (1.31-1.97)
EQ-5D-5L	1.17 (1.11-1.24)	1.13 (1.07-1.19)	EQ-5D-5L	1.47 (1.19-1.81)	1.21 (0.98-1.50)
HADS-A	1.03 (1.01-1.06)	1.02 (0.99-1.05)	HADS-A	1.31 (1.07-1.58)	1.18 (0.96-1.46)
HADS-D	1.05 (1.03-1.08)	1.04 (1.02-1.07)	HADS-D	1.33 (1.08-1.65)	1.21 (0.98-1.51)

[a]The Cox proportional hazards model; HR = hazard ratio; CI = confidence interval

[b]HR were adjusted for the following: age, sex, length of hospital stay, Charlson Comorbidity Index score, left ventricular ejection fraction, social support, device-related procedure, incident HF and systolic blood pressure (mmHg) at index hospitalisation

HeartQoL global = the HeartQoL global score; EQ-5D-5L = the EuroQoL five-dimensional, five-level questionnaire; the HADS-A and HADS-D = the Hospital Anxiety and Depression Scale, anxiety and depression subscale, respectively. Adapted from *Rasmussen et al.* (*Appendix III*)

Table 11. Health-related quality of life, symptoms of anxiety and depression and mortality, cardiovascular events and HF hospitalisation after three years (n=1,499)[a]

	PRO data, continuous scale			PRO data, dichotomised	
	Crude HR (95% CI)	Adjusted HR (95% CI) [b]		Crude HR (95% CI)	Adjusted HR (95% CI) [b]
All-cause mortality			**All-cause mortality**		
HeartQoL global	1.77 (1.50-2.09)	1.46 (1.22-1.74)	HeartQoL global	1.93 (1.50-2.50)	1.57 (1.21-2.03)
EQ-5D-5L	1.26 (1.19-1.34)	1.17 (1.10-1.25)	EQ-5D-5L	2.18 (1.70-2.80)	1.76 (1.36-2.27)
HADS-A	1.05 (1.02-1.07)	1.04 (1.01-1.07)	HADS-A	1.32 (1.03-1.69)	1.25 (0.96-1.62)
HADS-D	1.10 (1.07-1.14)	1.08 (1.05-1.11)	HADS-D	1.87 (1.46-2.41)	1.59 (1.21-2.08)
Cardiovascular mortality			**Cardiovascular mortality**		
HeartQoL global	1.97 (1.58-2.46)	1.60 (1.26-2.03)	HeartQoL global	2.20 (1.60-3.03)	1.73 (1.25-2.40)
EQ-5D-5L	1.27 (1.18-1.37)	1.18 (1.09-1.29)	EQ-5D-5L	2.23 (1.62-3.08)	1.75 (1.26-2.42)
HADS-A	1.05 (1.02-1.09)	1.05 (1.02-1.09)	HADS-A	1.32 (0.96-1.81)	1.29 (0.93-1.81)
HADS-D	1.10 (1.06-1.14)	1.07 (1.03-1.12)	HADS-D	1.55 (1.11-2.16)	1.28 (0.90-1.82)
Cardiovascular events			**Cardiovascular events**		
HeartQoL global	1.47 (1.32-1.63)	1.33 (1.20-1.42)	HeartQoL global	1.68 (1.42-1.97)	1.46 (1.24-1.73)
EQ-5D-5L	1.13 (1.08-1.18)	1.08 (1.04-1.14)	EQ-5D-5L	1.36 (1.15-1.61)	1.15 (0.96-1.36)
HADS-A	1.02 (1.01-1.04)	1.01 (0.99-1.03)	HADS-A	1.25 (1.07-1.47)	1.11 (0.94-1.32)
HADS-D	1.04 (1.02-1.07)	1.03 (1.01-1.05)	HADS-D	1.27 (1.07-1.51)	1.14 (0.96-1.36)
HF hospitalisation			**HF hospitalisation**		
HeartQoL global	1.57 (1.39-1.76)	1.43 (1.28-1.61)	HeartQoL global	1.80 (1.51-2.16)	1.61 (1.34-1.93)
EQ-5D-5L	1.14 (1.09-1.20)	1.09 (1.04-1.15)	EQ-5D-5L	1.41 (1.17-1.70)	1.18 (0.97-1.42)
HADS-A	1.02 (1.00-1.04)	1.01 (0.99-1.03)	HADS-A	1.24 (1.04-1.48)	1.13 (0.94-1.36)
HADS-D	1.04 (1.02-1.07)	1.03 (1.01-1.06)	HADS-D	1.28 (1.05-1.54)	1.16 (0.96-1.41)

[a]The Cox proportional hazards model; HR = hazard ratio; CI = confidence interval

[b]HR were adjusted for the following: age, sex, length of hospital stay, Charlson Comorbidity Index score, left ventricular ejection fraction, social support, device-related procedure, incident HF and systolic blood pressure (mmHg) at index hospitalisation

HeartQoL global = the HeartQoL global score; EQ-5D-5L = the EuroQoL five-dimensional, five-level questionnaire; the HADS-A and HADS-D = the Hospital Anxiety and Depression Scale, anxiety and depression subscale, respectively. Adapted from *Rasmussen et al.* (*Appendix III*)

3.4 Sensitivity analyses

In study II, sensitivity analyses were performed applying 14 grace days in the regression analyses of HF medication adherence to compare the estimates of the regression analyses using 30 grace days. This did not change the estimates.

In study I-III, all adjusted regression analyses were performed before and after multiple chained imputations to compare the estimates between not imputed and imputed datasets. No overall trend in change of estimates were revealed between datasets.

4. Discussion

4.1 Main findings

Self-reported data and data from medical records and registries provided several findings. In general, a consistent pattern of associations between several patient-related predictors and PROMs at discharge from a cardiac-related hospitalisation was identified in adjusted analyses. Patients having a high comorbidity level, >2 days in hospital during index hospitalisation and with low self-perceived social support were more likely to have a worse score across PROMs. Being male, having a device-related procedure, higher systolic blood pressure, having incident HF and increasing age was associated with a better score across the PROMs.

Symptoms of depression and low health-related quality of life at the time of hospital discharge were associated with being non-adherent to anticongestive medications in one and three-year follow up in adjusted analyses. No consistent pattern was revealed between PROMs and number of redeemed prescriptions in three time-periods in three-year follow-up in the adjusted analyses of the continuous PRO data.

Finally, symptoms of anxiety and depression and low quality of life at the time of hospital discharge was associated with increased risk of mortality in one and three-year follow-up in adjusted analyses. Moreover, patients reporting symptoms of depression and low health-related quality of life were more likely to experience a cardiovascular event or a HF hospitalisation in one and three-year follow-up in adjusted analyses of the continuous PRO data.

4.2 Comparison with existing literature

In the following section, a discussion of the findings in the context of the existing literature is provided (Table 2 - 6).

4.2.1 Patient-related characteristics and patient-reported outcomes in patients with HF

Only a few studies have focused on the association between patient-related characteristics and PROMs, few studies report these data, and often reported secondary to other study aims in descriptive analyses.

The literature search included all patient-related predictors and patient characteristics in relation to PROMs in patients with HF. The term predictors was used and referred to equally to the term

patient-related characteristics, though the term predictors are often used in follow-up studies and not in a cross-sectional design.

However several findings from this study were overall in concordance with those from the existing literature.

This study demonstrated that having a high comorbidity burden, low self-perceived social support and longer hospital stay were associated with a worse score across PROMs [68, 70, 71]. One Swedish cross-sectional study of 357 patients with HF found that elderly patients with comorbid diabetes mellitus and respiratory disease reported lower physical health on the SF-12 [70]. Another large cross-sectional study from Sweden including 10,575 patients with HF demonstrated a lower patient-rated health, using the EQ-5D visual analogue scale, in patients with comorbid conditions compared to patients without comorbid conditions. However a supplementary analysis found that the association depended on whether it was a cardiovascular or non-cardiovascular comorbid condition and concluded that the linkage was explained by depression, anxiety or symptoms [71]. Finally, one cohort study of 1,037 outpatients with HF found that patients with comorbid conditions, indexed by the Charlson Comorbidity Index, were more likely to report worse health status on the EQ-5D in adjusted analysis [68], and one cohort study from the US of 417 patients with HF found that patients with a comorbid condition and lower renal function were more likely to report a lower physical health status (SF-12) [73].

In relation to self-perceived social support, a consistent association between low social support and a worse score across PROMs was identified, and in contrast living alone was not nearly as strong associated to a worse PROM score. Social support covers several dimensions of emotional, appraisal, instrumental and informational support and is not restricted to include family members [126]. A Swedish study of social support in 349 patients with HF showed that patients reporting higher social support were more likely to have higher mental health [72]. Supportive of this, a Danish cohort study of supportive relatives in relation to anxiety and depression in 2,496 patients with cardiac heart disease demonstrated that patients reporting a low degree of supportive relatives or some degree of supportive relatives were more likely to suffer from depression. Moreover, patients with a low or some degree of support were more likely to have symptoms of anxiety and depression than patients with a high degree of social support, in married patients [74]. Traditionally, civil status or cohabitation status has been an indicator of social and emotional support but results from this study may indicate that the level of support is also of importance.

Finally, days in hospital was also associated with a worse score across the PROMs. No previous studies of the association between the six PROMs and length of hospital stay were identified, but the observation is interesting since it can be linked to severity of disease and consequently prolonged hospitalisation and is easily obtainable in the clinical setting with the purpose of risk stratification in relation to vulnerable patients.

4.2.2 Patient-reported outcomes and medication adherence

This is one of the largest studies of health-related quality of life and symptoms of anxiety and depression in relation to medication adherence after discharge from a cardiac-related hospitalisation in patients with HF, using the EQ-5D, the HeartQoL and the HADS. In 2001 a systematic literature review, including 11 studies on medication adherence in HF, found conflicting results in three studies addressing depression in relation to medication non-adherence [48]. The studies all used a PROM, though not the HADS [62, 127, 128]. A nonsignificant association between depression and medication adherence was shown in two studies [62, 127], and one study found "carelessness" in relation to the importance of being adherent, but not distinct non-adherence [128]. However, the population sizes in these three studies were small, ranging from 51-134 patients [62, 127, 128], and medication adherence was measured using self-reported tools, which could be influenced by recall bias [127, 128].

This study did not demonstrate any association between symptoms of anxiety and HF medication non-adherence. However, in relation to dispensed medication, patients with symptoms of anxiety were more likely to dispense only one drug compared to three drugs three to six months after discharge and no drugs compared to three drugs nine to twelve months after discharge. A US randomised trial of a three months collaborative care intervention in depressed cardiac patients demonstrated a decrease in symptoms of anxiety (HADS) and increased self-reported adherence after six weeks in patients allocated to intervention compared to patients allocated to usual care. However, the study was not able to show any association after six months [79]. Several factors can cause the lack of association over time, such as short follow-up or a small sample size [79]. Moreover, high-intensity interventions may led to immediate improvements, but it can be challenging to maintain achieved health-behaviours over time [127].

In summary, symptoms of anxiety were not associated with medication non-adherence, but in contrast, patients with symptoms of depression were more likely to be non-adherent across analyses. This could be explained by the core nature of how symptoms of anxiety and depression

affect the individual. Patients with symptoms of anxiety may be more focused on adherence to medication, life-style and healthcare recommendations in general as opposed to patients with depressive symptoms, where key symptoms might be loss of initiative and motivation potentially affecting medication adherence.

4.2.3 Mortality, CV events and HF hospitalisations

This study found that patients reporting a lower cardiac health-related quality of life, measured by the HeartQoL, were more likely to experience an adverse event in terms of mortality, a CV event and a HF hospitalisation in one- and three years of follow-up. The HeartQoL was developed to capture health-related quality of life in patients with heart disease and partly developed using a HF specific PROM questionnaire [119, 120]. The HeartQoL has been linked to risk of adverse events in patients with ischemic heart disease, though not in distinct HF populations. In a large Danish cohort study of patients with cardiac disease, including patients with HF, a lower HeartQoL score was associated with risk of experiencing a cardiac readmission and all-cause mortality within five years of follow-up. In a descriptive analysis, more than 50% of the population with comorbid HF had a low HeartQoL score [88].

Further, patients reporting a lower health-related quality of life, measured by the EQ-5D, experienced higher all-cause and CV mortality after one-and three-year follow-up. This is supported by a large US cohort study of patients with HF using longitudinal data on the EQ-5D, where EQ-5D was assessed at baseline, after 24 hours, ten days and 30 days of discharge from index hospitalisation [86]. Here, patients reporting a lower EQ-5D score at discharge had a higher risk of 30-days all-cause mortality, cardiac death, cardiac rehospitalisation and HF rehospitalisation and also six months mortality [86].

Finally, in this study of PROMs in relation to risk of adverse outcomes, symptoms of anxiety and depression were also associated with risk of mortality over time, which is in accordance with the literature [82-84, 87]. One smaller UK cohort study of patients with HF discharged from a HF hospitalisation found that moderate to severe symptoms of depression (HADS ≥ 11 points) were associated with one-year all-cause mortality [82], and a German cohort study of patients with HF demonstrated that a score above the median in HADS was associated with risk of mortality after 30 months [83]. In relation to symptoms of anxiety, one US cohort study of anxiety using the HADS showed that symptoms of anxiety and depression were independently associated with three-year risk of mortality in patients with HF, and after controlling for depression, symptoms of anxiety

remained associated to risk of mortality [87]. Finally, a small Swiss cohort study of patients with HF demonstrated that severe symptoms of anxiety (scores >10 points in HADS) were associated with increased risk of cardiac-related readmission in five-year period survival analyses [84].

In summary, in this study, symptoms of depression were associated with risk of adverse events and is in overall accordance with the literature, despite the fact that the cut-offs and follow-up time varied between this study and the identified literature in this field of research. Moreover as opposed to the literature, this study did not demonstrate any association between symptoms of anxiety and risk of non-fatal events. Symptoms of anxiety were expected to be associated with risk of HF hospitalisation since it mimics progression and could be interpreted as exacerbation of HF. Patients reporting palpations and difficulty in breathing would most likely be referred to a medical doctor and most likely admitted, resulting in a HF hospitalisation.

4.3 Methodological considerations

Below, a discussion of the methodological considerations in relation to study I-III is provided. Here, the assumptions behind methods of imputation to handle missing values are discussed, and the risk of bias in epidemiological research in terms of selection bias, information bias and confounding.

4.3.1 Missing values

In all three studies, missing values on exposures, outcomes and covariates were present, ranging from 1.5-21% in study I to 1.5-4.0% in study II-III. Assuming data to be missing at random (MAR), multiple imputations (MI) using multiple chained imputations (Markow Chain Method) was performed [121-124]. A model for the chained imputations was developed in each of the three studies, and using Rubins Rule, 50 datasets were imputed [124].

The MI approach and the assumption of data being MAR cannot be validated through statistical tests but relies on the decisions and knowledge in the research area and the research question asked. However, sensitivity analyses on non-imputed compared to imputed data were performed to challenge the assumptions, and the estimates did not change drastically.

4.3.2 Selection bias

All three populations (study I-III) were derived from the same study population, where approximately 50% were non-responders, potentially leading to selection bias. Patients were recruited to participate in a survey of PROMs in relation to discharge from a cardiac hospitalisation.

Non-responders were patients declining participation, not handing in the questionnaire or handing in a non-complete or blank questionnaire. A test of differences in the distribution of age and sex and comorbid burden, in patients with HF as a primary discharge diagnosis, in study I revealed no differences between responders and non-responders, indicating a low risk of selection bias. However, a test of difference in PROMs would potentially have added differentiated information on non-responders compared to non-responders, but naturally not an option. It is expected though that non-responders were more severely affected by their HF, potentially causing a worse score on the PROMs, not introducing selection bias, but potentially leading to an underestimation of the demonstrated association in the three studies and bias towards the null.
Approximately 5% were excluded due to congenital heart disease or severity of illness, potentially leading to selection bias, but due to the small number of excluded patients, this did not lead to any concerning selection bias. Finally, no loss to follow-up on outcome was present in study II-II, diminishing selection bias.

4.3.3 Information bias

The inclusion of patients with HF is dependent on the given HF diagnosis at discharge from any hospitalisation. The diagnosis can be coded as a primary (leading cause of hospitalisation) and as a secondary (underlying cause of hospitalisation) discharge diagnosis. A positive predictive value of >75% has previously been identified for diagnoses of HF in the DNPR [129, 130].

4.3.3.1 Misclassification of exposures

In study I, the exposures were patient-related predictors, including register-based information on patient demographics and socio-demographics, procedures during index hospitalisation and diagnoses at discharge, self-reported information on social support from the Survey and finally clinical HF-related characteristics at discharge, retrieved from the medical records. The coding in the DNPR reflects the validity of this information, and using data from the DNPR in epidemiological research has previously been validated [91].
One single question from the survey on lack of social support was used. This is prone to bias, due to the risk of different interpretations among patients. However, the wording of the question was open for interpretation and not restricted to a certain type of support or family members but instead indicating a broad understanding of concept of social support.

In study II-III, six PROMs were used as exposures, including five generic and one disease-specific questionnaire (Table 6). All questionnaires are validated in patients with medical conditions or in patients with heart disease [105-107, 109-112, 115-117, 119, 120]. Using self-report measures of health could potentially be influenced by comprehensive or interpretive differences by the patients raising information bias, which always must be considered. In general, patients answered the questionnaires by themselves, and if need of guidance, the healthcare staff guided the patients. However, using different PROMs, measuring both mental and physical health, demands that patients read and understand the questions. Using measures with different time perspectives requires attention when answering every single questionnaire, and when patients are asked to assess health within one or several weeks, depending on the measure, they may decide to evaluate their health in relation to a specific issue during that period or over the entire period.

Finally, studying the association between a single baseline measurement and long-term outcomes is challenged by the fact that fluctuations in subjective health and external influences of health are not captured. This may modify the pathway from the PRO assessment at baseline and the studied outcomes. However, the aim of this study was not to conduct repeated measures of health or time-varying effects of exposure on outcome, but rather to examine the clinical relevance of assessments at the time of hospital discharge.

4.3.3.2 Misclassification of outcomes

In study II, the outcome of interest was adherence to HF medication in one-and three years follow-up, using data from the RMPS which is considered valid for use in research [97]. Here, data on every redeemed prescription including date, strength and ATC code are available, and thus not prone recall bias. One limitation, though, is the lack of information on dosage of the drugs. Patients may redeem larger packages than expected, be instructed to take less medication over a period or even pausing in the use of medication, which is not possible to identify. This may potentially lead to an overestimation of medication non-adherence and risk of non-differentiated misclassification, leading to bias towards the null. Thirty grace days between every two redeemed prescriptions were applied, in order to decrease the risk of potential misclassification of adherence.

Due to missing information on the outcome PDC, and since information on cause of missing information was not obtainable, it was only possible to perform regression analyses on available data. This potentially led to an underestimation of the true association between PRO data and subsequent medication adherence.

Finally, in study III the main outcome was register-based information on all-cause and CV mortality. Information on CV mortality was retrieved from the RCD. Here, the medical doctor completes the immediate and underlying cause of death, which to some extent is prone to a subjective assessment, and classification of CV mortality from other causes of death must be interpreted with caution.

4.3.4 Confounding

In epidemiology, a potential risk of effect from a confounding factor is always to be considered and appropriately addressed. A confounding factor must be associated with the exposure of interest, a risk factor for the outcome and not a step in the causal pathway from exposure to outcome, i.e. an intermediary factor in the association between exposure and outcome, and classified into unmeasured compared to measured factors and unknown compared to known factors [131].
The combination of self-reported information combined with data from medical records and register-based information on a patient-level, enabled extensive regression analyses and confounding control. The clinical HF related information from the medical records, captured characteristics which was not possible to obtain from registries in relation to this population. As mentioned, Danish registries in general have a high completeness and validity, and data have been validated for use in healthcare research [90, 91, 97, 129].
In study I, patient-related predictors were identified through linear and multiple logistics regression analyses. Several patient-related predictors were identified as factors independently associated with the PRO data. The patient-related predictors were hence included a priory as potential confounding factors in study II and III. Though LVEF was not associated with all the PRO data in study I, it was included in all regression analyses, since it was considered possibly linked to RPO data and the outcome in study II and III. In study II and III, the estimates were in general robust before and after controlling for potential confounding.

It was chosen to dichotomise or categorise most potential confounding factors before entered into the regression analyses, which potentially cause residual confounding due to a too rough subdivision of data into categories, but easier to interpret for clinical purposes compared to continuous variables. It is also imperative to consider the possibility of confounding by indication. In study III, a robust association between PROMs and fatal outcomes was demonstrated, but these results may be affected by severity or duration of the disease, and hence not an association between worse PROMs scores and subsequently fatal outcomes.

The studies may also be influenced by unmeasured potential confounding factors, for example the New York Heart Association (NYHA) Functional Classification or heart valve disease, as proxies for the severity of illness and hence impact to alter the estimates. However due to pragmatic reasons, it was considered subjected to a larger risk of having missing data in these variables and left out in the data collection.

Finally, the results of the three studies may be influenced by unknown confounding factors, not accounted for in the analyses. This includes potential factors associated with the answering of the PROMs, i.e. a more in-depth assessing of social network and habitation would have been of interest, as well as factors associated to previous history of depression or use of anxiolytics or antidepressants or duration of disease.

4.4 Conclusion

Overall, this dissertation aimed to investigate the applicability of one disease-specific and five generic PROMs and whether these PROMs were associated with medication adherence, mortality and non-fatal adverse events following a cardiac-related hospitalisation in a national cohort of Danish patients with HF.

Study I demonstrated a consistent pattern of patient-related predictors being associated with a worse score across PRO data and patient-related predictors associated with a better score across PRO data. A high comorbidity level, lack of social support and hospitalisation for >2 days was associated with a worse PROM score across questionnaires, and in contrast, patients with advanced age, incident HF, males and patients undergoing a device-related procedure and having a higher systolic blood pressure were more likely to have a better PROM score across questionnaires. Information on these specific patient-related predictors provides the opportunity to identify the most vulnerable patients, which might be in risk of having lower physical or mental health, in an easy way and not time-consuming or dependent on clinical testing.

Study II demonstrated that lower health-related quality of life and more symptoms of anxiety and depression were independently associated with HF medication non-adherence in one and three-year follow-up in the use of ACEI/ARB/ARNI, β-blockers and MRAs across PRO data. The strongest associations were found for low generic health-related quality of life.

Study III showed that a lower health-related quality of life and more symptoms of anxiety and depression were associated with subsequent risk of mortality and risk of adverse events after one

and three-year follow-up. In this study, low health-related quality of life demonstrated the strongest associations and was a robust finding after control for potential confounding.

4.5 Perspectives

The findings from the three studies all contribute to the knowledge on PROMs in patients with HF. The patients included were a heterogenous population of patients with incident and prevalent HF and patients with an HF diagnosis, given either as a primary diagnosis or a secondary diagnosis, indicating the leading and secondary cause of hospitalisation. However, HF is a complex syndrome of different aetiology, symptoms and concomitant comorbidity, all factors influencing the HF in different ways, but characterises the vast majority of these patients with frequent contact to the healthcare system and emphasises the usefulness and potential of using PROMs in this group of patients.

The prevalence of HF is increasing which accentuates the need for more effective ways of identifying patients at risk of a poor prognosis equally to the use of objective risk factors routinely used in clinical practice. The findings of the three studies stress the potential of using PROMs, and more specific measuring health-related quality of life and symptoms of anxiety and depression in the clinical setting. The purpose is not only to map health status, but also to assist in the individual pathway towards differentiated treatment and care in patients with HF.

To establish these PROMs as prognostic factors, it is imperative to test and validate these PROMs in patients with HF in a prospective study design, where factors such as social support outside hospital and type of personality should be incorporated, since these factors may provide further information.

Finally, the perspective is to gain knowledge on how these PROMs can be incorporated in clinical care and the long-term perspective is to enhance health-related quality of life and diminish symptoms of anxiety and depression to prolong survival in patients with HF.

5. Summary

Heart failure is a complex condition, with a prevalence between 1% - 2%, expected to increase due to improved treatment strategies, an ageing population and increasing concomitant comorbidity burden. Worldwide, more than 37 million people are affected by heart failure, and healthcare costs are expected to increase over the next decades. The course of the disease is poor with a high risk of adverse outcomes and a five-year mortality of 50%. Evidence-based HF medication is essential to enhance physical ability and reduce the risk of adverse events and mortality in patients with heart failure. Knowledge of concomitant characteristics and mortality risk factors is essential to help guide the decision-making in relation to care.

Patient-reported outcome measures (PROMs) assess mental and physical health, symptom burden, and symptoms of anxiety and depression, reported by the patient, and help quantify the impact of the disease on every-day life in generic or disease-specific questionnaires. In the last decades, an increasing interest in PROMs in patients with cardiovascular (CV) disease as well as the potential of using this information in the clinical setting has emerged. However, knowledge of patient-reported outcomes (PRO) data in patients with heart failure at discharge from a cardiac-related hospitalisation is still not well-established.

This study used six PROMs from the Danish national DenHeart Survey and linked this information to health registries and clinical data from medical records.

This thesis explored patient-related predictors of patient-reported outcomes in patients with heart failure (study I). The aim was to identify patient-related predictors across PRO data in a cross-sectional design including 1,506 patients with heart failure at discharge from a cardiac-related hospitalisation. The study demonstrated that having more than two days at hospital, a higher comorbidity burden and a lack of self-reported social support was associated with a worse score across PROMs. In contrast, patients hospitalised with incident HF, male patients, patients with advanced age, patients undergoing a device-related procedure and patients having a higher systolic blood pressure were more likely to score better across PROMs.

Accordingly, the evidence on the role of PRO data and the risk of HF medication non-adherence is not well-established (study II). The aim was to study the association between PRO data at discharge from a cardiac-related hospitalisation and subsequent one and three-year HF medication in 1,464 patients with heart failure.

Having < 80% of proportion of days covered (PDC) defined non-adherence. The results showed that patients reporting lower health-related quality of life were more likely to be non-adherent in the

use of mineralocorticoid receptor antagonists (MRAs) in one-year follow-up and in the use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers/angiotensin receptor neprilysin inhibitors (ACEI/ARB/ARNI) and β-blockers in three-year follow-up. Patients with lower cardiac health-related quality of life were more likely to be non-adherent in the use of β-blockers in one year. Symptoms of depression were also associated with non-adherence in the use of ACEI/ARB/ARNI, β-blockers and MRAs in one-year follow-up and in the use of ACEI/ARB/ARNI and β-blockers after three years follow-up.

Finally, the prognostic impact of PRO data in relation to the risk of mortality and adverse events is still unknown (study III). The aim was to study the association between PRO data at discharge from a cardiac-related hospitalisation and subsequent risk of mortality and adverse events after one-and three-year follow-up in 1,499 patients with heart failure. The study found that a lower health-related quality of life and symptoms of anxiety and depression were associated with higher risk of all-cause and CV mortality after one and three-year follow-up. The analyses of non-fatal outcomes found that a lower health-related quality of life and symptoms of depression were associated with a higher risk of having a CV event or a HF-hospitalisation after one- and three years of follow-up.

In conclusion, the findings across study I-III demonstrate that patient-reported outcomes are associated with subsequent HF medication non-adherence and risk of mortality and adverse events in one and three-year follow up in this national cohort of Danish patients with heart failure.

6. Dansk resumé

Hjertesvigt er en alvorlig sygdom med en prævalens på 1%-2%, der forventes at stige som følge af forbedrede behandlingsstrategier, en aldrende population og flere patienter, der samtidig lider af andre betydende sygdomme. Mere end 37 millioner mennesker er berørt af hjertesvigt på verdensplan, og omkostninger som følge af hjertesvigt forventes at stige over de næste årtier. Prognosen ved hjertesvigt er dårlig og med en høj risiko for død, kardiovaskulære hændelser og genindlæggelser som følge af hjertesvigt. Brugen af evidensbaseret hjertesvigtsmedicin hos patienter med hjertesvigt er altafgørende for at øge patienternes fysiske formåen samt reducere risikoen for kardiovaskulære hændelser og genindlæggelser. Viden om risikofaktorer for en dårlig prognose er essentiel, når der tages beslutninger vedrørende strategier for behandling og pleje. Patient-rapporterede outcomes er generiske eller sygdomsspecifikke redskaber til at måle mental og fysisk helbred, symptombyrde, angst og depression, rapporteret af patienten selv, og medvirker til at kvantificere den indflydelse, sygdommen har på patientens aktivitetsniveau i dagligdagen.
I de seneste årtier er der sket en øget interesse for patientrapporteret helbred og for at bruge patientperspektivet i klinisk praksis hos patienter med hjertesygdom.
Viden om patientrapporteret helbred hos patienter med hjertesvigt ved udskrivelse fra en hjerterelateret indlæggelse er dog ikke velafdækket.
Dette Ph.d. studie anvendte data vedrørende patientrapporteret helbred ved brugen af seks spørgeskemaer fra den danske nationale DenHeart Spørgeskemaundersøgelsen og koblede denne information til registeroplysninger og kliniske data fra patienternes journal.
Denne afhandling undersøgte patient-relaterede prædiktorer for patientrapporteret helbred hos patienter med hjertesvigt (studie I). Formålet var at identificere patient-relaterede prædiktorer på tværs af seks patient-rapporterede spørgeskemaer i et tværsnitsstudie af 1.506 patienter med hjertesvigt ved udskrivelse fra en hjerterelateret indlæggelse. Studiets resultater viste, at patienter med høj grad af komorbiditet, en indlæggelse på mere end to dage samt patientrapporteret lavt socialt netværk havde en dårligere score på tværs af de selvrapporterede helbredsmål. Omvendt havde patienter med incident hjertesvigt, mænd, patienter i de højere aldersgrupper, patienter der gennemgik et pacemakerrelateret indgreb under indlæggelse samt patienter med et højere systolisk blodtryk, en bedre score på tværs af de selvrapporterede helbredsmål.
Evidensen af sammenhængen mellem patientrapporteret helbred og risikoen for lavere adhærens til hjertesvigtsmedicin er ikke velafdækket (studie II). Formålet med dette studie var at undersøge

associationen mellem patientrapporteret helbred ved udskrivelse fra en hjerte-relateret indlæggelse og efterfølgende adhærens til hjertesvigtsmedicin hos 1.464 patienter med hjertesvigt.
At få dækket mindre end 80% af behandlingsdagene med medicin, blev defineret som non-adhærens. Resultaterne viste, at patienter, der rapporterede lavere helbredsrelateret livskvalitet, i højere grad var non-adhærente efter et års opfølgning og non-adhærente i brugen af ACE-hæmmer/angiotensin II receptor blokker/angiotensin receptor neprilysin blokker (ACEI/ARB/ARNI) og Beta-blokkere efter tre års opfølgning. Patienter med lavere kardiel helbredsrelateret livskvalitet havde større sandsynlighed for at være non-adhærente i brugen af βeta-blokkere efter et års opfølgning. Sluttelig var symptomer på depression associeret med non-adhærens i brugen af ACEI/ARB/ARNI, βeta-blokkere og mineralocorticoid receptor antagonister (MRAs) efter et års opfølgning og i brugen af ACEI/ARB/ARNI og Beta-blokkere efter tre års opfølgning.
Endelig er den prognostiske indflydelse af patientrapporteret helbred på risikoen for mortalitet og kardiovaskulære hændelser ikke velafdækket (studie III). Formålet med studiet var at undersøge associationen mellem patientrapporteret helbred ved udskrivelse fra en hjerterelateret indlæggelse og efterfølgende øget risiko for mortalitet og kardiovaskulære hændelser efter et- og tre års opfølgning hos 1.499 patienter med hjertesvigt. Studiet viste, at lav helbredsrelateret livskvalitet og symptomer på angst og depression var associeret med øget mortalitet som følge af alle årsager til død og mortalitet som følge af kardiovaskulære årsager efter et- og tre års opfølgning.
Analysen af ikke-dødelige hændelser demonstrerede, at lav helbredsrelateret livskvalitet og symptomer på angst og depression var associeret med en øget risiko for en kardiovaskulær hændelse eller hjertesvigtsrelateret hospitalisering efter et- og tre års opfølgning.
Afslutningsvist demonstrerer fundene på tværs af studie I-III, at patientrapporteret helbred er associerede med efterfølgende non-adhærens til hjertesvigtsmedicin samt en øget risiko for mortalitet og kardiovaskulære hændelser efter et- og tre års opfølgning i denne nationale kohorte af danske patienter med hjertesvigt.

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8. Appendices

Full versions of studies I-III including supplementary material

Predictors of Patient-Reported Outcomes at Discharge in Patients with Heart Failure

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Background

It is well-established that heart failure (HF) has a negative impact on quality of life. However, little is known about patient-related predictors of health-related quality of life, anxiety and depression, symptoms and illness perception among patients with HF.

Aim

To study the association between patient-related predictors and patient-reported outcome measures (PROMs) at discharge from hospital in a cohort of patients with HF.

Methods

We used data from 1,506 patients with HF, participating in the national DenHeart Survey of PROMs in patients with heart disease. The potential patient-related predictors included demographic, administrative, clinical and socioeconomic factors. The PROMs included six questionnaires: The Short Form-12 (SF-12), the Hospital Anxiety and Depression Scale (HADS), the EuroQol five-dimensional, 5-level questionnaire (EQ-5D-5L), the HeartQoL, the Brief Illness Perception Questionnaire (B-IPQ) and the Edmonton Symptom Assessment Scale (ESAS). Data were linked to national patient registry data and medical records. We performed multivariable linear and logistic regression analyses.

Results

In adjusted linear regression analyses we found that length of hospital stay of >2 days was associated with worse scores across questionnaires, except for B-IPQ. Higher comorbidity level was associated with worse scores across all questionnaires, whereas low social support was associated with worse scores across questionnaires, except for the physical domain of the SF-12 and the HeartQoL global score.

Conclusions

This study identified length of hospital stay > 2 days, a higher comorbidity level and low social support to be associated with worse scores across questionnaires at discharge from a cardiac-related hospitalisation in patients with HF.

Keywords: cross-sectional, patient-reported outcomes, patient-related predictors, heart failure

Introduction

Worldwide, heart failure (HF) affects more than 37 million people and carries a high risk of adverse outcomes [1].

In recent years, there has been an increasing interest in patients self-reported health, also known as patient-reported outcome measures (PROMs), in patients with cardiovascular disease [2]. Patient-reported outcome (PRO) data measure functional status, symptoms of anxiety and depression, quality of life and burden of symptoms and reflect the patient's perspective on his or her own disease[2]. Use of PRO data in the clinical setting helps the clinician assess the impact of the disease on every-day life and may be used in the shared decision-making regarding treatment and care [2].

Studies have indicated that self-reported mental and physical health is associated with factors such as age, sex, comorbidity burden, left ventricular ejection fraction (LVEF) and prognosis [3-6]. However, previous studies have primarily been based on single-centre populations, patients with heart disease in general, small populations of patients with HF or outpatients [3, 4, 6]. Although HF is negatively associated with mental and physical health, evidence is sparse on patient-related predictors of PRO data at discharge from a cardiac-related hospitalisation. Moreover, there is also lack of knowledge on how PROMs can be incorporated in the planning of clinical care[7].

This study seeks to gain further knowledge on the clinical utilisation of PROMs as there is a need for establishing simple and effective ways for identifying the most vulnerable patients.

The aim of this study is to identify patient-related characteristics associated with PROMs reflecting both mental and physical health, symptom burden and illness perception in a large national cohort of patients with HF at discharge from a cardiac-related hospitalisation.

Methods

Setting and design

This study was based on data from the DenHeart Survey, a cross-sectional survey consecutively inviting patients with heart disease to answer a panel of PROMs and ancillary questions regarding lifestyle habits at discharge[8]. The survey data were combined with data from national health- and administrative registries and medical records. The healthcare system in Denmark is tax-financed and provides free access to healthcare. Each citizen in Denmark is assigned a unique civil registration number at birth and records of vital status and habitation is kept by the Danish Civil Registration System. Use of the civil registration number, enables individual-level linkage of information across all public Danish registries [9]. Data from the Civil Registration System were linked to the Danish National Patient Registry (DNPR), which entails information on all hospital contacts, hospital procedures and discharge diagnoses [10]. Data regarding socioeconomics and demographics were retrieved from Statistics Denmark. Finally, data on clinical characteristics and HF medication were obtained from medical records. This study only reports results on the population of patients with a HF diagnosis.

Study population

All patients with a primary (main cause of hospitalisation) or secondary HF diagnosis (secondary cause of hospitalisation) at discharge or transfer from one of the five tertiary heart centres in Denmark between April 15, 2013 and April 15, 2014 were eligible for inclusion in this study (International Classification of Diseases, 10th Revision (ICD-10): I110, I13.0, I13.2, I42, I43, I50, I517 and R570). Patients under the age of 18 years, patients without a Danish civil registration number, patients unable to speak and understand Danish, as well as patients unable to participate due to severe illness, were excluded. Severe illness was e.g. terminal illness or unconsciousness.

Patients were asked to fill in the questionnaire at discharge or transfer to another department or hospital, or within three days and return it in a pre-paid envelope. The nurses in the participating departments were informed about how to recruit patients for participation.

The investigation complies with the principles outlined in the Declaration of Helsinki. The study was accepted by the DenHeart Steering Committee (DenHeart registered at ClinicalTrials.gov: NCT01926145). According to Danish law, this study was approved by The Danish Data Protection Agency that approves health research projects (no: 2012-58-006). Written informed consent was obtained from the participants when answering the questionnaire and in addition, access to medical records was approved by The Danish Patient Safety Authority (no: 3-3013-1691). Observational studies do not require approval from an ethics committee according to Danish law.

Patient characteristics

We identified a panel of potential patient-related predictors a priori covering demographics, administrative, clinical and socioeconomic factors at discharge from hospital (Table 1). The patient-related predictors were chosen as they were considered to have potential prognostic significance, easy to obtain and routinely used in clinical practice. Demographic and administrative data were retrieved from the DNPR. Age was divided into three categories: < 65 years (likely workforce attachment), 65-74 years (retired, early pensioners) and ≥ 75 years (old age pensioners) [11]. Length of hospital stay was calculated as days in one of the five heart centres. The Charlson Comorbidity Index (CCI) was calculated as a weighted index, based on all recorded primary and secondary discharge diagnoses the past ten years leading up to the index admission, and categorised as no co-morbidity, moderate co-morbidity level, and high co-morbidity level [12, 13]. Undergoing a device-related procedure included a pacemaker or Implantable Cardioverter Defibrillator (ICD) implantation or replacement during the index hospitalisation. Information on LVEF, systolic blood

pressure and pharmacological therapy was collected from the medical records at index hospitalisation. LVEF was divided into three categories: >40% (reference group), 40-26% and ≤25%[14]. Systolic blood pressure was the last observed value before discharge. Data on HF medication were retrieved at the day of discharge and to indicate the severity of HF, it was dichotomised at ≥ 3 drugs related to treatment of patients with HF including: ACE-inhibitors/ATII-antagonists, Beta-blockers, Mineralocorticoid-receptor-antagonists and diuretics. A single question in the DenHeart Survey regarding social support in daily living was used: "Do you have somebody to talk to when you have problems or are in need of support?". The four response options were dichotomised into: "yes, often or mostly" versus "sometimes, almost never or never". Smoking habits were dichotomised as heavy smoker (≥15 cigarettes per day) among active smokers, and alcohol intake dichotomised at high risk alcohol intake (14 and 21 units in females and males per week, respectively), according to guidelines issued by the Danish Health Authority. Body mass index (BMI) was categorised according to World Health Organization guidelines[15]. Sociodemographic data were obtained from Statistics Denmark and presented from the index year or the previous years.

Patient-reported outcomes

The PROMs applied in this study are widely used in patients with heart disease and in HF and included the following six questionnaires (Table 2): The Short Form-12 (SF-12), a generic questionnaire, covering the past four weeks, measures eight domains of health and generates a mental component score (MCS) and a physical component score (PCS) on a scale from 0-100; a higher score indicates better status [16]. The Hospital Anxiety and Depression Scale (HADS) is a 14-item generic questionnaire, covering one week and produces an anxiety (HADS-A) and a depression (HADS-D) score on a scale from 0-21 with higher scores indicating a possible mood

disorder [17, 18]. The EuroQol five-dimensional, 5-level questionnaire (EQ-5D-5L) is a generic questionnaire measuring five domains of current health-related quality of life, summarised into a total score, where a higher score indicates better health-related quality of life [19, 20]. The HeartQoL questionnaire is a disease-specific measure of health-related quality of life in patients with cardiac disease within the past four weeks, consisting of an emotional and a physical score generating a summarised global score ranging from 0-3 points; higher scores indicating a better state [21, 22]. The Brief Illness Perception Questionnaire (B-IPQ) is a 9-item questionnaire assessing current cognitive and emotional representations of illness. In three items, a reverse score is calculated, since a higher score on the response scale indicates a positive answer, as opposed to the remaining items. The ninth item where patients list causal perceptions of their illness was left out, and total total scores range from 0-80 point [23]. Finally, the Edmonton Symptom Assessment Scale (ESAS) is a generic 10-item questionnaire rating current physical and psychological symptoms. The tenth optional item was left out in this study. The summarised total scores range from 0-90 points and a higher sum score indicates a higher symptom burden [24].

Statistical analysis

Patient characteristics and the scores of the PRO data were presented as numbers (%) or mean (standard deviation (SD)). All PROMs were analysed both on a continuous scale and presented as mean (SD), and dichotomised by the worst quartile on the response scale, presented as proportion (%). In HADS, a cut-off ≥ 8 points was used to indicate symptoms of anxiety and depression [17].

We compared the demographics of responders and non-responders, and patients with a primary versus a secondary HF diagnosis, respectively, using Chi-squared tests and Students *t*-tests. Analysis of variance (one-sided ANOVA) of the mean scores of the PRO data across the five heart centres was performed. Due to missing data on outcome and covariates (ranging from 4-21%),

multiple imputations (MI) was performed. Under the assumption of data being missing at random, we used multiple chained imputations (Markov Chain method) using Rubin's Rule and imputed (m=50) datasets [25, 26].

To analyse the association between patient characteristics and the PROMs on continuous scales, we performed univariable and multivariable linear regression analyses, and repeated the analyses by applying the PROMs dichotomised in a univariable and multivariable logistic regression analysis. All assumptions of statistical tests were tested before analysis. We tested for statistical interaction between sex and age, by introducing age as an interaction term in the regression analyses. All analyses were performed using STATA version 14.0 (StataCorp).

Results

Participants

A total of 3,114 patients were eligible for inclusion and 1,537 patients completed the questionnaire (Fig 1). We excluded 31 patients, due to congenital heart disease (n=8) or because of various acute and life-threatening conditions assessed by the discharge diagnoses: cardiac arrest, ventricular fibrillation and acute thoracic surgery (n=23). In total, 1,506 patients were included in the analyses. No differences were found between responders compared to non-responders in the distribution of sex, age or comorbidity (data not shown). Patients discharged with HF as their secondary discharge diagnosis were slightly older (mean age 65.5 years (95% CI: 64.7-66.3) vs. 67.6 years (95% CI: 66.6-68.6)) and had a higher mean global HeartQoL score than patients with HF as a primary discharge diagnosis (1.44 (95% CI:1.39-1.49) vs. 1.54 (95% CI: 1.47-1.61)). In all remaining PROMs, we found no differences between the two groups (data not shown). Finally, we found no difference in mean scores of the PRO data across the five heart centres in analyses of variance (range of p-values: 0.165-0.977).

Of the 1,506 patients included, 82% had an LVEF ≤40%, two thirds of the patients were outside the workforce and 74% were males. Slightly more than 60% of the patients were 65 years of age or older, had a moderate or high comorbidity level, were acutely admitted and had incident HF (Table 1). Table 2 shows the scores of the six PROMs.

Patient-related predictors and worse patient-reported outcomes

In adjusted linear regression analyses, we found that hospitalisation >2 days, high comorbidity level and low social support was associated with worse scores across the PRO data (fig. 1A-1H, supplementary material).

Overall, we found that hospitalisation >2 days and a high comorbidity level was associated with lower mental and physical health (SF-12), lower health-related quality of life (EQ-5D), lower cardiac health-related quality of life (HeartQoL), more symptoms of anxiety and depression (HADS) and a higher symptom burden (ESAS) in the adjusted analyses. Patients with a high comorbidity level also had a lower illness perception (B-IPQ), but there was no association with length of hospitalisation. Patients with low self-reported social support were more likely to report lower mental health (SF-12 MCS), lower health-related quality of life (EQ-5D), higher anxiety and depression symptom score (HADS), higher symptom burden (ESAS) and a lower illness perception (B-IPQ) in the adjusted analyses. Variances of the regression analyses ranged between (R-squared) 0.09 and 0.21. There was no statistical interaction between sex and age when introducing age as an interaction term in the regression analyses.

Patient-related predictors and better patient-reported outcomes

In adjusted linear regression analyses, we found that being male, undergoing a device-related procedure, increased age, incident HF and higher systolic blood pressure was associated with a better score across the PRO data (fig. 1A-1H, supplementary material).

Males and patients undergoing a device-related procedure were more likely to report better, such as a higher mental and physical health score (SF-12), higher health-related quality of life (EQ-5D), higher cardiac health-related quality of life (HeartQoL), less symptoms of anxiety (HADS-A), a lower symptom burden (ESAS) and a higher illness perception (B-IPQ) in adjusted analyses.

Increasing age and having incident HF was associated with a higher health-related quality of life (EQ-5D), a higher illness perception (B-IPQ) and a lower symptom burden (ESAS) in the adjusted analyses. Patients in the higher age categories also reported higher mental health (SF-12 MCS) and less symptoms of anxiety (HADS-A). Patients with incident HF reported a higher physical health (SF-12 PCS) and less symptoms of depression (HADS-D).

Finally, patients with higher systolic blood pressure were more likely to have higher physical health (SF-12 PCS) and a higher illness perception (B-IPQ), along with less depressive symptoms (HADS-D), higher health-related quality of life (EQ-5D), higher cardiac health-related quality of life (HeartQoL) and a lower symptom burden (ESAS) in the adjusted analyses.

Patient-related predictors in dichotomised patient-reported outcomes

The overall pattern from the multiple linear regression analysis was overall confirmed in an alternative analysis using multivariable logistic regression, where the PRO data were dichotomised and a score in the worst quartile (or a score ≥8 points in the HADS) defined the outcome (Fig. 2A-2H, supplementary material). In this analysis, underweight patients were more likely to have lower mental health (SF-12 MCS) and lower health-related quality of life (EQ-5D) and obese patients

were more likely to report lower physical health (SF-12 PCS), lower health-related quality of life (EQ-5D) and more symptoms of depression (HADS-D) in the adjusted analyses.

In this analysis, having a device-related procedure was no longer associated with higher mental health (SF-12 MCS) and length of hospitalisation and incident HF no longer associated with symptoms of depression (HADS-D) in the adjusted analyses.

Discussion

Our study used the combination of patient self-reported health, register-based and clinical data, which enabled us to characterise a large nationwide population of patients with HF in detail. In contrast to many other studies of PROMs, a comprehensive panel of six PROMs was available, where most often one or two PROMs are used. Thus, the PROMs in this study covered key areas including emotional and physical health-related quality of life, symptoms of anxiety and depression, symptom burden and illness perception.

An overall consistent pattern of associations between a range of patient-related predictors across the PROMs was found.

Comorbidity and length of hospital stay

Comorbidity and length of hospital stay were associated with poor scores across most PROMs. This is in line with a previous Swedish cross-sectional study reporting that having diabetes mellitus and respiratory disease was associated with lower physical health measured by SF-12 in elderly patients with HF [6]. Another Swedish cross-sectional study of comorbidity health-pathways in HF found that patients with comorbid diseases had lower patient-rated health (EQ-5D visual analog scale), than patients without comorbid diseases. The authors also found that these associations differed between

cardiovascular and non-cardiovascular comorbidities, and concluded that the association was explained by anxiety, depression or symptom burden depending on type of comorbidity [27].

The potentially negative impact of comorbidity and severity of HF is also reflected in patients with longer hospitalisations being more likely to report worse across PROMs, however, we have not identified previous studies which have examined length of hospital stay in relation to worse PRO data.

Social support

Another interesting observation in this cohort was that patients with low social support were more likely to report worse scores across almost all PROMs. Living alone was not as strongly associated with a worse score across questionnaires. Civil or cohabitation status is traditionally used as an indicator for practical and emotional support[6, 28, 29]. Our findings may contribute with additional information. Social support as a concept covers several dimensions and includes emotional, informational, instrumental and appraisal support, not only given by family members and spouses, but also by friends, neighbours and colleagues[30]. The association between low social support and worse scores in the PRO data might indicate that it is the substance of support which is of importance instead of solely having a spouse. This was supported in another Danish study of supportive relatives of cardiac patients with anxiety and depression [29]. The authors found that having low or only some degree of support from relatives was associated with depression. Further, stratified by marital status, a stronger association was found between low or some degree of support and anxiety and depression for married patients compared to non-married or widowers. Similarly, a Swedish study of complex social support in patients with HF found that a higher level of social support was associated with a higher mental health, though, in another analysis, not taking health-

related quality of life into account, the authors found that living alone was negatively associated with social support [28].

In conclusion, this result should be interpreted with extreme caution and further data on civil status and type of social support could produce valuable knowledge on the interplay between these factors and their association with PRO data.

Patient-related predictors and better scores

We demonstrated several patient-related predictors to be associated with better scores in adjusted analyses (supplementary material). In accordance with the literature, we found that patients with increased age and male patients were more likely to score better across several PROMs[4, 6]. Patients with incident HF, having a device-related procedure during hospitalisation and higher systolic blood pressure were also more likely to score better across PROMs. The literature is sparse in comparing these findings with our PROMs. Interestingly, undergoing a device-related procedure during hospitalisation is objectively an indication of progress of the disease. However, an active treatment status and possible relief of symptoms may be reflected in better scores. The association between a higher systolic blood pressure and incident HF and a higher score in PRO data may indicate a stable course of the disease without decline in health status yet, resulting in a tendency to report better scores across PROMs.

Strengths and limitations

In this study, we used data from Danish registries with a high completeness and validity[10]. By using data from the DNPR, we were able to collect information on patient demographics and administrative variables in relation to hospitalisation on a patient-level. Another major strength was the use of clinical data from medical records. This enabled us to perform extensive regression

analysis with confounder control. We included patients with HF from all parts of Denmark, which enhances generalisability.

A potential limitation of this study was the non-repsonse rate of 48%, potentially introducing selection bias. However, a sensitivity analysis revealed no differences in the distribution of age, sex and comorbidity between responders and non-responders, indicating a limited impact of selection bias. Missing information was present on the PROMs and on the covariates, potentially leading to biased estimates. To address this, we used multiple imputation, enabling us to perform regression analyses on our entire cohort. The PROMs used in this study were in general accepted in research of patients with heart disease, though not validated specifically in patients with isolated HF.

Finally, a potential risk of bias was the use of a supplementary question regarding level of social support. However, the wording of the question was open for interpretation and was not exclusively restricted to family members or a certain kind of social support.

Conclusion

Patients with HF having a high comorbidity level, hospitalised > 2 days and low social support had a lower mental and physical health, health-related quality of life, illness perception, a higher symptom burden and symptoms of anxiety and depression. These findings were consistent across PROMs and provide information on patient-related predictors associated with the risk of a worse score in the PRO data. This information could potentially help healthcare providers in clinical practice to easily identify the most vulnerable patients with HF and offer special attention towards this group of patients. By identifying the most vulnerable patients in contact with the healthcare system, it may be possible to give these patients a differentiated care to enhance their quality of life and ability for self-care.

Implications for practice

- Patient-related predictors are associated with PRO data at discharge from a cardiac-related hospitalisation
- PROMs have the potential to effectively identify the most vulnerable patients with HF
- PROMs can be incorporated in clinical care of patients with HF

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Declaration of conflicting interests

The authors declare that they have no conflict of interest.

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Figure 1: Flowchart

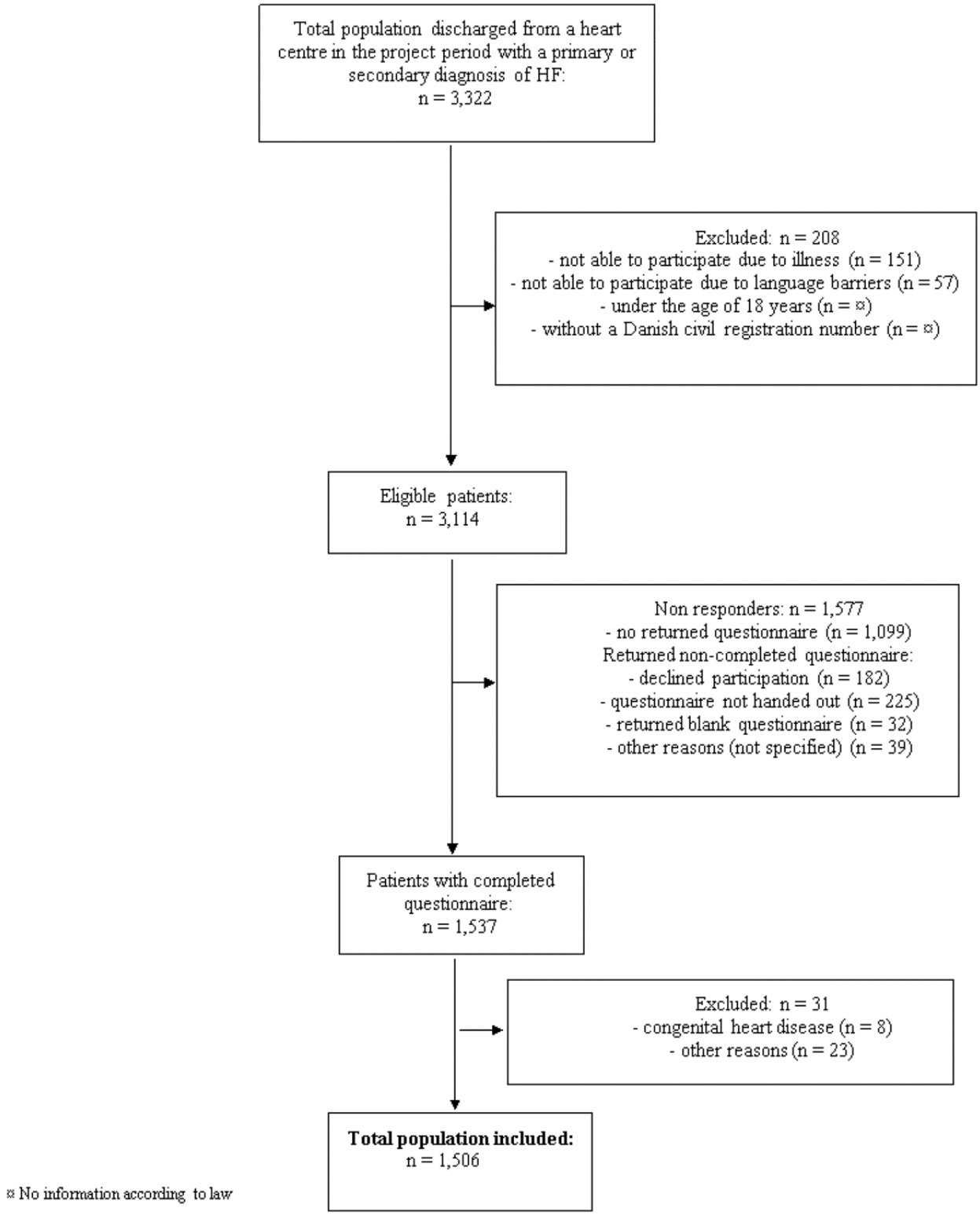


Table 1. Descriptive characteristics in the 1,506 patients[a]

Demographics, n (%)	
Age	
< 65 years	582 (38.7)
65-74 years	511 (33.9)
≥ 75 years	413 (27.4)
Males	1,117 (74.2)
Hospital-related, n (%)	
Length of hospital stay > 2 days	509 (33.8)
Acutely admitted	553 (36.7)
Undisclosed	45 (3.0)
Incident heart failure	552 (36.7)
Comorbidity, n (%)	
Charlson co-morbidity index (CCI)[b]	
No co-morbidity	569 (37.8)
Moderate co-morbidity level	652 (43.3)
High co-morbidity level	285 (18.9)
Clinical characteristics	
Left ventricular ejection fraction, n (%)	
> 40	266 (17.7)
26 - 40	577 (37.0)
≤ 25	622 (41.3)
Undisclosed	61 (4.1)
Systolic blood pressure, mean (SD)	125 (20.6)
Undisclosed	50 (3.3)
Body mass index, n (%)	
Underweight	25 (1.7)
Normal weight	480 (31.9)
Overweight	553 (36.7)
Obese	401 (26.6)
Undisclosed	47 (3.1)
Heavy smokers, n (%)	74 (5.1)
Undisclosed	52 (3.5)
High risk alcohol intake, n (%)	105 (7.0)
Undisclosed	150 (10.0)
Procedures, n (%)	
Device-related procedure	403 (26.8)
HF medication, n (%)[c]	
≥ 3 pharmaceutics, n (%)	899 (59.7)
Undisclosed	23 (1.5)
Sociodemographics, n (%)	
Living alone[d]	462 (30.7)
Undisclosed	6 (0.4)
Low social support	184 (12.2)
Undisclosed	32 (2.1)
Highest completed education[e]	
Basic school	518 (34.4)
Upper secondary or vocational school	666 (44.2)
Higher education	287 (19.1)
Undisclosed	35 (2.3)
Household income[f]	
Low	369 (24.5)

Intermediary high	377 (25.0)
High	371 (24.6)
Very high	378 (25.1)
Undisclosed	11 (0.7)
Attachment to labour market[e]	
Employed	430 (28.6)
Unemployed	32 (2.1)
Outside the workforce	1,041 (69.3)
Undisclosed	3 (0.2)

[a]If nothing stated, the descriptive characteristics are from the index hospitalisation
[b]CCI is calculated as a 10-year index
[c]Missing information on pharmacological treatment in 3 patients and not allowed access to the medical records in 20 patients (1.5%)
[d]Based on data one year prior to index hospitalisation
[e]Based on 2013 data for the entire cohort
[f]Calculated as a 5-year index one year prior to index hospitalisation and five years back

Table 2. Patient-reported outcomes in the 1,506 patients

SF-12 PCS, physical component score[a]	
Mean (SD)	37.5 (10.6)
Undisclosed, n (%)	315 (20.9)
Worst quartile, n (%)	298 (19.8)
SF-12 MCS, mental component score[a]	
Mean (SD)	46.7 (11.6)
Undisclosed, n (%)	315 (20.9)
Worst quartile, n (%)	298 (19.8)
HADS-A, anxiety subscale[b]	
Mean (SD)	5.9 (4.4)
Undisclosed, n (%)	60 (4.0)
≥ 8 points, n (%)	496 (32.9)
HADS-D, depression subscale[b]	
Mean (SD)	5.1 (3.9)
Undisclosed, n (%)	53 (3.4)
≥ 8 points, n (%)	366 (24.3)
EQ-5D-5L[c]	
Mean (SD)	0.73 (0.2)
Undisclosed, n (%)	65 (4.3)
Worst quartile, n (%)	351 (23.3)
HeartQoL, global score[d]	
Mean (SD)	1.5 (0.8)
Undisclosed, n (%)	37 (2.5)
Worst quartile, n (%)	349 (23.2)
Brief Illness Perception Questionnaire[e]	
Mean (SD)	36.1 (14.5)
Undisclosed, n (%)	140 (9.3)
Worst quartile, n (%)	355 (23.6)
Edmonton Symptom Assessment Scale[f]	
Mean (SD)	24.4 (17.7)
Undisclosed, n (%)	92 (6.1)
Worst quartile, n (%)	359 (23.8)

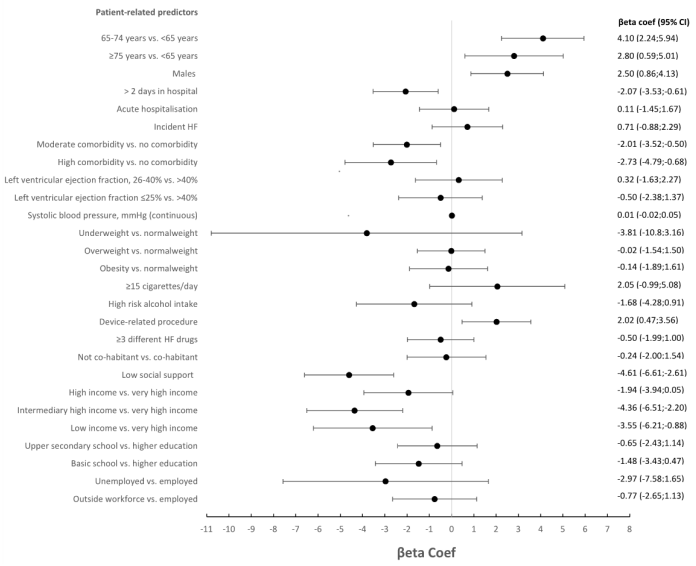
[a]SF-12, the Short Form-12. Range 0-100. A higher score indicates higher health-related quality of life
[b]HADS-A, the Hospital Anxiety and Depression Scale. Range 0-21. A higher score indicates symptoms of anxiety and/or depression
[c]EQ-5D-5L, the EuroQoL five-dimensional, 5-level questionnaire. A higher score indicates higher health-related quality of life
[d]HeartQoL, the HeartQoL global score. Ranges 0-3. A higher score indicates higher cardiac health-related quality of life
[e]Range 0-80. A higher score indicates a lower illness perception
[f]Range 0-90. A higher score indicates a higher symptom burden

Predictors of Patient-Reported Outcomes at Discharge in Patients with Heart Failure

Supplementary figures

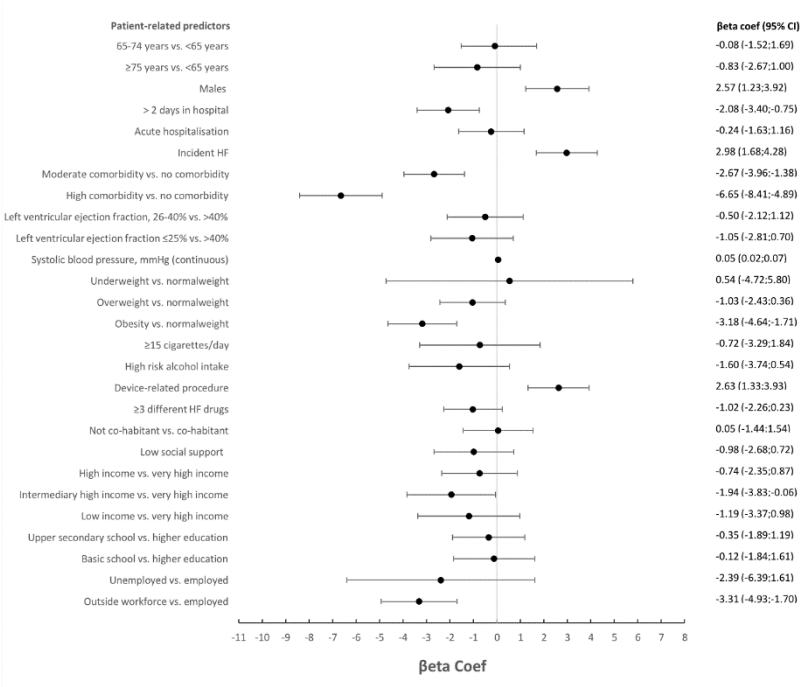
The forest plots 1A-1H are adjusted linear regression analyses of the association between the patient-related predictors and continuous PROMs and the forest plots 2A-2H are adjusted multivariable regression analyses of the association between patient-related predictors and dichotomised PROMs. The βeta coefficients in figure 1A-1H and the OR estimates in figure 2A-H are illustrated by a dot and corresponding 95% confidence intervals (95% CI) are illustrated by the horizontal line. All models are adjusted for all covariates in the model, and 95% CI overlapping the vertical line has not reached a significance level <5%.

Figure 1A: Association between patient-related predictors and the Short Form-12 mental component score (n=1,506)[a]



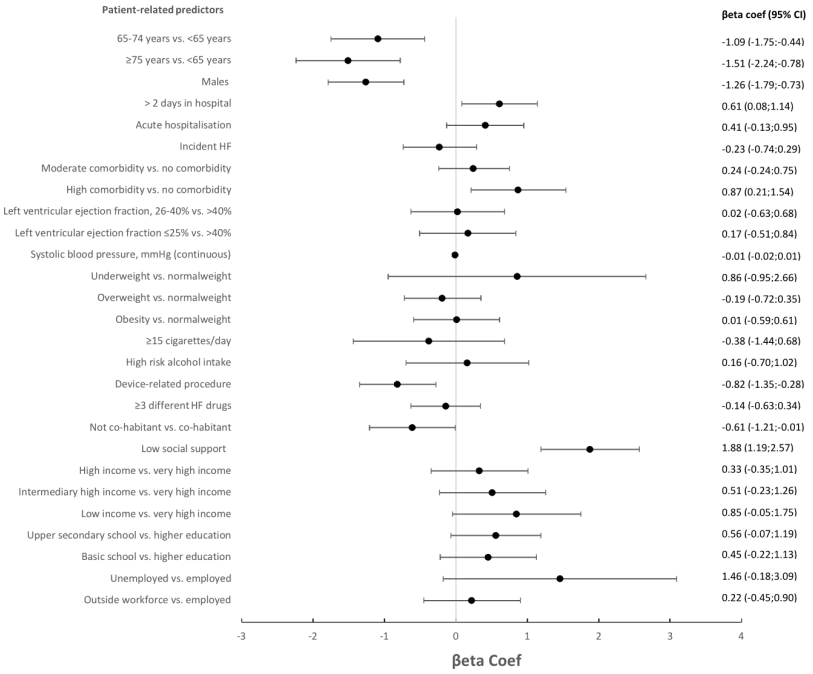
[a]Adjusted linear regression. βeta Coef indicates βeta coefficient; CI, confidence interval. Estimates adjusted for covariates in model

Figure 1B: Association between patient-related predictors and the Short Form-12 physical component score (n=1,506)[a]



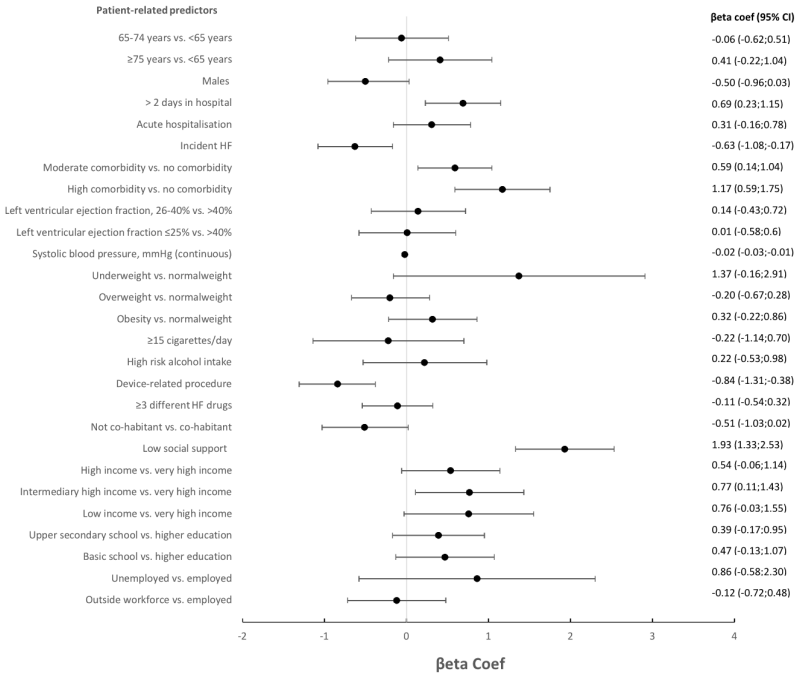
[a]Adjusted linear regression. βeta Coef indicates βeta coefficient; CI, confidence interval. Estimates adjusted for covariates in model

Figure 1C: Association between patient-related predictors and the Hospital Anxiety and Depression Scale, anxiety subscale (n=1,506)[a]



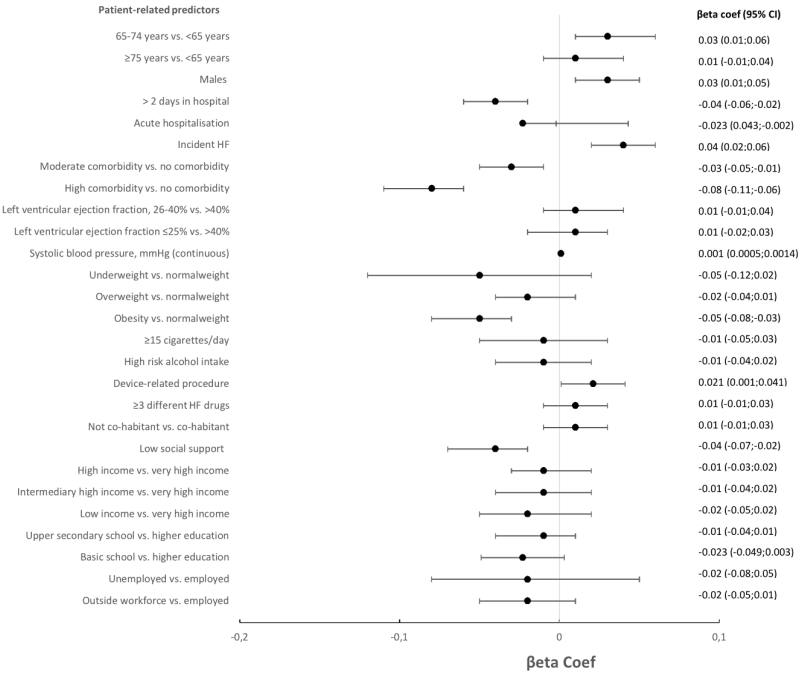
[a]Adjusted linear regression. βeta Coef indicates βeta coefficient; CI, confidence interval. Estimates adjusted for covariates in model

Figure 1D: Association between patient-related predictors and the Hospital Anxiety and Depression Scale, depression subscale (n=1,506)[a]



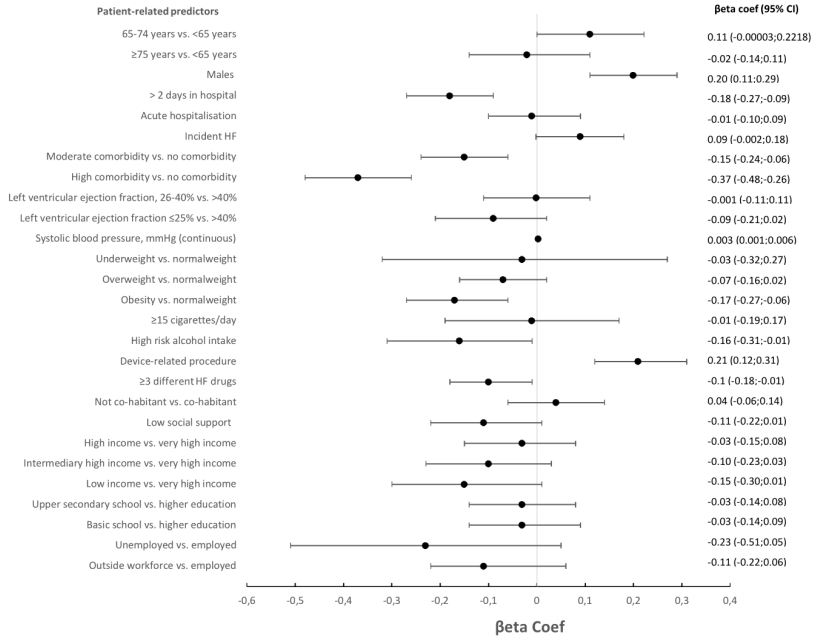
[a]Adjusted linear regression. βeta Coef indicates βeta coefficient; CI, confidence interval. Estimates adjusted for covariates in model

Figure 1E: Association between patient-related predictors and the EQ-5D-5L score (n=1,506)[a]



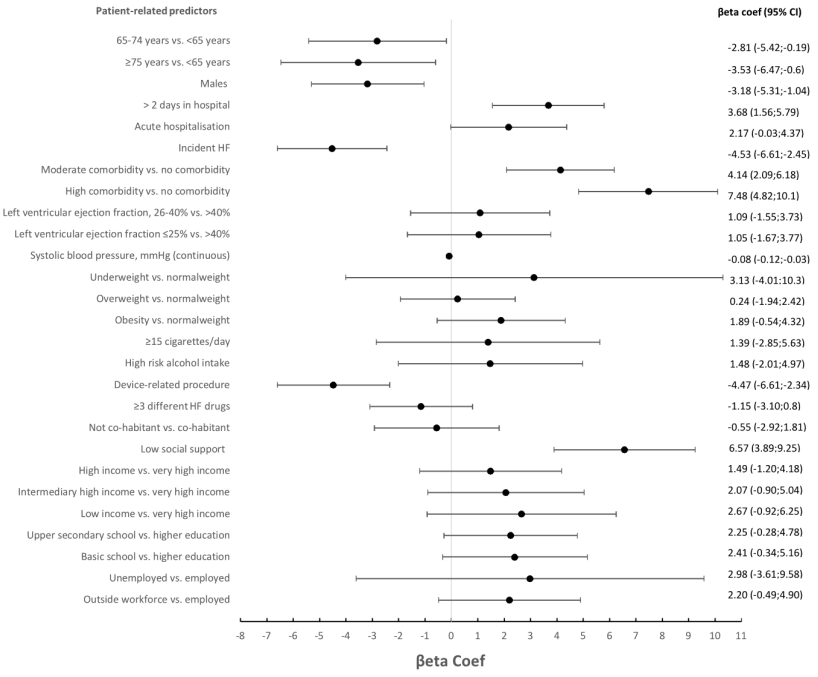
[a]Adjusted linear regression. βeta Coef indicates βeta coefficient; CI, confidence interval. Estimates adjusted for covariates in model

Figure 1F: Association between patient-related predictors and the HeartQoL global score (n=1,506)[a]



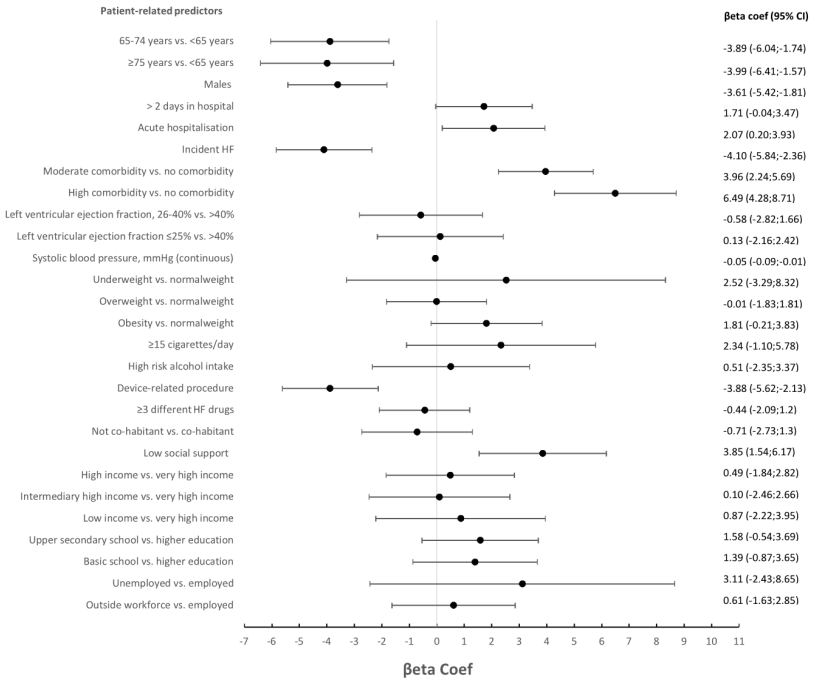
[a]Adjusted linear regression. βeta Coef indicates βeta coefficient; CI, confidence interval. Estimates adjusted for covariates in model

Figure 1G: Association between patient-related predictors and the Edmonton Symptom Assessment Scale (n=1,506)[a]



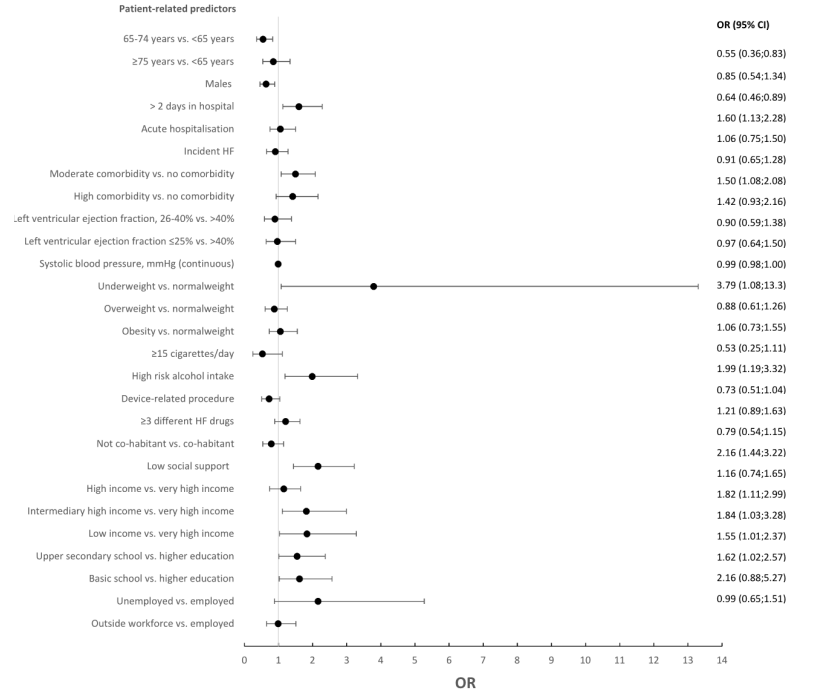
[a]Adjusted linear regression. βeta Coef indicates βeta coefficient; CI, confidence interval. Estimates adjusted for covariates in model

Figure 1H: Association between patient-related predictors and the Brief Illness Perception Questionnaire (n=1,506)[a]



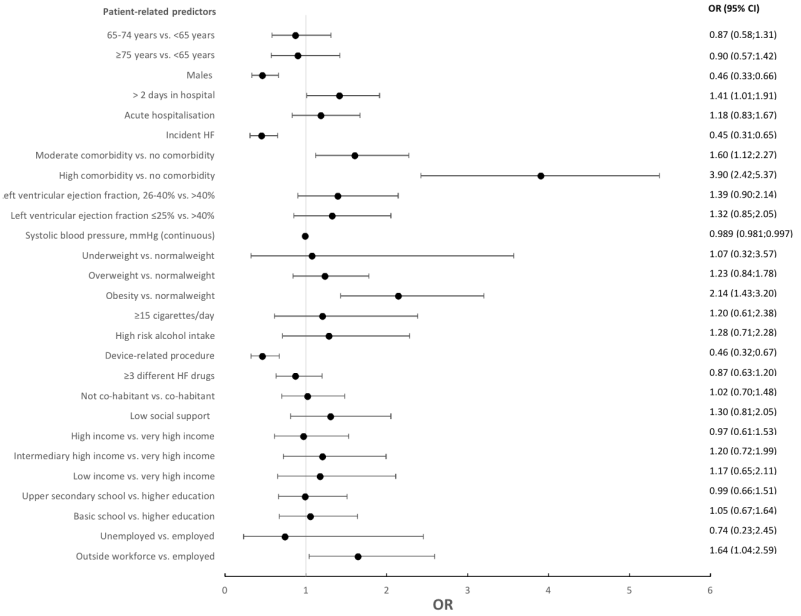
[a]Adjusted linear regression. βeta Coef indicates βeta coefficient; CI, confidence interval. Estimates adjusted for covariates in model

Figure 2A: Association between patient-related predictors and the Short Form-12 mental component score (n=1,506)[a]



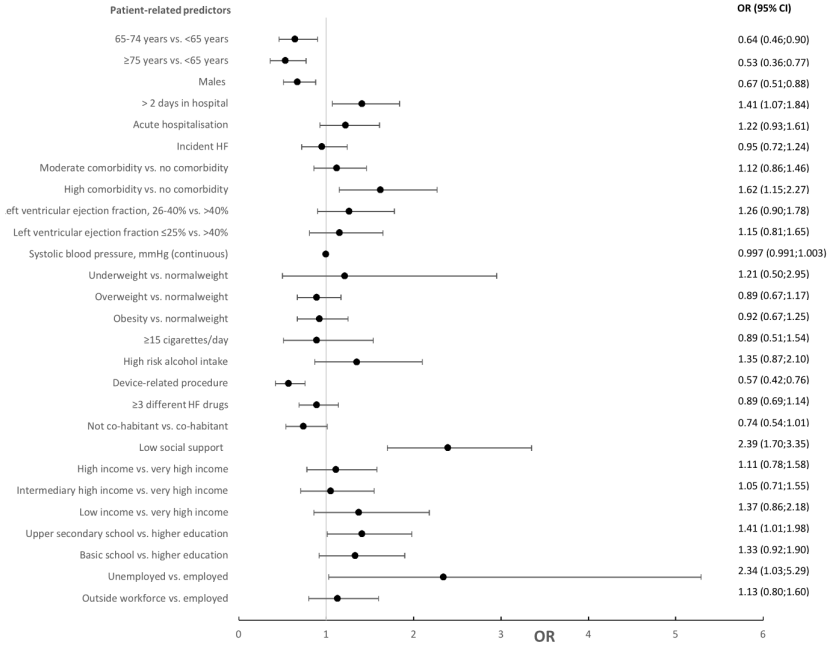
[a]Adjusted logistic regression. OR indicates odds ratios; CI, confidence interval. Estimates adjusted for covariates in model

Figure 2B: Association between patient-related predictors and the Short Form-12 physical component score (n=1,506)[a]



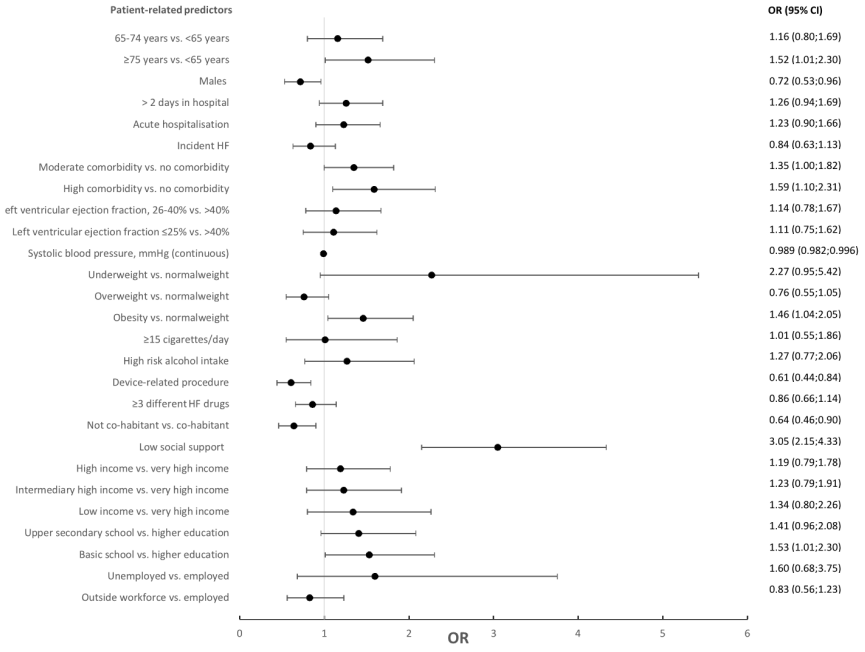
[a]Adjusted logistic regression. OR indicates odds ratios; CI, confidence interval. Estimates adjusted for covariates in model

Figure 2C: Association between patient-related predictors and the Hospital Anxiety and Depression Scale, anxiety subscale (n=1,506)[a]



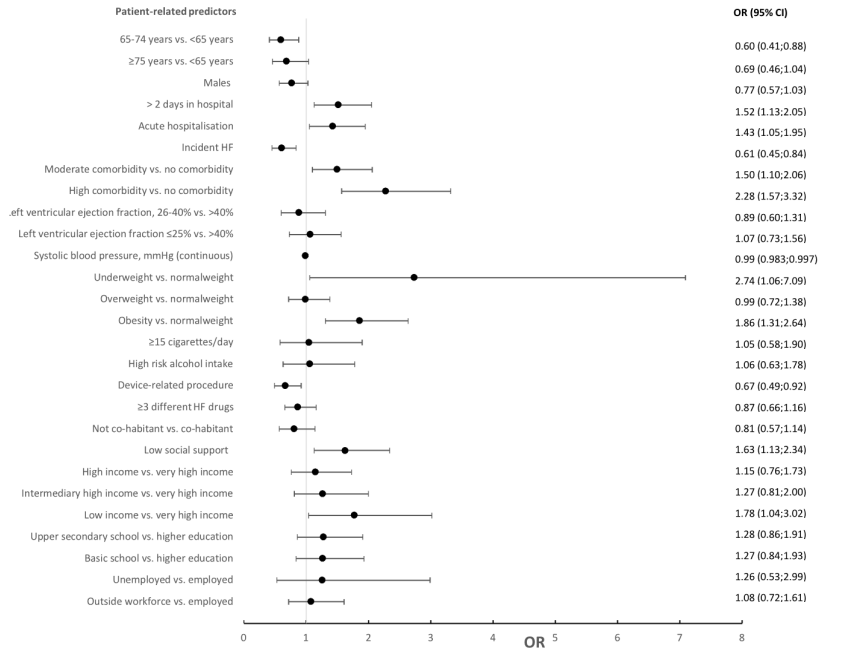
[a]Adjusted logistic regression. OR indicates odds ratios; CI, confidence interval. Estimates adjusted for covariates in model

Figure 2D: Association between patient-related predictors and the Hospital Anxiety and Depression Scale, depression subscale (n=1,506)[a]



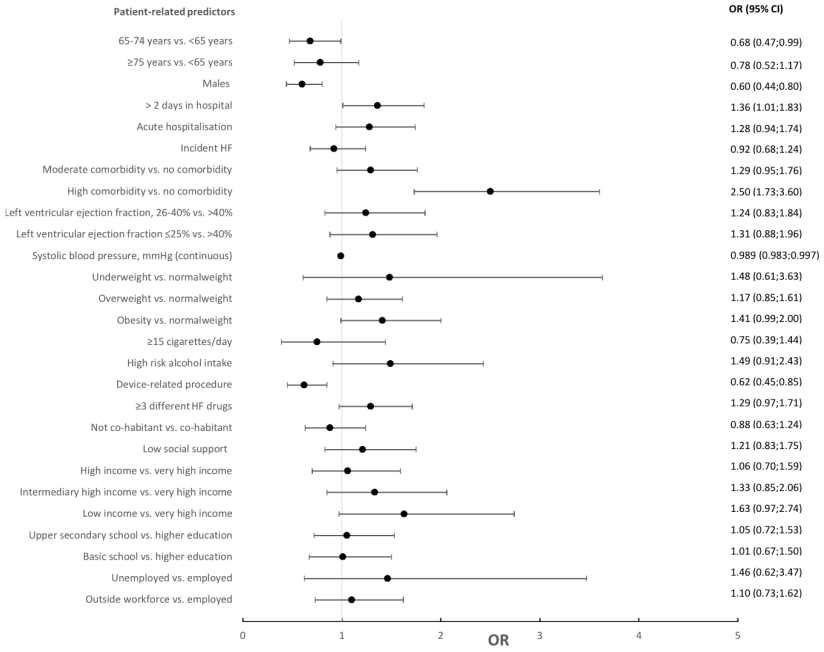
[a]Adjusted logistic regression. OR indicates odds ratios; CI, confidence interval. Estimates adjusted for covariates in model

Figure 2E: Association between patient-related predictors and the EQ-5D-5L score (n=1,506)[a]



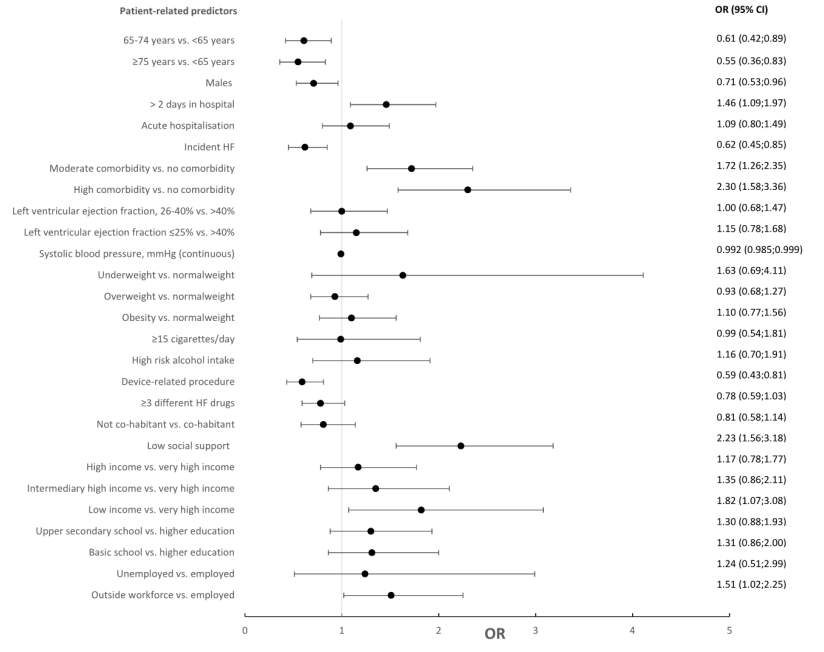
[a]Adjusted logistic regression. OR indicates odds ratios; CI, confidence interval. Estimates adjusted for covariates in model

Figure 2F: Association between patient-related predictors and the HeartQoL global score (n=1,506)[a]



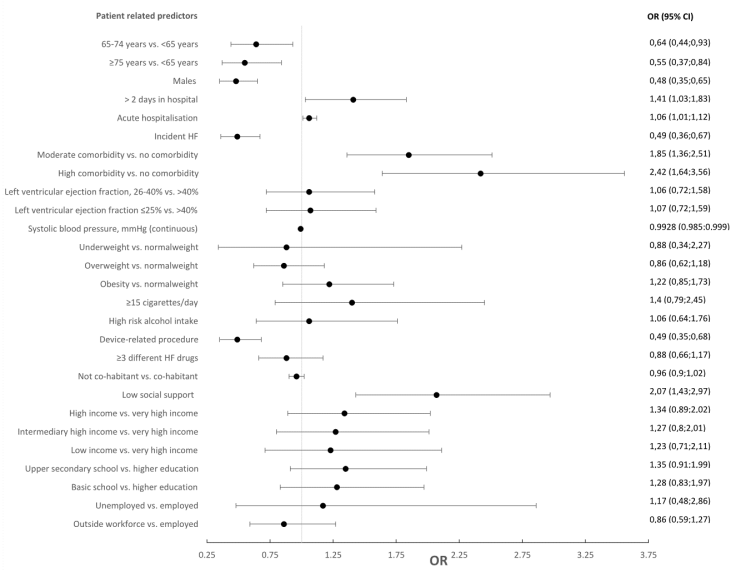
[a]Adjusted logistic regression. OR indicates odds ratios; CI, confidence interval. Estimates adjusted for covariates in model

Figure 2G: Association between patient-related predictors and the Edmonton Symptom Assessment Scale (n=1,506)[a]



[a]Adjusted logistic regression. OR indicates odds ratios; CI, confidence interval. Estimates adjusted for covariates in model

Figure 2H: Association between patient-related predictors and the Brief Illness Perception Questionnaire (n=1,506)[a]



[a]Adjusted logistic regression. OR indicates odds ratios; CI, confidence interval. Estimates adjusted for covariates in model

Patient-Reported Outcomes and Medication Adherence in Patients with Heart Failure

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Abstract

Aim

Patient-reported outcome measures (PROMs) may predict poor clinical outcome in patients with heart failure (HF). It remains unclear whether PROMs are associated with subsequent adherence to HF medication. We aimed to determine whether health-related quality of life, anxiety and depression were associated with long-term medication adherence in these patients.

Methods and results

A national cohort study of Danish patients with HF with three-year follow-up (n=1,464). PROMs included the EuroQol five-dimensional, five-level questionnaire (EQ-5D-5L), the HeartQoL and the Hospital Anxiety and Depression Scale (HADS). Patient-reported outcomes (PRO) data were linked to demographic and clinical data at baseline, and data on all redeemed prescriptions for angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers/angiotensin receptor neprilysin inhibitors (ACEI/ARB/ARNI), β-blockers and mineralocorticoid receptor antagonists (MRAs) during follow-up. Medication non-adherence was defined as <80% of proportion of days covered (PDC). In adjusted regression analyses, low health-related quality of life (EQ-5D and HeartQoL) and symptoms of depression (HADS-D) at discharge were associated with non-adherence. After three years of follow-up, low health-related quality of life (EQ-5D) was associated with non-adherence for ACEI/ARB/ARNI (adjusted OR 2.78, 95% CI:1.19-6.49), β-blockers (adjusted OR 2.35, 95% CI:1.04-5.29), whereas HADS-D was associated with non-adherence for ACEI/ARB/ARNI (adjusted OR 1.07, 95% CI:1.03-1.11) and β-blockers (adjusted OR 1.06, 95% CI:1.02-1.10).

Conclusion

Low health-related quality of life and symptoms of depression were associated with non-adherence across HF medications at one- and three years of follow-up. Person-centred care using PROMs may carry a potential for identifying patients at increased risk of future medication non-adherence.

Key words

Patient-reported outcomes, heart failure, medication adherence

Introduction

Patients with heart failure (HF) have a poor prognosis [1, 2] and are afflicted by a low quality of life including depressive symptoms, and frequent contacts with the healthcare system [3, 4]. Evidence-based HF medication is associated with improved survival and adherence to medical treatment is thus essential to improve prognosis [2]. Non-adherence to HF medication may lead to exacerbations, decline in physical functioning, readmission, death and high healthcare costs [5, 6].

Medication adherence has been estimated to range between 37%-71% in a large sample of healthcare beneficiary patients with HF [7].

A number of patient characteristics have been reported to be associated with non-adherence to HF medication, including age, sex, low health status, low health literacy, and medication side-effects. Better tools are required to identify and target patients at high risk of non-adherence to HF medication [8, 9].

Patient-reported outcome measures (PROMs) are questionnaires with self-reported information by patients regarding subjective health, such as health-related quality of life, symptoms of anxiety and depression or symptom burden. Patient-reported outcome (PRO) data may facilitate a more systematic person-centred approach to care [4, 10]. A few small-scale studies have found depression and anxiety to be associated with medication non-adherence [11, 12]. In addition, a systematic literature review on determinants of non-adherence to HF medication, identified depression as one of several factors [9]. Thus, using PROMs in the clinical setting may have the potential to identify patients at risk of lower adherence to medication, to target individualised care and ultimately lower the risk of adverse outcomes.

However, PROMs have not been investigated in relation to medication adherence in patients with HF using different domains of mental and physical health. We aimed to investigate the

association between health-related quality of life, anxiety and depression and long-term medication adherence among patients with HF.

Methods

Setting and design

This nationwide, cohort study was based on a population of Danish patients with heart failure (HF). We used data from the DenHeart Survey, a collaborative study between the five heart centres in Denmark, collecting PRO data and ancillary information on lifestyle and general health in patients with cardiac disease [13]. Healthcare in Denmark is tax-financed with free access for all citizens and out of hospital medicine expenses are partly reimbursed. The Danish Civil Registration System keeps records of vital status and habitation, using the unique civil registration number, given to each citizen at birth or immigration. This enables linkage of individual level data across all public registries [14].

The investigation conforms with the principles outlined in the *Declaration of Helsinki*. Approval for this study was given by the DenHeart Steering Committee (DenHeart registered at ClinicalTrials.gov: NCT01926145) and the Danish Data Protection Agency (no: 2012-58-006). Patients provided written consent when filling in the questionnaire and in addition, the study was approved by the Danish Patient Safety Authority, authorising access to information from medical records (no: 3-3013-1691).

Study population

Patients discharged from one of the five heart centres in Denmark between 15 April 2013 and 15 April 2014 with a HF diagnosis, either as a primary (main reason for hospitalisation) or secondary discharge diagnosis (secondary reason for hospitalisation) and participating in the DenHeart Survey

were eligible for inclusion in this study (Supplementary table S1: International Classification of Diseases, 10th Revision (ICD-10) codes).

Patients were invited to fill in the questionnaire at discharge, at transfer to another hospital or within three days after discharge. Patients < 18 years, not able to understand written or oral Danish, with no civil registration number or unable to participate due to severe illness such as unconscious or terminal illness were excluded.

Patient-reported outcomes measures

The PROMs included the EuroQol five-dimensional questionnaire five level (EQ-5D-5L), the HeartQoL and the Hospital Anxiety and Depression Scale (HADS). The EQ-5D-5L is a generic questionnaire measuring five domains of current health-related quality of life, where a higher index score indicates higher health-related quality of life. [15]. The HeartQoL is a disease-specific 14-item questionnaire. It measures health-related quality of life in patients with heart disease within the past four weeks. An emotional and a physical score provide a global score ranging from 0-3 points, and a higher score indicates a better state [16, 17]. The HADS is a 14-item generic questionnaire measuring symptoms of anxiety and depression within the last week. It is summarised into a total score between 0-21 points in each of the two subscales, where a higher score indicates a possible mood disorder. The HADS is not a diagnostic tool and will be referred to as symptoms of anxiety (HADS-A) and symptoms of depression (HADS-D) [18-20].

Outcome

Data on HF medication after discharge were retrieved from the Register of Medicinal Product Statistics, with information on all prescriptions redeemed at Danish pharmacies, including date of dispensing, strength and package size [21].

We traced all prescriptions for angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB), β-blockers and mineralocorticoid receptor antagonists (MRAs) using the Anatomical Therapeutic Chemical (ATC) coding system (Supplementary material table S2). In 2016, the Angiotensin receptor neprilysin inhibitor (ARNI) was introduced [2]. For patients dispensing ACEI/ARB, substitution to ARNI during follow-up was allowed and substitution of a within-group pharmaceutical agent was also allowed. Combination drugs defined by medication with ≥ two active drugs were excluded.

Medication non-adherence to ACEI/ARB/ARNI, β-blockers and MRAs was assessed as <80% of proportion of days covered (PDC) [22] according to an individual gold standard. We defined the gold standard in each patient as follows: the first and second redeemed prescription after day ninety in patients alive was traced and estimated the mean daily dose (MDD). The first 90 days following discharge were considered as a blanking period, to allow up-titration, breaks in therapy or change of drug. The MDD was calculated as the number of pills dispensed at the first redemption divided with the number of days between redemption one and two, multiplied with the strength of the pills. This MDD was defined as the maximum tolerable dosage and the gold standard for each patient during follow-up. Adherence was also assessed as dispensed HF medication across three time periods. Here, we estimated the dispensing of zero, one, two or three different drugs (ACEI/ARB/ARNI, βeta-blockers, MRAs) in patients alive in the three time-intervals: three to six months, nine to twelve months and thirty-three to thirty-six months after discharge from the index hospitalisation.

Patient characteristics

A range of demographic and clinical patient characteristics were a priori identified as potential confounding factors. The characteristics were identified based on extensive regression analyses of three PROMs in the DenHeart Survey, where all selected characteristics were associated with a

worse score across PROMs. One question in relation to self-perceived level of social support from the DenHeart Survey was used and the response options were dichotomised. Demographics and data from the index hospitalisation were retrieved from the Danish National Patient Registry (DNPR), including information on all contacts to the Danish healthcare system [23].

Length of hospital stay covered the total number of bed days at index hospitalisation, including any days after transfer from a heart centre, and dichotomised at median (>2) days. Comorbidity was indexed according to the weighted Charlson Comorbidity Index (CCI) using the ICD-10 coding system (Supplementary material table S3), based on every primary or secondary discharge diagnosis 10 years prior to the index hospitalisation and categorised into: no co-morbidity, moderate co-morbidity level and high co-morbidity level [24]. A device-related procedure during index hospitalisation included a pacemaker or an Implantable Converter Defibrillator implantation or replacement. Information on HF-related variables was retrieved from medical records. LVEF was the last measured LVEF, and if missing at index hospitalisation the last measured LVEF was used if referred to as unchanged. Systolic blood pressure (mmHg) was the last observed value during hospitalisation.

Statistical analysis

Baseline was the day of discharge in patients alive at discharge from index hospitalisation. After a blanking period of 90 days, all prescriptions were traced, and the index day was the date of the second redeemed prescription in patients surviving 90 days. Patients dying in the blanking period, were excluded from further analyses. All other patients were followed until emigration, death or end of follow-up after three years.

The PROM scores were presented with mean and standard deviation (SD) and analysed on a continuous scale. As an additional analysis, the scores were also dichotomised by the worst quartile,

except in HADS, where a cut-off at ≥8 points was used [18]. The EQ-5D and the HeartQoL response scales were reversed in the regression analyses, thus a higher score indicated a worse state in all three questionnaires in the regression analyses. A cut-off of <80% of PDC defined medication non-adherence in the primary analysis [22]. The PDC was estimated between every two redeemed prescriptions at one- and three years. To account for short breaks in therapy, 30 grace days between every two redeemed prescriptions were applied.

We used multivariable logistic regression presented with OR estimates and 95% confidence intervals (CI) and adjusted for the selected patient characteristics including age, sex, length of hospital stay, LVEF, comorbidity, systolic blood pressure, incident HF, device-related procedure and self-reported social support. In a secondary analysis, multinomial regression analysis was used to compute relative risk ratios (RRR) and 95% CI of number of dispensed HF medications in three periods after discharge. Dispensing of three different drugs was considered as reference value.

Multiple chained imputations (Markow Chain method) were performed to handle missing data (1.5% to 4.0%). We imputed 50 datasets, using Rubin's Rule, under the assumption of data being missing at random [25]. All assumptions behind the applied statistical tests were tested before analysis.

We performed sensitivity analyses and tested for interaction prior to the regression analyses. In the sensitivity analyses, 14 grace days were applied to assess the robustness of our primary analysis and tested for interaction by age and sex. Analyses were performed using STATA version 14.0 (StataCorp).

Results

Participants

Of 3,114 eligible patients with HF, a total of 1,537 patients completed the questionnaire. We excluded a total of 73 patients due to congenital heart disease (n=8) and acute life-threating conditions (n=23) including cardiac arrest, ventricular fibrillation and acute thoracic surgery. Finally, patients dying during the 90-day blanking period after discharge from index hospitalisation (n=42) were excluded. A total of 1,464 patients were included in the study (Figure 1).
In all, 74.1% of the patients were males and 81.3% had an LVEF ≤40%. A total of 61.7% of the patients had a moderate or a high comorbidity level and 37% of the patients had incident HF (Table 1). Table 2 shows the PROM scores at discharge.

Medication non-adherence

We found that 30.1% of the patients using ACEI/ARB/ARNI and 29.3% of the patients using β-blockers and 23.2% of the patients using MRAs were non-adherent at one-year follow-up (Table 3). After three years of follow-up, 64.2% of the patients were non-adherent in the use of ACEI/ARB/ARNI, 59.9% of the patients using β-blockers and 63.7% of the patients using MRAs (Figure 2).

Association between PROMs and medication non-adherence

Using multivariable logistic regression, we demonstrated associations between the PRO data at discharge from a cardiac-related hospitalisation and subsequent medication adherence.

We found that patients reporting a lower health-related quality of life (EQ-5D), were more likely to be non-adherent in the use of MRAs (adjusted OR 3.49, 95% CI: 1.10-11.1) at one-year follow-up. Low health-related quality of life was also associated with higher odds of being non-adherent

after three-year follow-up when using ACEI/ARB/ARNI and β-blockers (adjusted ORs 2.78, 95% CI: 1.19-6.49 and 2.35, 95% CI: 1.04-5.29, respectively). Patients reporting scores within the worst quartile of the EQ-5D were more likely to be non-adherent in β-blockers after three-year follow-up (Table 4).

Lower cardiac health-related quality of life (HeartQoL) was associated with non-adherence in the use of β-blockers at one-year follow-up, when analysing the HeartQoL on a continuous scale (adjusted OR 1.26, 95% CI: 1.06-1.49) and at three-year follow-up when dichotomising the HeartQoL (adjusted OR 1.37, 95% CI: 1.01-1.87) (Table 3 and 4).

Finally, patients with a higher score on the HADS-D, indicating symptoms of depression, were more likely to be non-adherent at one year for all three drug classes: ACEI/ARB/ARNI (adjusted OR 1.04, 95% CI: 1.01-1.07), β-blockers (adjusted OR 1.05, 95% CI: 1.02-1.09) and MRAs (adjusted OR 1.06, 95% CI; 1.01-1.11) (Table 3). At three-year follow-up, we also found an association between symptoms of depression (HADS-D) and non-adherence in patients using ACEI/ARB/ARNI (adjusted OR 1.07, 95% CI: 1.03-1.11) and β-blockers (adjusted OR 1.06, 95% CI: 1.02-1.10), but not in patients using MRAs (Table 4). When dichotomising the PROM scores at one and three-year follow-up, a score ≥ 8 points indicating symptoms of depression (HADS-D) remained associated with non-adherence in all estimates across drugs, except in the use of ACEI/ARB/ARNI at one-year follow-up (Tables 3 and 4). Symptoms of anxiety according to the HADS did not show any association with non-adherence in any analyses.

Association between PROMs and dispensed HF medication

The association between PRO data at discharge from a cardiac hospitalisation and number of subsequent dispensed HF medications were examined in multinomial adjusted regression analyses (Supplementary tables, S4-S6).

A lower cardiac health-related quality of life (HeartQoL) score was associated with the dispensing of one drug compared to three drugs nine to twelve months after discharge (adjusted RRR 1.32, 95% CI: 1.05-1.65). A score in the worst quartile of the HeartQoL was associated with a 1.5-fold to a 1.9-fold increase risk of dispensing two or one drug compared to three drugs after discharge nine to twelve and thirty-three to thirty-six months after discharge (Supplementary tables S5-S6).

Nine to twelve months after discharge, patients with a higher score on the HADS-D at discharge, indicating symptoms of depression, were more likely to dispense only one or zero drugs compared to three drugs (adjusted RRRs 1.05, 95% CI: 1.01-1.10 and 1.08, 95% CI: 1.03-1.14, respectively) (Supplementary table S5).

A score in the worst quartile on the respondent scale of the EQ-5D indicating lower health-related quality of life was associated with the dispensing of one drug compared to three drugs in nine to twelve months after discharge (Supplementary table S5).

Symptoms of anxiety (HADS-A) were associated with a higher risk of only dispensing one drug compared to three drugs, three to six months after discharge (adjusted RRR 1.06, 95% CI: 1.01-1.10) (Supplementary table S4-S6). When dichotomising the PROM scores, having ≥8 points on the anxiety subscale of HADS, nine to twelve months after discharge and ≥8 points on the depression subscale of HADS, 33-36 months after discharge was associated with a higher risk of dispensing no drugs compared to three drugs (Supplementary tables S4-S6).

Finally, none of the PROMs analysed on a continuous scale were associated with dispensing of drugs in the last period of 33-36 months after discharge in adjusted analyses (Supplementary tables S4-S6).

Discussion

The results from this large nationwide study suggest that low health-related quality of life and symptoms of depression at discharge from a cardiac hospitalisation were associated with HF medication non-adherence after follow-up at one- and three years.

PROMs and HF medication non-adherence

To our knowledge, this is one of the first nationwide cohort studies investigating the association between a combination of PROMs at discharge from a cardiac-related hospitalisation, including the EQ-5D, the HeartQoL and the HADS and subsequent medication non-adherence in patients with HF.

Medication adherence in HF has been widely investigated, but few studies have addressed the role of health-related quality of life or anxiety and depression. No studies of the EQ-5D or the HeartQoL in relation to medication adherence in patients with HF were identified. A systematic review from 2011 included 11 studies on determinants of medication adherence in HF and identified three studies presenting conflicting results regarding depression as a risk factor of medication non-adherence [9]. None of the three studies used PROMs assessed by the HADS [26-28]. Two studies found a non-significant association between depression and medication non-adherence [27, 28], whereas one study found "carelessness" from the patients about medication adherence in depressed patients [26]. The lack of evidence of a clear association in these studies may reflect small population sizes ranging from 51-134 patients [26-28], or that medication adherence was assessed by self-reported measurements rather than more objective methods [26, 27].

In the present study, we did not find any association between symptoms of anxiety and non-adherence. However, in the analyses of number of dispensed HF medications, symptoms of anxiety were associated with dispensing of only one drug in three to six months and no drugs in nine to

twelve months. These findings correspond to a randomised trial of a 12-week collaborative care intervention of health behaviours in 134 patients with cardiac disease, including HF. Patients were randomised to a care manager coordinating physiatrists recommendations or usual care and one of the items of assessed health behaviour was self-reported medication adherence [29]. Patients allocated to the intervention had significantly less symptoms of anxiety after six weeks and showed improvement in self-reported adherence. In contrast to our findings of dispensed medication, the association did not remain at six-month follow-up [29]. The lack of association over time may be a result of a small sample size, short follow-up, only one item of adherence covered medication or study design. High-intensity intervention has been shown to lead to immediate improvements, but maintenance of achieved health behaviours over time may be more challenging [27].

In our study, we did not identify an association between symptoms of anxiety and non-adherence to HF medication. However, symptoms of depression were associated with non-adherence across HF medication in our analyses. A possible explanation could be how these symptoms affect the individual person. Key symptoms of depression might be characterised by impaired motivation and loss of initiative, potentially leading to risk of lower medication adherence as opposed to symptoms of anxiety, where patients might be more focused on adherence to healthcare recommendations, including medication.

Clinical implications

It is well-established that adherence to evidence-based HF medication is pivotal when trying to reduce mortality and risk of adverse outcomes, and knowledge about modifiable factors in relation to medication adherence is essential.

Our findings support the utility of using PROMs in patients with HF. Use of PROMs does not only map the subjective health but appears also to provide valuable information on patients at risk of non-adherence to HF medication.

We demonstrated a consistent pattern of symptoms of low health-related quality of life and symptoms of depression at discharge and subsequent risk of medication non-adherence. This underlines the potential value of implementing PROMs in routine care. Hence, screening patients for symptoms of depression and mapping health-related quality of life may enable targeted individualised efforts to assist vulnerable patients, which could well be an efficient way of optimising and improving HF care in settings with limited resources.

Strengths and limitations

A major strength of this study was the combination of self-reported information, data from registries and clinical information from medical records, ensuring detailed data on all patients and enabling thorough adjustment for confounding. The nationwide design enhanced the generalisability of results.

Data from Danish registries have a high completeness and are validated for epidemiological use [23]. Using data from the Register of Medicinal Product Statistics enabled us to track every redeemed prescription over time, with no risk of recall bias from patients. However, although repeated redemption of prescriptions of patient co-paid HF medication would indicate that the patients also took the medication, we have no objective proof of that.

Using a blanking period and beginning the register-based follow-up with data from the Register of Medicinal Product Statistics approximately three months after completing the questionnaire could have influenced the given answers over time. Though it is not straightforward to predict

whether the time passed would reflect a better or worse score. Moreover, the PROMs used were survey data at discharge and hence no repeated measurements of the PRO data were available.

Non-response was 48%, but sensitivity analyses showed no differences between responders and non-responders, limiting the risk of selection bias. Furthermore, we were unable to distinguish between non-adherence and patients not prescribed the HF medication of interest in this study.

Conclusion

Lower health-related quality of life and symptoms of depression were associated with HF medication non-adherence over time. These findings were independent of other well-established prognostic factors. This knowledge stresses the potential of measuring health-related quality of life and symptoms of depression to target differentiated treatment and care and subsequently improve the prognosis in patients with HF.

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Conflicts of interest

SPJ has been paid as a consultant/speaker by Bayer, Bristol-Myers Squibb, Pfizer and Sanof and received research grants from Bristol-Myers Squibb and Pfizer (unrelated to the current study). None of the other authors have any conflicts to declare.

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Figure 1: Flowchart

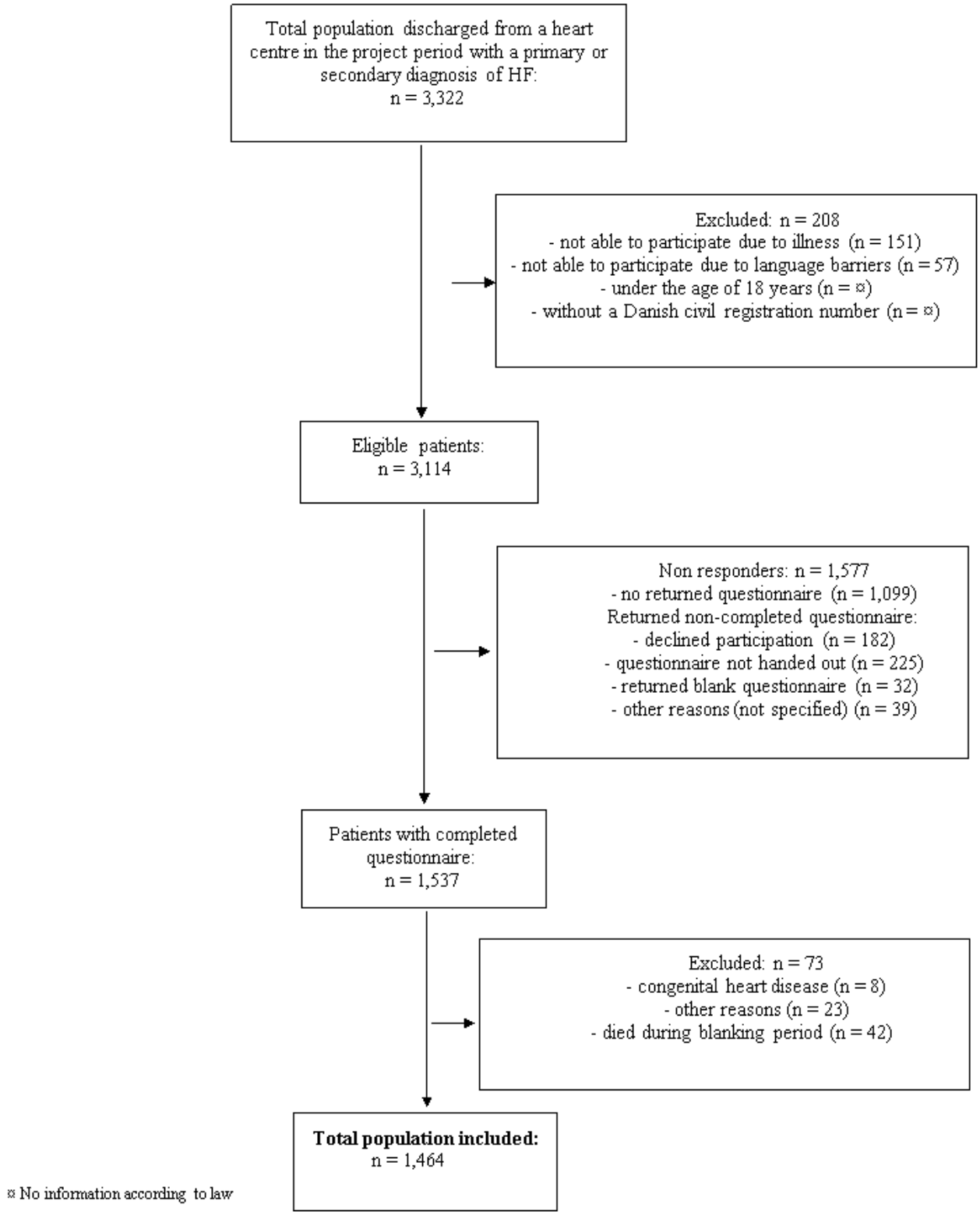


Table 1. Descriptive characteristics (n=1,464)[a]

Demographics	
Males, n (%)	1,085 (74.1)
Age, n (%)	
< 65 years	574 (39.2)
65-74 years	498 (34.0)
≥ 75 years	392 (26.8)
Low social support	181 (12.4)
Undisclosed	28 (1.9)
Comorbidity, n (%)	
Charlson co-morbidity index (CCI)[b]	
No co-morbidity	561 (38.3)
Moderate co-morbidity level	640 (43.7)
High co-morbidity level	263 (18.0)
Procedures, n (%)	
Device-related procedure	393 (26.8)
Clinical characteristics	
Length of hospital stay, > 2 days	513 (35.0)
Incident heart failure, n (%)	541 (37.0)
Left ventricular ejection fraction, n (%)	
> 40	261 (17.8)
26 - 40	549 (37.5)
≤ 25	596 (40.7)
Undisclosed	58 (4.0)
Systolic blood pressure (mmHg), mean (SD)	126 (20.4)
Undisclosed	48 (3.3)

[a]If nothing stated, the descriptive characteristics are from the index hospitalisation

[b]CCI is calculated as a weighted 10-year index

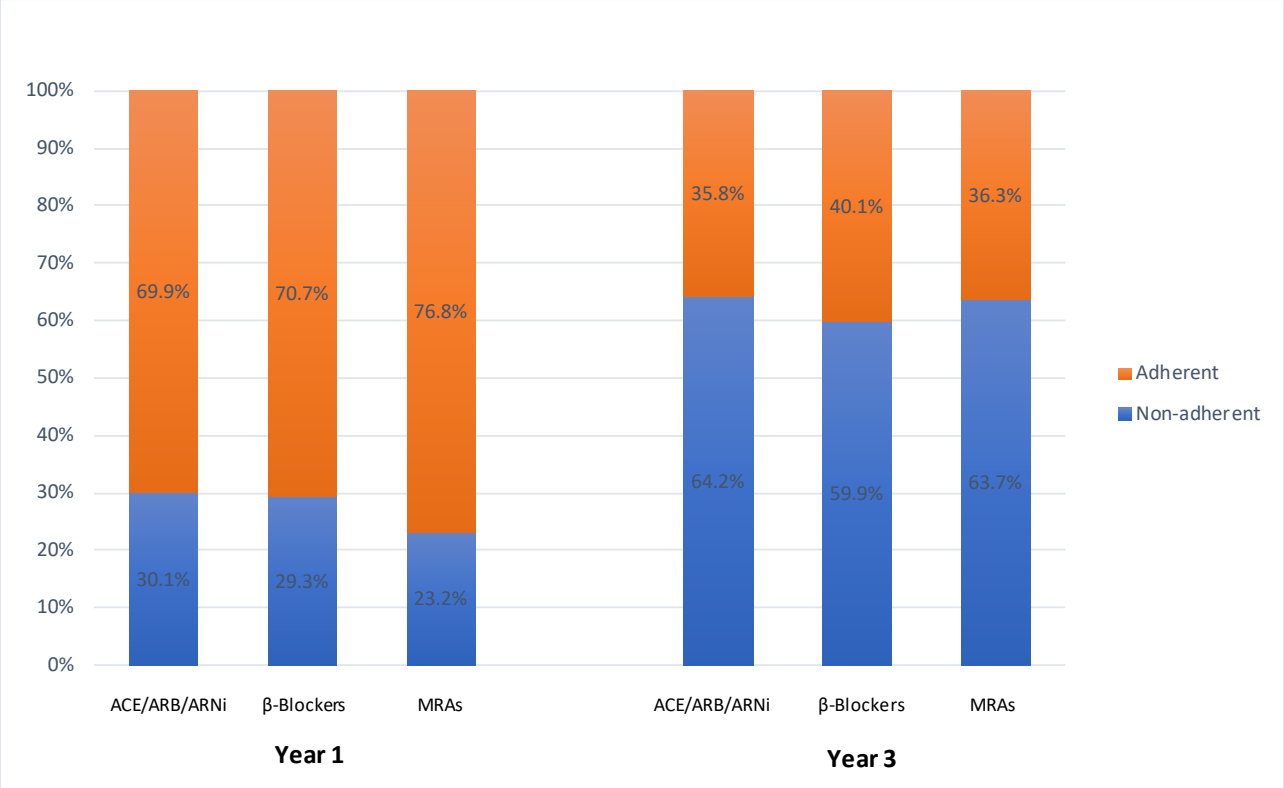
Table 2. Patient-reported outcomes at discharge (n=1,464)

EQ-5D-5L	
Mean (SD)	0.73 (0.2)
Worst quartile, n (%)	329 (22.5)
Undisclosed	59 (4.0)
HeartQoL global score	
Mean (SD)	1.5 (0.8)
Worst quartile, n (%)	331 (22.6)
Undisclosed	36 (2.5)
HADS, anxiety subscale	
Mean (SD)	5.8 (4.3)
≥ 8 points, n (%)	473 (32.3)
Undisclosed	57 (3.9)
HADS, depression subscale	
Mean (SD)	5.0 (3.8)
≥ 8 points, n (%)	345 (23.6)
Undisclosed	51 (3.5)

EQ-5D-5L, the EuroQoL five-dimensional, five-level questionnaire.

HeartQoL global score, the HeartQoL global score; HADS-A and HADS-D, the Hospital Anxiety and Depression Scale, anxiety and depression subscale, respectively

Figure 2: proportion of HF medication non-adherence after one- and three years*



*In patients redeeming at least two prescriptions after discharge from index hospitalisation

Table 3: Association between health-related quality of life, symptoms of anxiety and depression at discharge and one-year HF medication non-adherence[a]

	Continuous PRO data			Dichotomised PRO data	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**[b]		**Crude OR (95% CI)**	**Adjusted OR (95% CI)**[b]
ACEI/ARB/ARNI, n=1,118			**ACEI/ARB/ARNI, n=1,118**		
EQ-5D-5L	1.02 (0.48-2.17)	1.20 (0.53-2.70)	EQ-5D-5L	1.06 (0.79-1.42)	1.10 (0.81-1.50)
HeartQoL global	1.07 (0.91-1.26)	1.08 (0.91-1.28)	HeartQoL global	1.06 (0.79-1.42)	1.10 (0.81-1.49)
HADS-A	0.98 (0.96-1.01)	0.99 (0.96-1.02)	HADS-A	0.81 (0.62-1.06)	0.84 (0.63-1.11)
HADS-D	1.03 (0.99-1.06)	1.04 (1.01-1.07)	HADS-D	1.21 (0.90-1.60)	1.24 (0.92-1.66)
β -blockers, n=1,248			**β -blockers, n=1,248**		
EQ-5D-5L	2.47 (1.18-5.16)	2.11 (0.97-4.61)	EQ-5D-5L	1.38 (1.04-1.83)	1.31 (0.98-1.77)
HeartQoL global	1.31 (1.11-1.54)	1.26 (1.06-1.49)	HeartQoL global	1.33 (0.99-1.77)	1.25 (0.93-1.68)
HADS-A	1.01 (0.98-1.04)	1.01 (0.98-1.04)	HADS-A	1.13 (0.87-1.46)	1.10 (0.84-1.45)
HADS-D	1.06 (1.02-1.09)	1.05 (1.02-1.09)	HADS-D	1.52 (1.15-2.00)	1.47 (1.10-1.97)
MRAs, n=686			**MRAs, n=686**		
EQ-5D-5L	3.50 (1.17-10.4)	3.49 (1.10-11.1)	EQ-5D-5L	1.47 (0.97-2.24)	1.48 (0.96-2.29)
HeartQoL global	1.10 (0.87-1.40)	1.10 (0.86-1.42)	HeartQoL global	0.88 (0.57-1.35)	0.86 (0.55-1.34)
HADS-A	1.02 (0.98-1.06)	1.02 (0.98-1.07)	HADS-A	1.13 (0.78-1.65)	1.12 (0.75-1.67)
HADS-D	1.06 (1.01-1.11)	1.06 (1.01-1.11)	HADS-D	1.63 (1.09-2.44)	1.62 (1.06-2.48)

[a]Multivariable logistic regression; OR, indicates odds ratio; CI, confidence interval

[b]OR were adjusted for the following: age, sex, length of hospital stay, Charlson Comorbidity Index score, left ventricular ejection fraction, social support, device-related procedure, incident HF and systolic blood pressure (mmHg)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; EQ-5D-5L, the EuroQoL five-dimensional, five-level questionnaire; HADS-A and HADS-D, the Hospital Anxiety and Depression Scale, anxiety (HADS-A) and depression (HADS-D) subscale, respectively; HeartQoL global, the HeartQoL global score; MRAs; mineralocorticoid receptor antagonists

Table 4: Association between health-related quality of life, symptoms of anxiety and depression at discharge and three-year HF medication non-adherence[a]

	Continuous PRO data			Dichotomised PRO data	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**[b]		**Crude OR (95% CI)**	**Adjusted OR (95% CI)**[b]
ACEI/ARB/ARNI, n=1,118			**ACEI/ARB/ARNI, n=1,118**		
EQ-5D-5L	3.18 (1.42-7.09)	2.78 (1.19-6.49)	EQ-5D-5L	1.33 (0.97-1.82)	1.30 (0.94-1.79)
HeartQoL global	1.17 (0.99-1.37)	1.12 (0.94-1.33)	HeartQoL global	1.01 (0.75-1.36)	0.96 (0.71-1.31)
HADS-A	1.03 (0.99-1.06)	1.03 (0.99-1.06)	HADS-A	1.11 (0.85-1.45)	1.12 (0.84-1.48)
HADS-D	1.08 (1.04-1.12)	1.07 (1.03-1.11)	HADS-D	1.64 (1.20-2.23)	1.55 (1.12-2.14)
β -blockers, n=1,248			**β -blockers, n=1,248**		
EQ-5D-5L	3.51 (1.62-7.60)	2.35 (1.04-5.29)	EQ-5D-5L	1.55 (1.15-2.09)	1.38 (1.01-1.89)
HeartQoL global	1.27 (1.09-1.49)	1.17 (0.99-1.37)	HeartQoL global	1.54 (1.14-2.07)	1.37 (1.01-1.87)
HADS-A	1.02 (0.99-1.05)	1.01 (0.98-1.04)	HADS-A	1.11 (0.86-1.43)	1.03 (0.79-1.35)
HADS-D	1.07 (1.04-1.11)	1.06 (1.02-1.10)	HADS-D	1.70 (1.26-2.29)	1.53 (1.13-2.08)
MRAs, n=686			**MRAs, n=686**		
EQ-5D-5L	0.94 (0.34-2.55)	0.87 (0.30-2.53)	EQ-5D-5L	0.72 (0.49-1.05)	0.71 (0.47-1.06)
HeartQoL global	1.07 (0.87-1.33)	1.06 (0.85-1.33)	HeartQoL global	0.87 (0.60-1.27)	0.85 (0.57-1.26)
HADS-A	0.97 (0.94-1.01)	0.98 (0.94-1.02)	HADS-A	0.77 (0.55-1.08)	0.77 (0.54-1.10)
HADS-D	1.01 (0.96-1.05)	1.01 (0.96-1.05)	HADS-D	0.94 (0.64-1.38)	0.97 (0.64-1.46)

[a]Multivariable logistic regression; OR, indicates odds ratio; CI, confidence interval

[b]OR were adjusted for the following: age, sex, length of hospital stay, Charlson Comorbidity Index score, left ventricular ejection fraction, social support, device-related procedure, incident HF and systolic blood pressure (mmHg)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; EQ-5D-5L, the EuroQoL five-dimensional, five-level questionnaire; HADS-A and HADS-D, the Hospital Anxiety and Depression Scale, anxiety (HADS-A) and depression (HADS-D) subscale, respectively; HeartQoL global, the HeartQoL global score; MRAs; mineralocorticoid receptor antagonists

Supplementary material

Table S1: Codes used to include patients

Name	
International Classification of Diseases, 10th Revision (ICD-10) codes	I110, I13.0, I13.2, I42, I43, I50, I517 and R570

Table S2: List of ATC codes

Name	**ATC code**
angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers	C09AA-C09AA16 C09CA01-C09CA10
β-blockers	C07-C07AG02
mineralocorticoid receptor antagonists	C03DA-C03DA04
ARNI	C09DX04

Table S3: Charlson Comorbidity Index Score

	ICD-10	Weight
Myocardial infarction	I410 I21 I22 I252	1
Congestive heart failure	I099, I110, I13.0, I13.2, I42, I43, I50, I255, I517, P290, R570	1
Peripheral vascular disease	I70, I71, I73, I77, I79, K551 K558 K559 Z958 Z959	1
Cerebrovascular disease	G45, G46, H340, I6, I61, I62, I63, I64, I65, I66, I67, I68, I69	1
Dementia	F00 F01 F02 F03 F051 G30 G311	1
Chronic pulmonary disease	I278, I279, J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J684, J701, J703	1
Rheumatic disease	M05, M06, M315, M32, M33, M34, M351, M353, M360	1
Peptic ulcer disease	K25, K26, K27, K28	1
Mild liver disease	B18, K700 K701 K702 K703, K709, K73, K74, K712, K712, K713, K714 K715 K717, K760 K762 K763 K764 K768 K769 DB18, Z944	1
Diabetes without organ damage	E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149	1
Diabetes with end-organ damage	E102, E103, E104, E105, E107, E112, E113, E114, E115, E117, E122, E123, E124, E125, E127, E132, E133, E134, E135, E137, E142, E143, E144, E145, E147	2
Hemiplegia	G041, G114, G801, G802, G830, G831, G832, G833, G834, G839, G81, G82	2
Moderate/severe renal disease	I120 I131, N032, N033, N034, N035, N036, N037, N052, N053, N054, N055, N056, N057, N250, N18, N19, Z490 Z491 Z492, Z940, Z992	2
Cancer	C0, C1, C20, C21, C23, C24, C25, C26, C27, C28, C29, C3, C31, C32, C33, C34, C40 C41 C43 C45 C46 C47 C48 C49 C5 C6, C70, C71, C72, C73, C74, C75, C76, C81, C82, C83, C84, C85, C88, C9, C91, C92, C93, C94, C95, C96, C97	2
Moderate to severe liver disease	I850 I859 I864 I982, K704, K711, K721, K729, K765, K766, K767	3
Metastatic solid tumor	C77, C78, C79, C80	6
AIDS	B20, B21, B22, B24	6

Table S4: Association between health-related quality of life, symptoms of anxiety and depression at discharge and dispensing of drugs after three to six months (n=1,464)[a]

	Unadjusted, RRR (95% CI) [b]			Adjusted, RRR (95% CI) [b,c]		
Continuous	**2 drugs**	**1 drug**	**0 drugs**	**2 drugs**	**1 drug**	**0 drugs**
EQ-5D-5L	1.25 (0.55-2.82)	2.24 (0.91-5.54)	1.58 (0.48-5.20)	1.13 (0.48-2.69)	1.75 (0.65-4.72)	1.10 (0.29-4.15)
HeartQoL	1.10 (0.93-1.30)	1.20 (0.99-1.46)	0.98 (0.76-1.26)	1.09 (0.91-1.31)	1.14 (0.93-1.42)	0.94 (0.71-1.24)
HADS-A	1.02 (0.99-1.05)	1.05 (1.01-1.09)	1.04 (0.99-1.09)	1.03 (0.99-1.06)	1.06 (1.01-1.10)	1.04 (0.98-1.09)
HADS-D	1.02 (0.99-1.06)	1.04 (0.99-1.08)	1.02 (0.97-1.07)	1.02 (0.98-1.06)	1.03 (0.99-1.08)	1.01 (0.95-1.07)
Dichotomised						
EQ-5D-5L	1.05 (0.76-1.43)	1.13 (0.79-1.61)	1.02 (0.64-1.63)	1.04 (0.75-1.45)	1.07 (0.73-1.57)	0.97 (0.58-1.60)
HeartQoL	1.46 (1.06-2.03)	1.76 (1.23-2.51)	1.18 (0.72-1.91)	1.51 (1.08-2.13)	1.73 (1.17-2.54)	1.19 (0.71-1.20)
HADS-A	1.14 (0.86-1.51)	1.37 (0.99-1.89)	1.37 (0.91-2.07)	1.23 (0.91-1.66)	1.44 (1.02-2.03)	1.37 (0.88-2.15)
HADS-D	1.28 (0.94-1.76)	1.31 (0.92-1.87)	1.36 (0.86-2.15)	1.28 (0.92-1.78)	1.30 (0.88-1.90)	1.28 (0.78-2.11)

[a]Multinomial logistic regression; RRR, relative risk ratio; CI, confidence interval

[b]Dispensing of three different drugs is reference category in the multinomial regression analysis

[c]Adjusted for the following baseline characteristics: age, sex, length of hospital stay, Charlson Comorbidity Index score, left ventricular ejection fraction, social support, device-related procedure, incident HF and systolic blood pressure (mmHg)

EQ-5D-5L, the EuroQoL five-dimensional, five-level questionnaire; HADS-A and HADS-D, the Hospital Anxiety and Depression Scale, anxiety (HADS-A) and depression (HADS-D) subscale, respectively; HeartQoL global, the HeartQoL global score

Table S5: Association between health-related quality of life, symptoms of anxiety and depression at discharge and dispensing of drugs after nine to twelve months (n=1,384)[a]

	Unadjusted, RRR (95% CI) [b]			Adjusted, RRR (95% CI) [b,c]		
Continuous	**2 drugs**	**1 drug**	**0 drugs**	**2 drugs**	**1 drug**	**0 drugs**
EQ-5D-5L	1.09 (0.45-2.66)	2.47 (0.93-6.53)	1.84 (0.58-5.84)	1.04 (0.40-2.67)	2.39 (0.82-6.99)	2.07 (0.58-7.36)
HeartQoL	1.07 (0.89-1.28)	1.30 (1.06-1.60)	1.16 (0.91-1.48)	1.06 (0.87-1.29)	1.32 (1.05-1.65)	1.25 (0.96-1.63)
HADS-A	1.01 (0.98-1.05)	1.01 (0.98-1.05)	1.04 (0.99-1.05)	1.02 (0.98-1.06)	1.02 (0.98-1.06)	1.04 (0.99-1.09)
HADS-D	1.03 (0.99-1.07)	1.05 (1.01-1.09)	1.07 (1.01-1.12)	1.03 (0.99-1.07)	1.05 (1.01-1.10)	1.08 (1.03-1.14)
Dichotomised						
EQ-5D-5L	1.39 (0.98-1.98)	1.55 (1.05-2.29)	1.23 (0.77-2.96)	1.42 (0.98-2.05)	1.58 (1.04-2.40)	1.32 (0.80-2.17)
HeartQoL	1.36 (0.95-1.95)	1.84 (1.25-2.70)	1.41 (0.90-2.25)	1.40 (0.96-2.03)	1.90 (1.26-2.87)	1.56 (0.95-2.54)
HADS-A	1.24 (0.91-1.68)	1.15 (0.82-1.63)	1.61 (1.09-2.39)	1.30 (0.94-1.80)	1.19 (0.82-1.72)	1.74 (1.14-2.67)
HADS-D	1.38 (0.97-1.95)	1.48 (1.01-2.16)	1.52 (0.97-2.36)	1.40 (0.97-2.02)	1.45 (0.96-2.19)	1.62 (1.01-2.62)

[a]Multinomial logistic regression; RRR, indicates relative risk ratio; CI, confidence interval

[b]Dispensing of three different drugs is reference category in the multinomial regression analysis

[c]Adjusted for the following baseline characteristics: age, sex, length of hospital stay, Charlson Comorbidity Index score, left ventricular ejection fraction, social support, device-related procedure, incident HF and systolic blood pressure (mmHg)

EQ-5D-5L, the EuroQoL five-dimensional, five-level questionnaire; HADS-A and HADS-D, the Hospital Anxiety and Depression Scale, anxiety (HADS-A) and depression (HADS-D) subscale, respectively; HeartQoL global, the HeartQoL global score

Table S6: Association between health-related quality of life, symptoms of anxiety and depression at discharge and dispensing of drugs after thirty-six months (n=1,224)[a]

	Unadjusted, RRR (95% CI)[b]			Adjusted, RRR (95% CI)[b,c]		
Continuous	**2 drugs**	**1 drug**	**0 drugs**	**2 drugs**	**1 drug**	**0 drugs**
EQ-5D-5L	0.49 (0.18-1.32)	0.97 (0.34-2.78)	1.36 (0.41-4.52)	0.38 (0.13-1.10)	0.85 (0.26-2.73)	1.10 (0.24-4.20)
HeartQoL	0.88 (0.72-1.07)	0.89 (0.72-1.11)	0.98 (0.76-1.27)	0.83 (0.66-1.02)	0.85 (0.66-1.08)	0.96 (0.73-1.27)
HADS-A	0.99 (0.96-1.03)	0.98 (0.94-1.02)	1.03 (0.99-1.08)	0.99 (0.96-1.04)	0.99 (0.95-1.04)	1.02 (0.98-1.08)
HADS-D	1.00 (0.96-1.05)	0.99 (0.95-1.05)	1.05 (0.99-1.10)	0.99 (0.95-1.04)	0.99 (0.94-1.04)	1.04 (0.98-1.10)
Dichotomised						
EQ-5D-5L	0.69 (0.47-1.01)	0.85 (0.57-1.28)	1.04 (0.66-1.64)	0.64 (0.43-0.96)	0.85 (0.54-1.31)	0.98 (0.60-1.62)
HeartQoL	0.78 (0.54-1.14)	0.90 (0.60-1.34)	0.94 (0.59-1.49)	0.74 (0.50-1.10)	0.87 (0.56-1.34)	0.90 (0.55-1.48)
HADS-A	0.98 (0.70-1.36)	1.81 (0.56-1.16)	1.17 (0.78-1.76)	0.98 (0.69-1.39)	0.86 (0.58-1.27)	1.13 (0.73-1.75)
HADS-D	1.36 (0.92-2.00)	1.22 (0.80-1.87)	1.72 (1.08-7.73)	1.32 (0.87-1.98)	1.17 (0.74-1.86)	1.66 (1.01-2.74)

[a]Multinomial logistic regression; RRR, indicates relative risk ratio; CI, confidence interval

[b]Dispensing of three different drugs is reference category in the multinomial regression analysis

[c]Adjusted for the following baseline characteristics: age, sex, length of hospital stay, Charlson Comorbidity Index score, left ventricular ejection fraction, social support, device-related procedure, incident HF and systolic blood pressure (mmHg)

EQ-5D-5L, the EuroQoL five-dimensional, five-level questionnaire; HADS-A and HADS-D, the Hospital Anxiety and Depression Scale, anxiety (HADS-A) and depression (HADS-D) subscale, respectively; HeartQoL global, the HeartQoL global score

Prognostic Impact of Self-Reported Health on Clinical Outcomes in Patients with Heart Failure

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Abstract

Aim

An in-depth understanding of the prognostic value of patient-reported outcomes (PRO) is essential to facilitate person-centred care in heart failure (HF). This study aimed to clarify the prognostic role of subjective mental and physical health status in patients with HF.

Methods

Patients with HF were identified from the DenHeart Survey (n=1,499) and PRO data were obtained at hospital discharge, including the EuroQol five-dimensional questionnaire (EQ-5D), the HeartQoL and the Hospital Anxiety and Depression Scale (HADS). Clinical baseline data were obtained from medical records and linked to nationwide registries with patient-level data on sociodemographics and healthcare contacts. Outcomes were all-cause and cardiovascular (CV) mortality, CV events and HF hospitalisation with one- and three-year follow-up.

Results

Analysing the PRO data on a continuous scale, a worse score in the following were associated with risk of all-cause and CV mortality after one year: the HeartQoL (adjusted HRs 1.91, 95% CI:1.42-2.57 and 2.17, 95% CI:1.50-3.15, respectively), the EQ-5D (adjusted HRs 1.26, 95% CI: 1.15-1.38 and 1.27, 95% CI: 1.13-1.42, respectively), the HADS depression subscale (adjusted HRs 1.12, 95% CI: 1.07-1.17 and 1.11, 95% CI: 1.05-1.17, respectively), and the HADS anxiety subscale (adjusted HRs 1.08, 95% CI: 1.03-1.13 and 1.09, 95% CI: 1.04-1.15, respectively). Three-year results were overall in concordance with the one-year results. A similar pattern was also observed for non-fatal outcomes.

Conclusion

Health-related quality of life and symptoms of anxiety and depression at discharge were associated with all-cause and CV mortality at one- and three-year follow-up.

Key words: Heart failure, patient-reported outcomes, cardiovascular mortality, cardiovascular events, heart failure hospitalisation

Introduction

The burden of heart failure (HF) is growing. Due to improved survival of patients with HF and an ageing population, the prevalence of HF is expected to increase in the coming decades (1-3). This development challenges healthcare systems and requires that a continuous effort is made to optimise patient pathways and ensure the delivery of high-quality care.

Recently, there has been an increasing interest in a more systematic use of the perspectives of each individual patient (4-6). Self-reported information, also known as patient-reported outcome measures (PROMs), are questionnaires that quantify the patient's perspective on his/her own disease, and the impact of the disease on every-day life. Patient-reported outcomes (PRO) data cover a variety of dimensions including quality of life, health-related quality of life, anxiety and depression, physical health and symptom burden (7, 8). PRO data have been reported to be associated with the subsequent course of the disease in patients with HF (9, 10). Thus, comorbid depression has been reported to be associated with a higher mortality in patients with HF, and lower self-reported health-related quality of life has been found to be associated with increased risk of readmission (9, 11-14). However, existing studies have typically been carried out in older populations, in mixed heart disease populations, or in small populations with insufficient control for potentially confounding factors (11-13).

A detailed understanding of the relation between PRO data and clinical outcomes is essential when aiming at integrating PROMs in the health service delivery to patients with HF. Hence, it is important to understand the interplay between PRO data, severity of the disease and the effect of the treatment offered (7). We therefore aimed to investigate whether PRO data at discharge from a cardiac hospitalisation were associated with mortality at one and three years after discharge, cardiovascular events (CV events) and HF hospitalisation in patients with HF, combining PRO data with register-based information and individual level data from medical records.

Methods

Setting and design

This study was based on a Danish cohort of patients with HF. PRO data were obtained from the DenHeart Survey, a nationwide collaborative study between the five heart centres in Denmark collecting PRO data and supplementary data on lifestyle in patients with cardiac disease (15).
The Danish healthcare system is primarily tax-financed and offers free and equal access to healthcare for all citizens. At birth, every citizen is given a unique civil registration number by the Civil Registration System. Information on vital status and emigration is continuously updated, enabling linkage of register-based information across all Danish public registries (16).
This study followed the principles of the Declaration of Helsinki and was approved by the DenHeart Steering Committee (DenHeart registered at ClinicalTrials.gov: NCT01926145) and the Danish Data Protection Agency (no: 2012-58-006). Patients gave written consent when answering the questionnaire, and The Danish Patient Safety Authority approved access to relevant medical records (no: 3-3013-1691).

Study population

Patients with a HF diagnosis, either as a primary (main reason for hospitalisation) or secondary diagnosis (secondary reason for hospitalisation) at discharge from one of the five heart centres in the period between 15 April 2013 and 15 April 2014 and completing the DenHeart Survey at discharge or within three days after discharge were eligible for inclusion in this study (Supplemental material Table S1: included International Classification of Diseases, 10th Revision (ICD-10) codes). Patients < 18 years of age, without a Danish civil registration number, or unable to participate due to severe illness or language barriers were excluded.

Patient-reported outcome measures

The PROMs included originated from the disease-specific HeartQoL measuring health-related quality of life in patients with heart disease within the past four weeks. The 14 items includes an emotional and a physical score and can be summarised into a global score, ranging from 0-3 points, with higher scores reflecting higher cardiac health-related quality of life (17, 18). The EuroQol five-dimensional, five-level questionnaire (EQ-5D-5L) is a generic questionnaire that measures five domains of current health status. It is summarised into a total score, and a higher score reflects a higher health-related quality of life (19). The Hospital Anxiety and Depression scale (HADS) measures symptoms of anxiety and depression within the past week. It is a 14-item generic questionnaire summarised into a score between 0-21 points, with higher scores indicating symptoms of anxiety and depression (20-22). In the primary analyses, all PROMs were analysed on a continuous scale. To obtain a measure for use in clinical practice, the PROMs were dichotomised into a secondary analysis. In the EQ-5D and the HeartQoL, the worst quartile on the respondents scale defined the exposure of interest and in HADS a cut-off ≥8 points indicated symptoms of anxiety and depression (21).

Outcomes

The co-primary outcomes were all-cause and cardiovascular (CV) mortality. The secondary outcomes were CV events and HF hospitalisation.

Information on mortality was obtained from the Civil Registration System and from the Registry of Causes of Death, including information on the immediate and underlying cause of death.

Information on CV events and HF hospitalisation was retrieved from the Danish National Patient Registry (DNPR), containing individual-level information on all hospital contacts, including inpatient and outpatient contacts (23). The primary and secondary discharge diagnoses from the

DNPR were used to identify the outcome of interest, except in HF hospitalisation, where only primary discharge diagnoses defined the outcome (Supplemental material Table S2). CV events included a first-time event after index hospitalisation in one of the following events: HF hospitalisation, stroke, arrhythmia, acute coronary syndrome, cardiac revascularisation and heart transplantation.

Patient characteristics

A number of clinical and demographic patient characteristics were all considered potential confounding factors and therefore included as covariates in the analyses. Clinical characteristics retrieved from the patient's medical record included a left ventricular ejection fraction (LVEF) and systolic blood pressure (mmHg). LVEF was recorded as the last measured LVEF, and if not measured at index hospitalisation, the last measured LVEF was noted if referred to as stable. Systolic blood pressure was the last observed value during the index hospitalisation.

Data on other characteristics were collected from the DNPR. Length of hospital stay covered days in index hospitalisation at a heart centre, including any days in immediate continuation of index hospitalisation, and dichotomised at the median days (>2 days). Comorbidity was based on the complete hospital contacts, including both inpatient and outpatient contacts, primary and secondary discharge diagnoses from the past ten years leading up to index hospitalisation and categorised according to the weighted Charlson Comorbidity Index (CCI) using the ICD-10 coding system (Supplemental material Table S3). Comorbidity was categorised into no co-morbidity, moderate co-morbidity level and high co-morbidity level (24). A device-related procedure during index hospitalisation covered having a pacemaker or an Implantable Cardioverter Defibrillator implantation or replacement. Finally, we included one question about the level of self-perceived social support from the DenHeart Survey.

Statistical analysis

All patients were followed from the day of discharge from index hospitalisation and until the event of interest, emigration or end of follow-up. In the analyses of CV events and HF hospitalisation, patients were censored in the event of emigration or mortality. To avoid immortal time bias, patients transferred from a heart centre or having a new hospitalisation at the day of discharge from index hospitalisation did not start follow-up until the date of discharge from the subsequent hospitalisation. We computed cumulative incidence using the Aalen-Johansen estimator at one- and three-year follow-up, with emigration and mortality considered as competing events in the analyses of CV events and HF hospitalisation.

The PRO data were presented with mean and standard deviation (SD) and analysed both on a continuous scale and dichotomised by the worst quartile, except for HADS, which was dichotomised at ≥ 8 points (21). When analysing the PRO data on a continuous scale in the regression analyses, the EQ-5D and the HeartQoL scores were reversed, and a higher score indicated worse health in all three PROMs. The Cox proportional hazard model was used to analyse mortality, CV events and HF hospitalisations adjusted for patient characteristics, presented as hazards ratios (HR) with 95% confidence interval (95% CI).

Missing data were present in 1.5-4.2% of the PROMs or patient characteristics. Under the assumption of data being missing at random, we used chained imputation, using Rubin's Rule and imputed 50 datasets (25). We performed a sensitivity analysis by comparing the results from the non-imputed versus the imputed dataset. All assumptions behind the statistical tests were checked before analyses. All analyses were performed using STATA version 14.0 (StataCorp).

Results

Participants

A total of 3,114 patients were discharged with a HF diagnosis, and 1,537 of these completed the questionnaire during the inclusion period (Figure 1). We excluded a total of 38 patients, where 23 were patients with a discharge diagnosis assessed to have a different acute and life-threatening hospitalisation defined by diagnoses with cardiac arrest, ventricular fibrillation and acute thoracic surgery. Finally, patients with congenital heart disease (n=8) and patients not discharged alive (n=7) were excluded. A total of 1,499 patients were included in the study (Figure 1).

In this cohort, 82.2% had an LVEF ≤40%, and 62.1% had a moderate or high comorbidity level. A total of 74.1% were males and 61.2% of the patients were 65 years of age or older (Table 1). Table 2 shows the scores of the HeartQoL, the EQ-5D and the HADS.

Association between PROMs and mortality

One-year all-cause mortality was 7.6% and three-year mortality was 18.4%. A total of 10.9% of the patients died from cardiovascular causes within three years of follow-up (Table 3). Kaplan Meier cumulative incidence curves showed that risk of death was constant over time (Figure 2).

We found an association between a worse score in all the PROMs at discharge from the index hospitalisation and a higher mortality at one and three-year follow-up, when analysing the PRO data on a continuous scale after adjusting for other clinical factors such as LVEF and comorbidity (Tables 4 and 5). Patients reporting lower cardiac health-related quality of life (HeartQoL) had an approximately two-fold increase in the risk of all-cause mortality (adjusted HR 1.91, 95% CI: 1.42-2.57) and CV mortality (adjusted HR 2.17, 95% CI: 1.50-3.15) at one-year follow-up (Table 4). Lower health-related quality of life (EQ-5D), was associated with nearly a 1.3-fold increase in the risk of all-cause mortality and CV mortality after one year. Symptoms of anxiety and depression

showed a less strong association with mortality. After three years from the index hospitalisation, a lower health-related quality of life (HeartQoL and EQ-5D) was still associated with the highest risk of death, whereas symptoms of anxiety and depression displayed a weaker association. Thus, patients reporting lower cardiac health-related quality of life (HeartQoL) had an approximately 1.5-fold increased risk of all-cause mortality (adjusted HR 1.46, 95% CI: 1.22-1.74) and CV mortality (adjusted HR 1.60, 95% CI: 1.26-2.03) at three-year follow-up (Table 5).

The same consistent pattern was present in the dichotomised analyses after one year of follow-up, where the highest HRs were demonstrated for low health-related quality of life (EQ-5D) (Tables 4 and 5). However, in relation to symptoms of anxiety and depression, we only observed an association between symptoms of depression and the risk of all-cause mortality after three years (adjusted HR 1.59, 95% CI: 1.21-2.08) (Table 5).

Association between PROMs, CV events and HF hospitalisation

After three years, a total of 45.5% had experienced a first-time CV event, and 36.6% a HF hospitalisation (Table 3). The cumulative incidence curve for CV events with death as a possible competing risk showed that incidence of CV events was highest within the first year after discharge from index hospitalisation (Figure 3).

When analysing the PRO data on a continuous scale, we found that a worse score at discharge from index hospitalisation was associated with a higher risk of CV events and HF hospitalisation across all our PROMs, after one- and three years of follow-up, except for symptoms of anxiety (HADS-A). Patients reporting a lower cardiac health-related quality of life (HeartQoL) had an increased risk of HF hospitalisations at one- and three years of follow-up (adjusted HRs 1.47, 95% CI: 1.29-1.68 and 1.43, 95% CI: 1.28-1.61, respectively) (Tables 4 and 5). Finally, lower cardiac health-related quality of life (HeartQoL) at discharge showed the strongest association with risk of

CV events after three years (adjusted HR 1.33, 95 % CI: 1.20-1.42) (Table 5). Patients reporting lower health-related quality of life (EQ-5D) had an approximately 1.1-fold increased risk of CV events and HF hospitalisations. In relation to symptoms of anxiety and depression, only symptoms of depression were associated with increased risk of CV events and HF hospitalisations during follow-up (Tables 4 and 5).

In the dichotomised analyses, only low cardiac health-related quality of life (HeartQoL) was associated with the risk of a non-fatal event during follow-up. Thus, patients reporting lower cardiac health-related quality of life had a 40%-60% increased risk of experiencing a CV event or HF hospitalisation during follow-up (Table 4 and 5).

Sensitivity analyses, comparing the results from the adjusted analyses of PRO data and risk of adverse outcomes, between the imputed and non-imputed dataset, did not change the estimates.

Discussion

In this nationwide population of patients with HF, low self-reported cardiac health-related quality of life (HeartQoL), low health-related quality of life (EQ-5D) and higher symptoms of anxiety and depression (HADS-A and HADS-D) at discharge from a cardiac-related hospitalisation were associated with increased one and three-year all-cause and CV mortality. In addition, low health-related quality of life (HeartQoL and EQ-5D) and symptoms of depression (HADS-D) were associated with CV events and HF hospitalisations during one- and three years of follow up. The strongest associations across fatal and non-fatal events were demonstrated for the HeartQoL.

PROMs, CV events and HF hospitalisation

The existing evidence on the association between the PROMs used in our study and the risk of mortality, CV events and HF hospitalisation are sparse in patients with HF.

We demonstrated that a lower cardiac health-related quality of life (HeartQoL) was associated with an increased risk of adverse outcomes after one- and three years of follow-up. The HeartQoL was developed to measure health-related quality of life in patients with heart disease (17, 18) and has been demonstrated to be associated with risk of cardiac readmission and all-cause mortality after five-year follow-up in a large cohort of patients with ischemic heart disease (26). However, similar associations in patients with isolated HF have, until now, not been demonstrated.

Further, a lower overall health-related quality of life, measured by the generic measure of the EQ-5D, was associated with risk of all-cause and CV mortality in one- and three-year follow-up. Our findings are in accordance with a large global cohort study with longitudinal data on the EQ-5D in a randomised trial of nesiritide, where patients with lower EQ-5D scores at hospital discharge had a significantly higher risk of 30-day all-cause mortality, HF rehospitalisation, cardiac death, cardiac rehospitalisation and six-month mortality (27). In contrast to our study with three years of follow-up, the follow-up was shorter, and the study analysed both non-fatal and fatal events after 30-days, but only mortality after a total of 180 days of follow-up.

Finally, symptoms of anxiety and depression were associated with increased risk of mortality, which concur with other studies. A German cohort study of 209 patients with HF, found a HADS score above the median to be associated with higher risk of mortality after 30 months (11). A UK study of 242 patients with HF found a moderate to severe depression score (HADS-D score ≥ 11) to be associated with the risk of all-cause mortality within one year following discharge from a HF hospitalisation (9). In this study, symptoms of depression (HADS-D) were also associated with risk of CV events and HF hospitalisation, though the association was weaker than in health-related quality of life (EQ-5D and HeartQoL). A possible mechanism behind this result might be the core nature of depressive symptoms, characterised by impaired initiative and self-care leading to a potential delay in seeking medical attention; this is not, however, supported by the literature. A

Swedish study of 958 patients with HF, found a 1.5-fold increased risk of delay ≥72 hours between HF deterioration and hospitalisation in patients with depressive symptoms (28). We also identified an association between symptoms of depression and risk of all-cause and CV mortality, which might indicate that patients with symptoms of depression die before they are admitted to hospital, resulting in a weaker association between symptoms of depression and non-fatal events such as myocardial infarction and stroke. In line with our results, a larger US cohort study of 934 patients with chronic heart disease found that symptoms of anxiety (HADS-A score ≥8) were associated with three-year mortality (13). In contrast to our findings, a Swiss cohort study investigating 111 patients with HF over a five-year period, found severe symptoms of anxiety (HADS-A score >10) to be associated with increased risk of cardiac-related readmission, but not mortality (12).

Clinical implications

To our knowledge, this is one of the largest nationwide studies investigating self-reported mental and physical health and subsequent risk of adverse events using the HeartQoL, the EQ-5D and the HADS at discharge from a cardiac-related hospitalisation in patients with HF. Moreover, this study used the combination of self-reported, clinical and register-based information.

The results extend findings in the existing evidence, indicating that low health-related quality of life and symptoms of anxiety and depression are associated with increased risk of adverse outcomes in patients with HF. The results were robust after controlling for potential confounding. The three PROMs overlap in their assessment of mental and physical health, whereas the HADS only capture mental health and does not provide information on physical health. Our findings indicate that there is potential for using both generic and disease-specific PROMs in patients with HF to identify patients at risk of adverse events and guide differentiated treatment and care.

Strengths and limitations of the study

Our study has the strength of being a nationwide cohort study of patients with HF using PRO data and clinical HF specific characteristics on a patient-level in combination with register-based follow-up enabling thorough confounder control. Our study included both patients with HF as a primary and secondary discharge diagnosis, hence a larger population size compared to previous publications using data from the DenHeart Survey on patients with HF.

The nationwide design enhanced the generalisability of the findings by not only including patients from one geographical region or a single hospital. The use of data from the DNPR are validated for research, and a positive predictive value of above 75% has been found for the HF diagnosis (29, 30). The DNPR and the Civil Registration System have no loss to follow-up, thus diminishing selection bias.

Our study has several limitations. Non-response was present in 48% of the patients, possibly introducing selection bias. However, sensitivity analyses of responders versus non-responders of baseline patient demographics revealed no differences between groups. Furthermore, the observational design, carries a risk of potential unmeasured confounding. Still, we were able to adjust for baseline LVEF and systolic blood pressure, in addition to comorbidity and demographic characteristics. Missing information on exposures and potential confounding factors were present in 1.5-4.0% of the data. This could lead to potentially biased estimates; we, however, aimed at addressing this by using models for chained imputations. Sensitivity analyses, comparing the results from the adjusted regression analyses between the non-imputed and imputed dataset, did not change the estimates. There will be a risk of residual confounding. However, our unadjusted and adjusted estimates did not differ significantly; we thus conclude that our estimates were not likely to be strongly influenced by residual confounding.

Conclusion

We found that low health-related quality of life and symptoms of anxiety and depression measured at discharge from a heart centre were independently associated with subsequent increased risk of adverse outcomes including mortality after one and three years of follow up. The strongest associations were observed for the HeartQoL and the EQ-5D. The results were consistent after controlling for potential confounding factors, indicating that subjective health is an independent prognostic factor in patients with HF. These findings demonstrate the potential of using PROMs in patients with HF, not only to map out mental and physical health, but also to help identify, vulnerable patients at increased risk of experiencing adverse events. By including PROMs in addition to the other well-known objective clinical risk factors, clinicians now have additional tools to support further individualised treatment and care.

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Disclosures

None of the other authors have any conflicts to declare.

Perspectives

Competency in medical knowledge: This study underpins that patients with low self-reported health have a higher risk of all-cause, CV mortality and non-fatal outcomes one and three years after discharge from a cardiac hospitalisation. This knowledge offers potential for differentiated care in patients at risk of adverse events.

Translational outlook: Future studies should test and validate PROMs in patients with HF with the long-term perspective of gaining knowledge on how PROMs can be incorporated in clinical care in order to improve outcomes.

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Figure 1: Flowchart

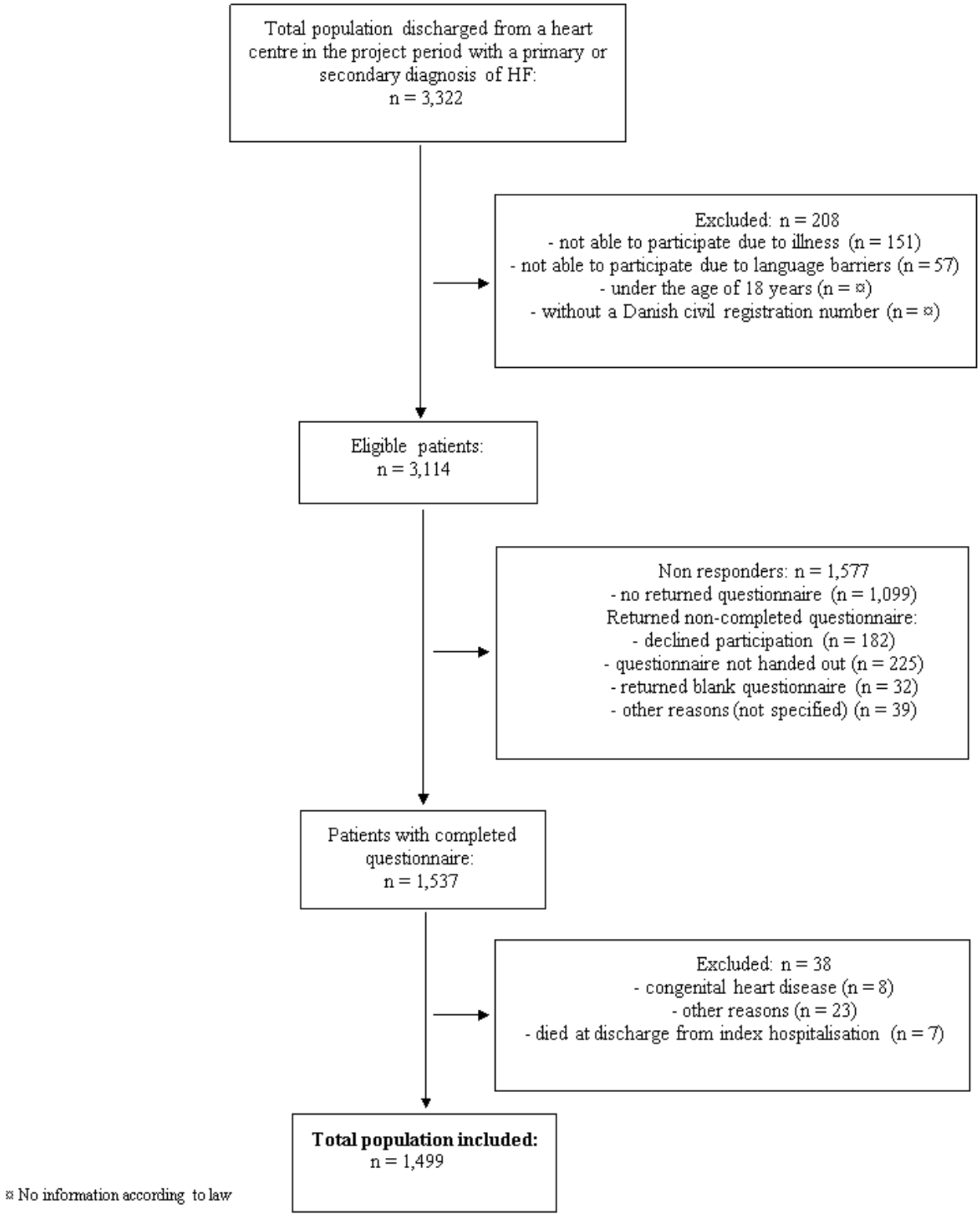
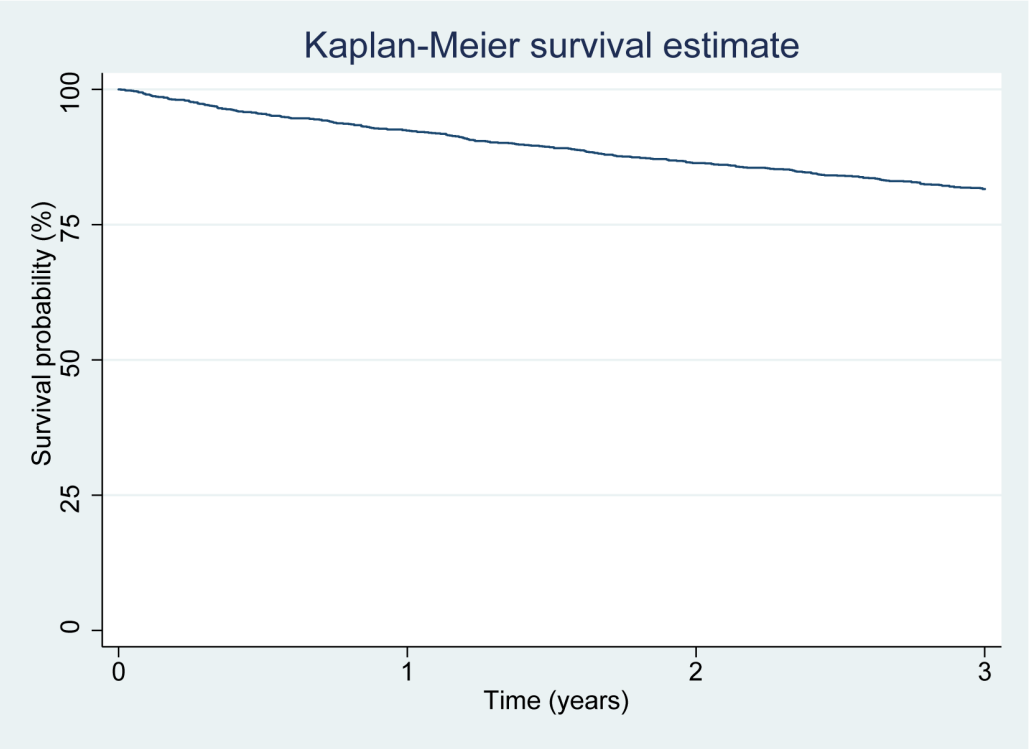
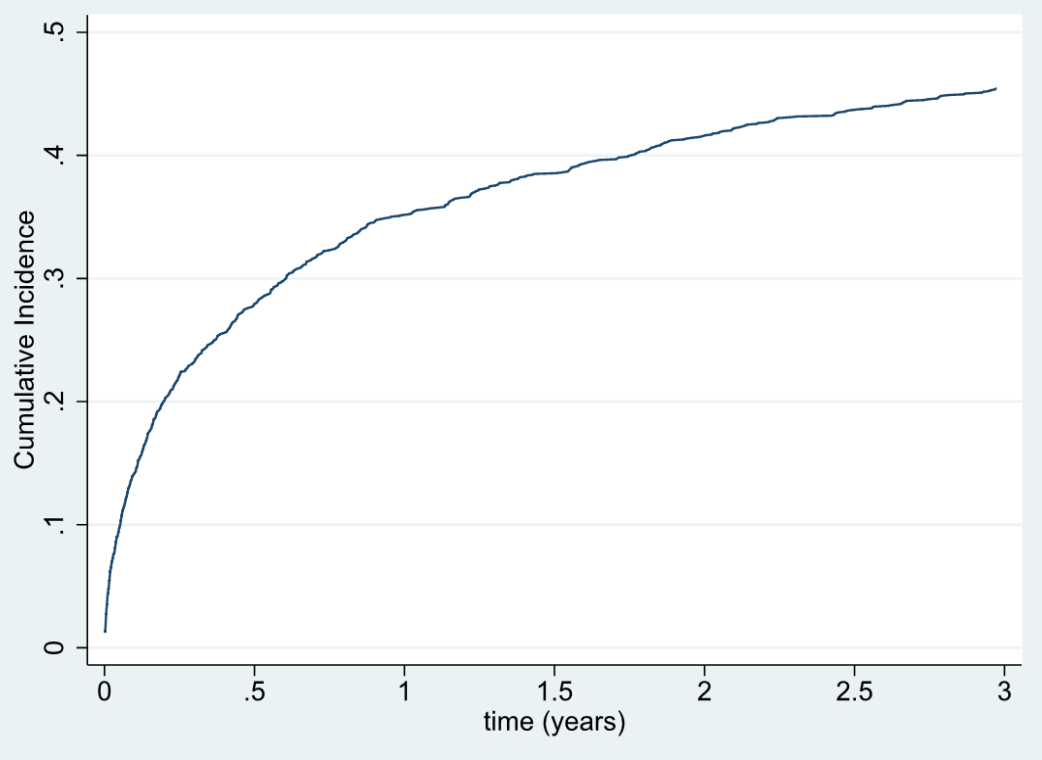


Figure 2: Survival curve of the cohort (n=1,499)*



*In patients at risk

Figure 3: Cumulative incidence of cardiovascular events (1,499)*



*In patients at risk

Table 1. Descriptive characteristics (n=1,499)*

Demographics	
Males, n (%)	1,111 (74.1)
Age, n (%)	
< 65 years	582 (38.8)
65-74 years	507 (33.8)
≥ 75 years	410 (27.4)
Low social network	183 (12.2)
Undisclosed	31 (2.1)
Comorbidity, n (%)	
Charlson co-morbidity index (CCI) †	
No co-morbidity	568 (37.9)
Moderate co-morbidity level	651 (43.3)
High co-morbidity level	280 (18.7)
Procedures, n (%)	
Device-related procedure	401 (26.8)
Clinical characteristics	
Length of hospital stay, > 2 days	535 (35.7)
Incident heart failure, n (%)	551 (36.8)
Left ventricular ejection fraction, n (%)	
> 40	266 (17.8)
26 - 40	556 (37.1)
≤ 25	616 (41.1)
Undisclosed	61 (4.1)
Systolic blood pressure (mmHg), mean (SD)	125 (20.5)
Undisclosed	50 (3.3)

*If nothing stated, the descriptive characteristics are from the index hospitalisation

†CCI is calculated as a weighted 10-year index

Table 2. Health-related quality of life and symptoms of anxiety and depression (n=1,499)

HeartQoL global score	
HeartQoL global, mean (SD)	1.5 (0.8)
HeartQoL global, worst quartile, n (%)	346 (23.1)
Undisclosed	37 (2.5)
EQ-5D-5L	
EQ-5D 5L, mean (SD)	0.73 (0.2)
EQ-5D 5L, worst quartile, n (%)	348 (23.2)
Undisclosed	63 (4.2)
HADS, anxiety subscale	
HADS-A, mean (SD)	5.9 (4.4)
HADS-A ≥ 8 points, n (%)	492 (32.8)
Undisclosed	60 (4.0)
HADS, depression subscale	
HADS-D, mean (SD)	5.1 (3.9)
HADS-D ≥ 8 points, n (%)	363 (24.2)
Undisclosed	53 (3.5)

The HeartQoL global score ranges from 0-3. A higher score indicates higher cardiac health-related quality of life; EQ-5D-5L = the EuroQoL five-dimensional questionnaire. A higher score indicates higher health-related quality of life; the HADS-A and HADS-D = the Hospital Anxiety and Depression Scale, anxiety and depression subscale, respectively. Ranges 0-21. A higher score indicates symptoms of anxiety and/or depression

Table 3. Proportion of events after one- and three year (n=1,499)

	One-year events, n (%)	Three-year events, n (%)
All-cause mortality	114 (7.6)	276 (18.4)
Cardiovascular mortality	78 (5.2)	163 (10.9)
Cardiovascular events*	527 (35.2)	681 (45.4)
HF hospitalisation†	425 (28.4)	549 (36.6)

*Includes the following events: stroke, cardiac arrest, ventricular tachycardia, ventricular fibrillation, acute coronary syndrome, percutaneous coronary intervention, coronary artery by-pass grafting and heart transplant as a primary or secondary diagnosis and HF hospitalisation as the primary diagnosis.

†Defined by a primary discharge diagnosis

Table 4. Association between health-related quality of life, symptoms of anxiety and depression and mortality, cardiovascular events and HF hospitalisation after one year (n=1,499)*

	PRO data, continuous scale			PRO data, dichotomised	
	Crude HR (95% CI)	Adjusted HR (95% CI) †		Crude HR (95% CI)	Adjusted HR (95% CI) †
All-cause mortality			**All-cause mortality**		
HeartQoL global	2.32 (1.76-3.06)	1.91 (1.42-2.57)	HeartQoL global	2.41 (1.66-3.52)	1.90 (1.29-2.80)
EQ-5D-5L	1.35 (1.24-1.46)	1.26 (1.15-1.38)	EQ-5D-5L	3.08 (2.10-4.50)	2.43 (1.68-3.66)
HADS-A	1.08 (1.04-1.13)	1.08 (1.03-1.13)	HADS-A	1.80 (1.24-2.61)	1.74 (1.17-2.58)
HADS-D	1.15 (1.10-1.19)	1.12 (1.07-1.17)	HADS-D	2.18 (1.49-3.19)	1.86 (1.25-2.77)
Cardiovascular mortality			**Cardiovascular mortality**		
HeartQoL global	2.52 (1.79-3.55)	2.17 (1.50-3.15)	HeartQoL global	2.59 (1.64-4.07)	2.07 (1.30-3.30)
EQ-5D-5L	1.34 (1.21-1.48)	1.27 (1.13-1.42)	EQ-5D-5L	2.95 (1.87-4.65)	2.44 (1.53-3.90)
HADS-A	1.08 (1.03-1.14)	1.09 (1.04-1.15)	HADS-A	1.80 (1.14-2.83)	1.90 (1.19-3.04)
HADS-D	1.13 (1.07-1.19)	1.11 (1.05-1.17)	HADS-D	1.85 (1.16-2.96)	1.63 (1.01-2.64)
Cardiovascular events			**Cardiovascular events**		
HeartQoL global	1.46 (1.29-1.64)	1.17 (1.18-1.49)	HeartQoL global	1.62 (1.35-1.95)	1.41 (1.17-1.70)
EQ-5D-5L	1.14 (1.08-1.20)	1.10 (1.04-1.16)	EQ-5D-5L	1.32 (1.09-1.59)	1.10 (0.91-1.34)
HADS-A	1.03 (1.01-1.05)	1.01 (0.99-1.04)	HADS-A	1.27 (1.06-1.52)	1.11 (0.92-1.35)
HADS-D	1.05 (1.02-1.07)	1.03 (1.01-1.06)	HADS-D	1.25 (1.03-1.51)	1.12 (0.91-1.36)
HF hospitalisation			**HF hospitalisation**		
HeartQoL global	1.60 (1.40-1.83)	1.47 (1.29-1.68)	HeartQoL global	1.81 (1.48-2.22)	1.60 (1.31-1.97)
EQ-5D-5L	1.17 (1.11-1.24)	1.13 (1.07-1.19)	EQ-5D-5L	1.47 (1.19-1.81)	1.21 (0.98-1.50)
HADS-A	1.03 (1.01-1.06)	1.02 (0.99-1.05)	HADS-A	1.31 (1.07-1.58)	1.18 (0.96-1.46)
HADS-D	1.05 (1.03-1.08)	1.04 (1.02-1.07)	HADS-D	1.33 (1.08-1.65)	1.21 (0.98-1.51)

*The Cox proportional hazards model; HR = hazard ratio; CI = confidence interval

†HR were adjusted for the following: age, sex, length of hospital stay, Charlson Comorbidity Index score, left ventricular ejection fraction, social support, device-related procudere, incident HF and systolic blood pressure (mmHg) at index hospitalisation

HeartQoL global = the HeartQoL global score; EQ-5D-5L = the EuroQoL five-dimensional, five-level questionnaire; the HADS-A and HADS-D = the Hospital Anxiety and Depression Scale, anxiety and depression subscale, respectively

Table 5. Association between health-related quality of life, symptoms of anxiety and depression and mortality, cardiovascular events and HF hospitalisation after three years (n=1,499)*

	PRO data, continuous scale			PRO data, dichotomised	
	Crude HR (95% CI)	Adjusted HR (95% CI) †		Crude HR (95% CI)	Adjusted HR (95% CI) †
All-cause mortality			**All-cause mortality**		
HeartQoL global	1.77 (1.50-2.09)	1.46 (1.22-1.74)	HeartQoL global	1.93 (1.50-2.50)	1.57 (1.21-2.03)
EQ-5D-5L	1.26 (1.19-1.34)	1.17 (1.10-1.25)	EQ-5D-5L	2.18 (1.70-2.80)	1.76 (1.36-2.27)
HADS-A	1.05 (1.02-1.07)	1.04 (1.01-1.07)	HADS-A	1.32 (1.03-1.69)	1.25 (0.96-1.62)
HADS-D	1.10 (1.07-1.14)	1.08 (1.05-1.11)	HADS-D	1.87 (1.46-2.41)	1.59 (1.21-2.08)
Cardiovascular mortality			**Cardiovascular mortality**		
HeartQoL global	1.97 (1.58-2.46)	1.60 (1.26-2.03)	HeartQoL global	2.20 (1.60-3.03)	1.73 (1.25-2.40)
EQ-5D-5L	1.27 (1.18-1.37)	1.18 (1.09-1.29)	EQ-5D-5L	2.23 (1.62-3.08)	1.75 (1.26-2.42)
HADS-A	1.05 (1.02-1.09)	1.05 (1.02-1.09)	HADS-A	1.32 (0.96-1.81)	1.29 (0.93-1.81)
HADS-D	1.10 (1.06-1.14)	1.07 (1.03-1.12)	HADS-D	1.55 (1.11-2.16)	1.28 (0.90-1.82)
Cardiovascular events			**Cardiovascular events**		
HeartQoL global	1.47 (1.32-1.63)	1.33 (1.20-1.42)	HeartQoL global	1.68 (1.42-1.97)	1.46 (1.24-1.73)
EQ-5D-5L	1.13 (1.08-1.18)	1.08 (1.04-1.14)	EQ-5D-5L	1.36 (1.15-1.61)	1.15 (0.96-1.36)
HADS-A	1.02 (1.01-1.04)	1.01 (0.99-1.03)	HADS-A	1.25 (1.07-1.47)	1.11 (0.94-1.32)
HADS-D	1.04 (1.02-1.07)	1.03 (1.01-1.05)	HADS-D	1.27 (1.07-1.51)	1.14 (0.96-1.36)
HF hospitalisation			**HF hospitalisation**		
HeartQoL global	1.57 (1.39-1.76)	1.43 (1.28-1.61)	HeartQoL global	1.80 (1.51-2.16)	1.61 (1.34-1.93)
EQ-5D-5L	1.14 (1.09-1.20)	1.09 (1.04-1.15)	EQ-5D-5L	1.41 (1.17-1.70)	1.18 (0.97-1.42)
HADS-A	1.02 (1.00-1.04)	1.01 (0.99-1.03)	HADS-A	1.24 (1.04-1.48)	1.13 (0.94-1.36)
HADS-D	1.04 (1.02-1.07)	1.03 (1.01-1.06)	HADS-D	1.28 (1.05-1.54)	1.16 (0.96-1.41)

*The Cox proportional hazards model; HR = hazard ratio; CI = confidence interval

†HR were adjusted for the following: age, sex, length of hospital stay, Charlson Comorbidity Index score, left ventricular ejection fraction, social support, device-related procudere, incident HF and systolic blood pressure (mmHg) at index hospitalisation

HeartQoL global = the HeartQoL global score; EQ-5D-5L = the EuroQoL five-dimensional, five-level questionnaire; the HADS-A and HADS-D = the Hospital Anxiety and Depression Scale, anxiety and depression subscale, respectively

Supplemental material

Table S1: Codes used to include patients

Name	
International Classification of Diseases, 10th Revision (ICD-10) codes	I110, I13.0, I13.2, I42, I43, I50, I517 and R570

Table S2: International Classification of Diseases, 10th Revision (ICD-10) codes and NOMESCO surgical codes

Outcome	Definition	ICD-10 codes
Mortality	All-cause mortality	DA00-DZ99
	Cardiovascular mortality	DI00-DI99
Cardiovascular events		
HF hospitalisation		DI11.0 DI13.0 DI13.2 DI50-DI509 DI42-DI429 DI43-DI438 DI517-DI517C DR570
Arrhythmia	Cardiac arrest	DI46-DI469
	Ventricular tachycardia	DI470-DI470HB DI472-DI472NA
	Ventricular fibrillation	DI490B
Stroke	Specified ischemic stroke	DI63-DI639
	Unspecified ischemic stroke	DI64-DI649
	Intracerebral hemorrhage	DI61-DI619
	Subarachnoid hemorrhage	DI60-DI609A
	Transient ischemic attack	G45.9
Acute coronary syndrome		DI21-DI219
Cardiac revascularisation	Coronary artery by-pass grafting	KFNA-KFNA96 KFNB-KFNB96 KFNC-KFNC96 KFND-KFND96 KFNE-KFNE96 KFNH20
	Percutaneous Coronary Intervention	KFNG00-KFNG96
Heart transplant		KFQA-KFQA96

Table S3: Charlson Comorbidity Index Score

	ICD-10	Weight
Myocardial infarction	I410 I21 I22 I252	1
Congestive heart failure	I099, I110, I13.0, I13.2, I42, I43, I50, I255, I517, P290, R570	1
Peripheral vascular disease	I70, I71, I73, I77, I79, K551 K558 K559 Z958 Z959	1
Cerebrovascular disease	G45, G46, H340, I6, I61, I62, I63, I64, I65, I66, I67, I68, I69	1
Dementia	F00 F01 F02 F03 F051 G30 G311	1
Chronic pulmonary disease	I278, I279, J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J684, J701, J703	1
Rheumatic disease	M05, M06, M315, M32, M33, M34, M351, M353, M360	1
Peptic ulcer disease	K25, K26, K27, K28	1
Mild liver disease	B18, K700 K701 K702 K703, K709, K73, K74, K712, K712, K713, K714 K715 K717, K760 K762 K763 K764 K768 K769 DB18, Z944	1
Diabetes without organ damage	E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149	1
Diabetes with end-organ damage	E102, E103, E104, E105, E107, E112, E113, E114, E115, E117, E122, E123, E124, E125, E127, E132, E133, E134, E135, E137, E142, E143, E144, E145, E147	2
Hemiplegia	G041, G114, G801, G802, G830, G831, G832, G833, G834, G839, G81, G82	2
Moderate/severe renal disease	I120 I131, N032, N033, N034, N035, N036, N037, N052, N053, N054, N055, N056, N057, N250, N18, N19, Z490 Z491 Z492, Z940, Z992	2
Cancer	C0, C1, C20, C21, C23, C24, C25, C26, C27, C28, C29, C3, C31, C32, C33, C34, C40 C41 C43 C45 C46 C47 C48 C49 C5 C6, C70, C71, C72, C73, C74, C75, C76, C81, C82, C83, C84, C85, C88, C9, C91, C92, C93, C94, C95, C96, C97	2
Moderate to severe liver disease	I850 I859 I864 I982, K704, K711, K721, K729, K765, K766, K767	3
Metastatic solid tumor	C77, C78, C79, C80	6
AIDS	B20, B21, B22, B24	6