Fatigue and dyspnoea in heart failure: insights from two large randomised clinical trials

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Summary

Heart failure is a complex clinical syndrome characterised by typical symptoms (like dyspnoea, fatigue, palpitations or chest pain) and signs (like oedema, pulmonary crackles, displaced apex beat and increased jugular venous pressure). The possible importance of symptoms as predictors of subsequent outcomes has received little attention in the medical literature yet is clearly of great potential clinical importance (for example in identification, monitoring and treatment of high risk patients).

Fatigue and dyspnoea are the two most prevalent symptoms in patients with heart failure ranging from 50-91% for fatigue and similar (53-89%) for dyspnoea. However, the underlying pathophysiological mechanisms of dyspnoea and fatigue in heart failure remain unclear. It has been proposed that decreased oxygen delivery to muscle due to an impaired pump function of the failing heart leads to a build-up of anaerobic metabolic products which may account for both symptoms. Some hypotheses attribute the impaired oxygen delivery to muscle to reduced blood flow due to persistent vasoconstriction and endothelial dysfunction, rather than just to a limited cardiac output. Other potential mechanisms include abnormalities in muscle metabolism, possibly due to changes in cellular subtype, which limit the ability to utilise oxygen and a miss-match between energy requirement and energy production. It has now been recognised that disturbances of central hemodynamic function are no longer the major determinants of exercise capacity in patients with heart failure. If central hemodynamic parameters are improved, there is no immediate change in symptoms, which points to an impaired ability of the muscle to extract oxygen, leading to dyspnoea.

The lack of consensus and understanding of the pathophysiological mechanisms of heart failure symptoms, together with poor and subjective tools for their measurement has led to a delay in the development of effective symptomatic treatment. This in turn may have important prognostic implications such as decreased quality of life, increased hospital admissions and even increased mortality.

The aim of this work was to examine the correlates of symptoms and change in symptoms. Additionally I set out to examine the association between symptom severity (at baseline and the change in symptom severity over 6 months) and clinical outcomes (namely heart failure hospitalisation, cardiovascular death and all-cause mortality) after adjustment for a series of other known prognostic factors.

A cohort of 3830 men and women with LVEF (left ventricular ejection fraction) ≤35% who participated in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) was examined. This population was chosen because the trial medication (rosuvastatin) had no effect on the primary outcome (composite of death form cardiovascular causes, nonfatal myocardial infarction and nonfatal stroke) (HR 0.92; 95% CI 0.83 to 1.02; P = 0.12) or death from any cause (HR 0.95 in the rosuvastatin group 95% CI, 0.86 to 1.05; P=0.31) compared to placebo, meaning that any result I obtain is unlikely to be due to an effect of the trial drug and because this cohort would be representative of a population with heart failure who were well treated with contemporary evidence-based medicine

CORONA was a multicentre, randomised, double-blind, placebo-controlled study which enrolled a total of 5011 patients aged ≥ 60 years with symptomatic (NYHA class II-IV), systolic (LVEF ≤ 40% but no more than 35% in patients with NYHA class II) heart failure. Patients were randomised to receive 10 mg of rosuvastatin or matching placebo once daily.

Symptoms were measured at baseline (randomisation visit), 6 weeks after randomisation, and 3 monthly thereafter in this trial population. (1) Investigators were asked to evaluate symptoms using the following statement: “State symptoms during the past few days: Tick lowest level of physical activity causing symptoms”.

Fatigue *“during the past few days”* was measured using a five-point exertion scale (0 none, 1 heavy exertion, 2 moderate exertion, 3 slight exertion, 4 rest), recorded by the investigator. Dyspnoea *“during the past few days”* was measured using a four-point exertion scale (1 heavy exertion, 2 moderate exertion, 3 slight exertion, 4 rest); a four- rather than five-point scale was used

for dyspnoea because the presence of dyspnoea at baseline was an inclusion criterion for CORONA.

Data were analysed in several ways to comply with the objectives of this thesis. I examined prevalence and severity of fatigue and dyspnoea by using descriptive statistics. I also analysed baseline characteristics (at visit prior to randomisation and randomisation visit) according to fatigue and dyspnoea severity, reporting means and standard deviations for continuous variables (medians and interquartile ranges for variables that were not normally distributed) and percentages for categorical variables and comparing across symptom groups by running appropriate tests.

Ordered logistic regression was used to examine which baseline characteristics were independently associated with symptom severity at baseline, while Cox proportional hazards regression was used to examine how symptoms were related to the risk of clinical events. I used multinomial logistic regression to identify independent predictors of change in symptom severity from baseline to the 6 month visit (chi^2 was used to obtain p values), classifying patients as showing a decrease (reduction in score), an increase (an increase in score) or no change (unchanged score) in symptoms and analysed the relationship between change in symptoms and subsequent clinical outcomes using Cox regression. Finally, I examined the effect of rosuvastatin treatment for six months on symptom severity using Cox regression survival analysis.

Additionally, a cohort of 8399 patients with chronic symptomatic heart failure with reduced ejection fraction from PARADIGM-HF was examined. Dyspnoea and fatigue on effort in PARADIGM-HF were recorded in every visit as “present” or “absent”.

I found that at baseline 95% of CORONA trial participants reported some level of fatigue on exertion and most of them (85%) reported high symptom severity (from moderate exertion to symptoms at rest). In PARADIGM-HF 52% reported fatigue on effort. Dyspnoea showed a similar pattern, although some level of dyspnoea was an inclusion criterion for CORONA where 91% reported dyspnoea from moderate exertion to dyspnoea at rest, while 86% reported dyspnoea on effort in PARADIGM-HF.

I found that a limited number of variables (history of hypertension and coronary heart disease; NYHA functional class; and use of mineralocorticoid receptor antagonists) were independently associated with both fatigue and dyspnoea (only with fatigue for PARADIGM-HF), with no variables clearly associated with only one of these symptoms. This similarity in variables associated with each symptom and the lack of association of dyspnoea with ejection fraction or NT-proBNP suggests that "peripheral" (i.e. changes in muscle bulk and metabolism), rather than "central" mechanisms may explain the origin of both symptoms.

I also found that worst baseline symptom severity is strongly associated with adverse clinical outcomes, but this association is lost after adjustment for other well-known cardiovascular prognostic variables like NT-proBNP, LVEF and NYHA class, in both cohorts. However in CORONA, *change* in symptom severity after 6 months was strongly associated with clinical outcomes, even after adjustment for the previously mentioned prognostic factors; with a decrease in symptom severity proving to be protective while an increase over six months being associated with a higher risk of CV death, HF hospitalisation of all-cause mortality. Statin treatment had no convincing effect on symptom severity.

In conclusion, I found that both fatigue and dyspnoea were highly prevalent in both cohorts and that they seem to have the same baseline correlates. This supports the theory that both symptoms might be different expressions of the same pathophysiological process. Change in symptom severity after 6 months seems to be strongly associated with outcomes independent of other known prognostic factors, which shines a light on the importance of prompt and targeted interventions to improve symptom severity, or at the very least to prevent deterioration.

Table of Contents

List of Tables

List of Figures

Definitions/Abbreviations

95% CI- 95% confidence interval

ACE- angiotensin converting enzyme

AF-atrial fibrillation/flutter

AHA- American Heart Association

ApoA-1-apolipoprotein A1

ApoB- apolipoprotein B

ARB- angiotensin II receptor blocker

ARNI- angiotensin receptor neprilysin inhibitor

BHF-British Heart Foundation

BMI- body mass index

BP-blood pressure

bpm-beats per minute

CABG/PCI-coronary artery bypass grafting/percutaneous coronary intervention

COMET- Carvedilol or Metoprolol European Trial

CORONA- Controlled Rosuvastatin Multinational Trial in Heart Failure

ESC- European Society of Cardiology

HF- heart failure

HF-PEF- heart failure with preserved ejection fraction

HF-REF- heart failure with reduced ejection fraction

hs-CRP- high-sensitivity C-reactive protein

HR- hazard ratio

ICD-implantable cardioverter defibrillator

I-PRESERVE- Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction

IQR- interquartile range

LDL- low density lipoprotein

LVEF- left ventricular ejection fraction

LVEDP- left ventricular end-diastolic pressure

MAR- missing at random

MCAR-missing completely at random

MERIT-HF- Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure

MeSH- Medical subject headings

MI-myocardial infarction
MNAR- missing not at random
MRA- mineralocorticoid receptor antagonist
NHS- National Health Service
NT-pro-BNP- N-terminal of the prohormone brain natriuretic peptide
NYHA- New York Heart Association
OR- odds ratio
PARADIGM-HF- Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial
PCWP-pulmonary capillary wedge pressure
POM- proportional odds model
PROTECT-Placebo-controlled Randomised Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal FuncTion
SBP- systolic blood pressure
SD- standard deviation
SOLVD- Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure trial
Statin-HMG CoA reductase inhibitor
TSH-thyroid stimulating hormone
USA- United States of America
WHO- World Health Organisation

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Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Ana Cristina Pérez Moreno

1 Introduction

In this thesis I will examine the two most common symptoms of heart failure (i.e. shortness of breath and fatigue) in a clinical trial population.

The thesis will be organised in the following way:

In this first chapter I will start off by briefly defining and describing heart failure and its epidemiology in Europe and the United states. I will then review the published literature surrounding fatigue and shortness of breath in heart failure patients in chapters 2 and 3.

In chapter 4 I will present the data source and methods and briefly describe the general principles surrounding the statistical procedures I selected to analyse data. From chapter 5 to chapter 10 I will report the results of analyses relating to these prominent symptoms performed on a cohort of patients from a clinical trial, CORONA where the investigated treatment (rosuvastatin) had no effect on the primary outcome of the trial. (2)

I will then report in chapter 11 the results of analyses relating to symptoms on effort performed on another cohort of patients from a contemporary clinical trial PARADIGM-HF, which had hardly any missing data and is the most important heart failure clinical trial of recent years. (3)

Finally, I present a summary and discuss my findings in chapter 12.

Results from sensitivity analyses will be presented in supplementary appendices.

1.1 Definition of heart failure

The American Heart Association defines heart failure as “a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood”(4), while the European Society of Cardiology defines heart failure as “an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures)”. (5, 6)

Whichever the definition, heart failure is widely recognised as a clinical syndrome that is characterised by typical symptoms like breathlessness (from now on referred to as dyspnoea) and fatigue, and signs like oedema, pulmonary crackles, displaced apex beat and increased jugular venous pressure. (4, 5)

1.2 Diagnosis of heart failure

Several criteria have been described to diagnose heart failure (7-10) and they all share symptoms together with an adequate medical history and physical examination as a crucial part of the diagnosis. However, because many of the symptoms are not specific to heart failure, and thus non-discriminating, the European Society of Cardiology requires the demonstration of an underlying cardiac dysfunction at rest for diagnosis. (5, 10) This evidence can derive from an echocardiogram, an electrocardiogram and/or laboratory tests. (5)

1.2.1 Symptoms and signs in heart failure

Signs and symptoms are essential in the initial evaluation of patients with suspected heart failure, however they are, as previously mentioned, not specific. The characteristic symptoms of heart failure are dyspnoea, fatigue and ankle swelling. The origin of such symptoms is not fully understood and it is well known that they correlate poorly with level of cardiac dysfunction. (11, 12)

Once the diagnosis of heart failure has been made, symptoms should be used to guide therapy and classify the disease. The most widely used nomenclature to quantify the degree of functional limitation caused by heart failure symptoms is the New York Heart Association classification (NYHA) first conceived in 1928 (13)

which was revised and widely accepted by 1964. (14) With this tool, patients are classified into a functional class, depending on the degree of effort needed to provoke symptoms:

- Class I patients have no limitation of physical activity; ordinary activity does not cause undue fatigue, dyspnoea or palpitations.

- Class II patients have a slight limitation of physical activity, but are comfortable at rest; ordinary activity results in fatigue, dyspnoea or palpitations.

- Class III patients have marked limitation of physical activity and are still comfortable at rest; less than ordinary activity results in fatigue, dyspnoea or palpitations.

- Class IV patients are unable to carry out any physical activity without discomfort; symptomatic at rest.

The American Heart Association proposed in 1994 an additional classification complementary to the traditional NYHA classification. It also classifies patients into four categories (4):

- A - No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity;

- B - Objective evidence of minimal cardiovascular disease with mild symptoms and slight limitation during ordinary activity but comfortable at rest;

- C - Objective evidence of moderate cardiovascular disease with marked limitation in activity due to symptoms, even during less than ordinary activity and comfortable only at rest;

- D - Objective evidence of severe cardiovascular disease with severe limitations and symptomatic even at rest.

In Europe, this “objective assessment classification” is seldom used, but objective evidence of cardiac dysfunction is embedded in the definition of the disease.

NYHA class is widely accepted and correlates to quality of life measures (15-17) and prognosis. (18) However, it is also recognised that NYHA classification reflects a subjective assessment by a medical professional and some authors have shown that there can be large variation between clinicians while determining and assigning NYHA class (19-22) and symptoms (weighted kappa values[1] ranging from 0.55 to 0.78 (20, 24)). Additionally, NYHA class can change in short periods of time; this is why the American Heart Association argues that their objective assessment classification proposed in 1994 should be widely implemented, as although NYHA class can fluctuate widely over time, once a patient has developed a heart failure syndrome and been classified as either C or D, they can never go back to not having heart failure and should receive medical treatment accordingly.

As I have mentioned in a previous paragraph, symptoms in heart failure are quite nonspecific, subjective and often difficult to assess (5). More importantly, the mechanisms underlying the exercise intolerance in patients with heart failure are not fully understood. As mentioned previously, symptoms correlate poorly to measures of cardiac performance (11, 12) and often patients with low left ventricular ejection fractions are asymptomatic, while patients with preserved ejection fraction may be very symptomatic. (25) The reasons behind this discordance are not fully understood, but may well reside in the pathophysiology of each individual symptom.

The prototypical symptoms in heart failure are fatigue and dyspnoea on exertion; though relatively recently, a new symptom has been described: bendopnea (or shortness of breath when bending forward) (26) and seems to be associated with elevated right and left ventricular filling pressures, similar to another common symptom of heart failure which is orthopnoea (shortness of breath while in the supine position). (27-29) It has been hypothesised that this

[1] A weighted Kappa adjusts for the chance agreement and can range from -1 (no agreement) to +1 (complete agreement) with 0 indicating agreement due to chance alone.
23. Fleiss JL, Cohen J. The Equivalence of Weighted Kappa and the Intraclass Correlation Coefficient as Measures of Reliability. Educational and Psychological Measurement. 1973;33(3):613-9.

symptom of bendopnea could be associated with worse outcomes in patients with heart failure.

1.3 Classification of heart failure

Traditionally, heart failure has been described on the basis of left ventricular ejection fraction, which is the end-diastolic volume minus the end-systolic volume (also known as stroke volume) divided by the end-diastolic volume. This characterisation of heart failure is commonly used in clinical trials as inclusion/exclusion criteria; and classifies patients as having heart failure with reduced ejection fraction (commonly abbreviated as HF-REF) with a traditional cut-off point at ≤35% (>50% is considered normal) and heart failure with a preserved ejection fraction (abbreviated as HF-PEF) with a cut-off point at >45-50%. (5) The above is due to the fact that historically the major heart failure trials where effective therapies have been identified mainly enrolled patients with a LVEF ≤ 35% (30-37), additionally patients with LVEF≤35% have been shown to have shorter survival times when compared to those patients with LVEF >35% (38-40) and benefit the most from an implantable cardioverter defibrillator (again due to their high risk of death). (38) It is important to note that these are the criteria used by the European Society of the Cardiology, although other cut-off points and criteria have been proposed and are used in other parts of the world. (41-43)

Another way of classifying heart failure involves symptoms using NYHA class and is typically used to identify patients who would benefit from therapy.

A further approach to classifying patients with heart failure relates to the time-course of the disease, where patients who have had heart failure for some time are referred to as having chronic heart failure. Patients with chronic heart failure whose symptoms have remained largely unchanged for at least 30 days are classified as stable. If such a patient would worsen, then he or she would be considered to have a decompensated chronic heart failure; if this deterioration should happen suddenly, then the patient would be considered to have acute-decompensated heart failure. (44, 45)

Congestive heart failure is a historical term that is falling into disuse although it is sometimes still employed in the United States to describe patients with a

diagnosis of heart failure and evidence of fluid retention or congestion. This is often determined by an elevated jugular venous pulsation, which is estimated by distension of the jugular veins with the patient sitting at 45°. This sign correlates to with elevated pulmonary artery occlusion pressure. (46) Congestive heart failures merits immediate medical attention.

1.4 Treatment in heart failure

The aims of treatment in patients with heart failure revolve around relieving symptoms and signs, preventing hospitalisation and reducing mortality. (5) Although most clinical trials focus on the latter, the relief of symptoms that leads to an improvement in quality of life and increase in functional capacity is of paramount importance to patients and effective treatment that would improve mortality and hospitalisation should also impact signs and symptoms. (47)

There are three pivotal drugs in the treatment of heart failure, as they have been shown to modify the course of systolic heart failure. These are: an angiotensin converting enzyme inhibitor (ACE inhibitor)-or an angiotensin II receptor blocker, a beta-blocker and a mineralocorticoid receptor antagonist. They are usually combined with a diuretic to alleviate symptoms of congestion. (4, 5)

Recently, a new drug has been identified that has shown to reduce risk of death and hospitalisation due to heart failure. This angiotensin-neprilysin inhibitor called LCZ696 was compared to enalapril in a double-blind multinational trial that was stopped early because the boundary for an overwhelming benefit had been crossed. (3) This drug was approved for marketing by the FDA (Food and Drug Administration in the US) in July 2015.

1.5 Epidemiology of heart failure

1.5.1 Prevalence

Heart failure is a major and devastating health problem that impacts patients and healthcare systems all over the world. It was estimated in 2010 that approximately 900,000 people in the UK have heart failure;(48) with around 1-2% in the western world (49), and greater than 10% prevalence in the elderly (≥70

years of age). A more recent US study reports a prevalence of 2.2% (95%CI 1.6-2.8%), increasing to 8.4% in patients 75 years or older. (50) The Rotterdam study, a large population based cohort from the Netherlands estimated in 2004 that the prevalence of heart failure was 0.9% in those aged 55-65 increasing to over 17% in those aged ≥85. (51) The British Heart Foundation estimates that about 1-2% of the population in the UK is affected by heart failure (52) and more than 23-26 million people worldwide have the disease (45, 53) with prevalence rising.

Although the incidence of heart failure seems to be stabilising (see section 1.5.2), the prevalence continues to rise (54, 55), probably due to an increased survival associated with better recognition and treatment of the disease (56, 57). The most common underlying aetiology of heart failure is coronary heart disease, and the improved survival rates for myocardial infarction (58) leads to an aging population which could largely be driving the increasing prevalence of heart failure.

1.5.2 Incidence

The annual incidence in the UK is about 1.85/1000 population (52), rising to 11.6 per 1000 population per year in the elderly (over 85 years of age) with approximately 60,000 new cases each year (59, 60); although there is less information on incidence than there is on prevalence. The Rotterdam study group report an incidence rate of 14.4/1000 (95% CI 13.4-15.5) person-years. (51) The Framingham heart study (61) provides insight on the incidence of heart failure over a 34 year follow up period in the United States of America. They reported an annual incidence 2 new cases/1000 in persons aged 45–54 years increasing to 40 new cases/1000 in men aged 85–94 years. The incidence is higher in men than in women, independent of age. (51, 60)

1.5.3 Costs of heart failure

Heart failure is a very expensive problem. It has been estimated that heart failure's direct costs can range anywhere from €26 to €70 (in one million € per one million population) (62) and that it accounts for 1-2% of total healthcare costs in developed countries. (56) In the UK, heart failure accounts for 1 million inpatient beds per year and 5% of all emergency medical admissions to hospital

per year, and it is estimated that the total annual cost of heart failure to the NHS is about 2% of the total budget (with approximately 70% of this total due to the costs of hospitalisation). (63, 64) According to the CDC (Centers for Disease Control and prevention) in the United States of America it is estimated that the costs derived from heart failure are around $32 billion (about £20 billion) per year. (65)

1.5.4 Prognosis of heart failure

Thanks to the implementation of evidence-based medicine provided by large clinical trials, treatment for heart failure has greatly improved in the past decades, leading to a reduction in mortality and increasing prevalence. It was estimated in the year 2000 that survival probability for heart failure was 50% and 10% at 5 and 10 years respectively and for patients with severe disease, more than half will die within a year (66, 67). Nonetheless, estimates for heart failure with reduced ejection fraction differ from those for heart failure with preserved ejection fraction. Patients with HF-PEF (it is estimated that about half the patients with heart failure have a preserved ejection fraction) seem to have a better prognosis than those with HF-REF. (68-70)

1.6 Summary and rationale

Heart failure is a highly prevalent, expensive, devastating, and complex clinical syndrome, characterised by evidence of cardiac dysfunction and typical symptoms like fatigue, dyspnoea, chest pain and ankle swelling. Signs include elevated jugular venous pressure and pulmonary crackles. (5) Symptoms in heart failure provide important insight on deteriorating status which in turn may affect both patients' and clinicians' decision for seeking/providing treatment. (71) However, they are subjective and difficult to assess. (5) Consequently, they are frequently underestimated and overlooked as an important factor related to quality of life, morbidity and prognosis in heart failure both by patients and doctors. (72-74) This is compounded by the fact that their identification relies mostly on self-reporting. (71, 75)

Traditionally, it has been said that fatigue and dyspnoea are caused, respectively, by the inability of the heart to function as a pump leading to reduced oxygen supply to the muscle (fatigue) and fluid backlog due to the

requirement for increased left ventricular filling pressures to maintain cardiac output leading to pulmonary interstitial oedema (dyspnoea). (76-78) It is now well known that left ventricular function relates poorly to symptoms and still their cause remains unclear and little is known about their prevalence, severity and predictors. (73, 76, 79-83) It has even been suggested that both symptoms might be different manifestations of the same pathophysiological process. (76, 80, 84) However, in two separate studies each symptom has been shown to predict outcome independently of the other, suggesting they might be biologically distinct. (85, 86)

As I mentioned in section 1.4 above, the main focus of clinical trials studying heart failure has been a reduction of mortality and hospitalisation, although improvement of symptoms is considered a therapeutic goal. If more studies show that independent symptoms (and change in symptom severity) are associated with outcome (not only NYHA class, as it does not distinguish between individual symptoms), then clinicians should be do more to investigate and record symptoms and identify red flags that might predict how symptoms will evolve.

Given the importance of fatigue and dyspnoea in heart failure and the uncertainty surrounding them I have set out to determine which patient characteristics are associated with each of these symptoms and whether the variables related to fatigue and dyspnoea are similar or different. Additionally, I will examine how these two symptoms (and their change over time) relate to outcomes.

2 Fatigue in heart failure

Fatigue is a subjective symptom and is difficult to assess, it is distressing and persistent (87) and some argue that it might be underreported due to being attributed to aging (88, 89). Fatigue has a large impact on the quality of life of patients and its wide prevalence has led to an increasing interest in the study of fatigue in heart failure (90, 91), though prior studies have been small or failed to examine the relationship with outcomes. (71, 73, 91-102)

The importance of fatigue as a marker of prognosis has not been fully studied. I will examine the factors associated with fatigue in HF and whether it predicts morbidity and mortality.

2.1 Methods

2.1.1 Search Strategies

Electronic databases MEDLINE and EMBASE were searched (MEDLINE from 1946 to July week 1 2015; EMBASE 1996 to 2015 week 28), limited to human subjects and English language (for EMBASE additional limits were applied, excluding reviews and meta-analysis and limiting to adults). Relevant MeSH (Medical Subject Headings) terms were identified. Terms and keywords were combined according to the search criteria and to the requirements of the database. Hand searching the bibliographies of relevant studies identified no further publications.

Heart failure was defined using MeSH terms “Heart Failure”, “Cardiomyopathy, Dilated”, “Ventricular Dysfunction”, and “Cardiac Output, Low” and the following keywords: heart failure; congestive heart; cardiac failure; heart decompensation; myocardial failure; paroxysmal dyspnoea; cardiac asthma; cardiac oedema; congestive heart failure; left sided heart failure; right sided heart failure; congestive cardiomyopathy; low cardiac output; left ventricular dysfunction; right ventricular dysfunction.

Fatigue was defined using MeSH terms “Fatigue” and “Asthenia”, and the following keywords: asthenia, fatigue, exhaustion, muscle fatigue, tiredness and lassitude.

Search strategies and terms were discussed with and approved by the College Librarian for the School of Medicine (Ms Heather Worlledge). I screened titles and abstracts to identify relevant studies. All relevant publications with a focus on heart failure that looked at individual symptoms were included in this literature review. Detailed search strategies can be found in Appendix 1.

2.2 Aims

The aims of this review were to: 1) Identify the demographic characteristics associated with fatigue in patients with heart failure; 2) Determine whether fatigue (and change in fatigue over time) is associated with worse morbidity and mortality in patients with heart failure and 3) Determine if fatigue is associated with statin use and if treatment with co-enzyme Q_{10} plays a role in fatigue severity. A secondary aim was to identify literature describing the aetiology of fatigue in heart failure.

2.3 Results

1243 studies were identified in the MEDLINE (OVID) search and a further 1478 were identified in EMBASE (OVID).

2.3.1 Aetiology of fatigue

Sixteen publications describing the aetiology of fatigue in heart failure were identified. Most of the publications are reviews looking at the possible mechanisms underlying the origin of symptoms on exertion in patients with heart failure. In 2005, Mann *et al* (103) published a review summarising advances in the study of heart failure, with a focus on therapeutic and including an overview of the origin of symptoms. Similarly, in 2010 Piepoli *et al* (104, 105) published a 2-part review aiming to summarise the existing evidence for the origin of symptoms in heart failure with reduced ejection fraction. A further review was published by Witte and Clarke in 2007 (106) describing the possible mechanisms by which heart failure causes fatigue and dyspnoea. Generally, although the authors present a thorough and clear description of the aetiology of symptoms in heart failure, the summaries are largely descriptive and the authors fail to clearly state how the evidence was selected to be included in the review.

In 1994, a study was published by Carell *et al* (107) looking at the relationship between maximal exercise tolerance and resting radionuclide indexes of left ventricular systolic and diastolic function. It involved 64 patients with cardiomyopathy (ischemic or idiopathic) who underwent symptom-limited exercise testing with on-line measurement of oxygen consumption. Their results determined that resting left ventricular ejection fraction poorly predicts maximal exercise capacity, contradicting the perception of symptoms being caused by reduced pump function of the heart.

Clarke *et al* (108) in 2005 published a detailed summary of the possible pathophysiological mechanisms underlying the origin of dyspnoea and fatigue on exertion in patients with heart failure; however, the authors fail to clearly define objectives and methodology in their paper. On the other hand, in 2008 another group of investigator led by Bunny Pozehl (109) ran a pilot study with 23 patients looking at the effect of a 24-week exercise training program on fatigue and dyspnoea in patients with heart failure with reduced ejection fraction; their results provide some support to the theory attributing symptoms to a build-up of metabolic products. Even though the study was very small, it seems to be robust and results analysed in an adequate manner (as per their methods section).

In summary, the aetiology of fatigue in HF is unclear and numerous mechanisms have been proposed. (103-105) It has long been recognised that there is little relation between measures of haemodynamic function and exercise capacity (110), and the lack of relationship between left ventricular filling pressures and maximal oxygen uptake is well known (111, 112). It is now generally accepted that fatigue arises from decreased oxygen delivery to muscle due to an impaired pump function of the failing heart, which leads to a build-up of anaerobic metabolic products. (108, 109) Some approaches attribute the impaired muscle blood flow to persistent vasoconstriction and endothelial dysfunction, rather than to limited cardiac output. (76, 84, 107, 113) Other potential mechanisms include abnormalities in muscle metabolism, which limit their ability to utilize oxygen and a miss-match between energy requirement and energy production. (76, 90, 113, 114) Although the controversy persists, the theory that intrinsic muscle abnormalities are responsible for the exercise limitation in patients with heart failure (115) is gaining acceptance and is now commonly recognised as the main mechanism. (115-118)

It has been shown that there is evidence of a switch from aerobic to anaerobic metabolism in the skeletal muscle of patients with chronic heart failure, a reduced activity of oxidative enzymes, this together with muscle wasting-which has been recognised since the times of Hippocrates- and reduced blood flow probably secondary to alterations in vasomotor tone make up what is called the "muscle hypothesis" for the origin of symptoms in heart failure. (84, 113, 119-121)

2.3.2 Correlates of fatigue

Thirty publications were identified in relation to the correlates of fatigue in heart failure. Four papers (75, 99, 122-124) were excluded because they did not distinguish between individual symptoms (i.e. did not discriminate between dyspnoea and fatigue) and 2 more (75, 108) due to them being reviews.

Fatigue in HF has been associated with NYHA functional class in several studies (71, 93, 96, 100, 101, 125), however several other studies could not confirm this association (91, 95, 97, 98). The association between sex and fatigue in HF patients has had similar conflicting results with some authors finding that women report more fatigue than men (94, 100, 102) and other authors finding no association between the two. (92, 95, 96, 101)

Except for one study by Smith et al. (100), fatigue and age have not been significantly correlated (95-97, 101, 102, 125). The authors who examined 6 fatigue trajectories found that age equal or greater than 60 years was associated with a lower likelihood of being in group reporting a low exertion fatigue (OR 0.35 p value=0.02; meaning that younger patients were more likely to be in the low exertion fatigue group). They chose to dichotomise age, leading to a substantial loss of information and potentially leading the reader to make incorrect assumptions as they fail to provide confidence intervals for these results which makes it difficult to assess the magnitude of the effect of age on fatigue.

Depression, on the other hand, has been clearly identified as a predictor of fatigue in HF patients. (73, 93, 95, 97, 101, 125, 126) Depression was said to explain anywhere from 6.5% to 74% of the variance in fatigue in the cited studies. All these studies report exclusively the r-squared (it measures how close

the data are to the fitted regression line in a linear regression model), but authors fail to provide residual plots. While r-squared will provide an estimate of the strength of the relationship between the chosen model and the response variable, it does not provide a proper hypothesis test for said relationship. (127) It has also been stated that up to 30% of patients with heart failure also report depression, this data is derived from observation alone, providing no evidence on the statistical significance of the association. (128, 129)

Other factors found to be associated with fatigue are: dyspnoea with a correlation coefficient of 0.30 in one study, and 0.45 in the other, both relatively weak correlations(130, 131); anaemia both studies reporting that 30% of the variance in fatigue was explained by a decreased haemoglobin level (one considered low haemoglobin ≤125 g/L while the other considered ≤11.0 mg/dl) (96, 97); symptom distress, or degree of discomfort associated with fatigue (measured by Swedish version of Symptom Distress Scale) with one study reporting a 39% of the variance in fatigue was explained by symptom distress while the other reported only 4% of the variance in fatigue was due to symptom distress (93, 95).

Poor sleep quality (98, 125) has also been linked to fatigue, however both studies derived their conclusions from univariate analyses using a chi^2 test; however, chi^2 tests do not provide information about the strength of the relationship between the two variables, they are sensitive to small expected frequencies and are sensitive to sample size.

Left ventricular ejection fraction (LVEF) has been inversely correlate to fatigue in patients with heart failure (lower ejection fraction is associated with higher fatigue), although only beta coefficients are reported for both studies (one reports a ß-value of 0.14 and the other of -0.72; they fail to report individual R^2 values however) (101, 126).

Others factors that have been associated with fatigue in patients with heart failure are: decreased exercise capacity (73, 100, 131); comorbidities such as hypertension (131) or diabetes mellitus (100); not having a biventricular pacemaker (126); use of beta-blockers (associated with chronic fatigue, not fatigue on exertion) (126) or psychotropic agents (100); type D personality (131);

quality of life (92); and finally marital status, with married patients reporting higher levels of fatigue (91).

Although several studies have looked at the relationship between resting haemodynamic indices and exercise capacity in patients with heart failure (107, 132-136), few studies have looked at objective haemodynamic findings and their association to individual symptoms (as opposed to exercise tolerance or overall NYHA class) (137, 138). Guglin *et al* found a weakly positive correlation between pulmonary artery pressures and fatigue as the main reason for stopping exercise training (137). They also found that fatigue was inversely correlated to serum sodium, potassium and albumin. Correlations are linear associations between variables, meaning that as the average value of one variable changes, so does the average value of the other variable, and this association can be influenced or caused by other observed or unobserved variables. Although correlations are commonly used and relatively easy to interpret, a correlation does not tell us how the two variables are interacting, the do not indicate direction of interaction. Is fatigue decreasing as sodium increases or is sodium increasing as fatigue decreases? Correlation does not imply causation- a correlation merely tells us that the two variables are interacting. Lipkin et al found that fatigue was inversely correlated to maximal cardiac output during exercise (138). Again, the same problem arises, where correlation does not imply causation.

Equally important as correlates of fatigue in heart failure are the markers that have been found to have no association to symptoms, such as NT-proBNP and improved haemodynamic measures (137, 139), lending support to the muscle hypothesis as an origin of symptoms in heart failure (described in section 2.3.1)

Table 2-1 presents a summary of the publications I found to be relevant in identifying the correlates of fatigue in patients with heart failure. I present the objectives of each study, the number of patients included in each one, the method used to measure fatigue and the relevant findings.

2.3.3 Prognostic value of fatigue

Only 5 studies investigating the prognostic value of fatigue in heart failure patients were identified. The Carvedilol or Metoprolol European Trial (COMET) enrolled 3029 patients with HF. In a secondary analysis of COMET, fatigue, as

well as dyspnoea and orthopnoea, correlated significantly with mortality and hospitalisation due to worsening HF (worse fatigue associated with higher event rates). However, after performing multivariable Cox regression analysis (adjusted for the baseline characteristics of age, gender, NYHA class, duration of HF, aetiology of HF, previous myocardial infarction, coronary artery disease, angina, hypertension, diabetes; stroke, and concomitant medication) the authors found that only dyspnoea and not fatigue was associated with increased mortality. Fatigue remained a significant predictor for the development of worsening heart failure (RR 1.09 per unit increase of fatigue; 95% CI 1.02–1.17; P =0.02). (86) This study remains the most important one looking at the prognostic value of symptoms in heart failure as the model was adjusted for well-known prognostic factors (including NYHA class though they did not measure NT-proBNP) and analysed a large number of patients, even though it is a secondary analysis, which deducts weight from their results. Additionally, the cohort was not very different from the patients studied in CORONA, which provides a solid base for performing further analyses in said cohort.

Two more studies identified fatigue as a predictor of adverse events. (100, 126) The first examined fatigue as measured by the Dutch Exertion Fatigue Scale (DEFS) and identified six fatigue categories with the third level (moderate offset exertional fatigue with an observed mean DEFS score at baseline of 19.94) as the reference group. The study reported that compared the reference group mentioned above, the low exertion fatigue class was associated with lower all-cause mortality (HR=0.12, 95% CI 0.02-0.93, p=0.04) and severe exertion fatigue class with greater all-cause mortality (HR2.59, 95% CI 1.09-6.19, p=0.03). (100) In another study, patients with high levels of fatigue on exertion had an approximately two fold increased risk of experiencing an adverse cardiac event such as cardiovascular hospital readmission or death (HR=1.78, 95% CI 1.18-2.68, P=0.006). (126) Importantly, these studies measure fatigue on exertion as opposed to chronic fatigue; fatigue on exertion has an acute onset, has a short duration and a short recovery period(140-142).

Another small (n=61), a 9 months prospective study of older patients (mean age 61 ± 15 years) identified anergia (defined as criterion-based syndrome based on 7 questions) as an independent predictor of hospitalisation due to any cause (odds ratio of 7.7, 95% CI 1.43–41.56,p= 0.02) after a 3-month follow up period.

(143) From their methods section, although it is not completely clear it seems that the multivariate logistic regression looks at the prognostic significance of the presence of anergia in this cohort (with the outcome being hospitalisation or no hospitalisation), however the authors do not specify if they are referring to a lack of energy at baseline, or during follow up. Additionally, survival analysis would be more adequate than multivariate logistic regression when analysing the prognostic value of a symptom, and an outcome of hospitalisation due to heart failure, as opposed to hospitalisation due to any cause, would be more acceptable because such an outcome would address how fatigue is associated with heart failure as elderly patients can be hospitalised for a number of reasons which have nothing to do with their heart failure status.

A further study by Chase *et al* analysed the reason for stopping cardiac exercise testing (fatigue vs. dyspnoea), investigating 183 patients with heart failure who were followed up for time to first cardiac-related event for a maximum of 2 years. They found that differences in event-free survival were significant between patients who had stopped due to dyspnoea and those who stopped due to fatigue, with a higher event rate in the dyspnoea group. Their results show that within the fatigue group, 84.6% were event free at 20 months (16 events in 104 patients), vs. 68.4% in the dyspnoea group (25 events in 79 patients); log rank p value=0.02. (144) These results are derived from univariate analysis and do not look at the prognostic significance of individual symptoms, but rather a comparison between the two symptoms. Additionally, the authors looked at the reason for stopping exercise testing, which addresses a slightly different issue than fatigue (or symptoms) during daily living.

2.3.4 Statin use/co-enzyme Q_{10} and fatigue

I was able to find some references on the association between statin use and fatigue in patients with heart failure by hand searching the literature, as well as the association between co-enzyme Q10 and fatigue. I summarise my findings next.

Although there is evidence of muscle related adverse events associated with treatment with high doses of simvastatin (145), and it is well known that the most common adverse events associated with statin use are muscle related (146, 147), there is no convincing evidence that low dose statins impair muscle

function or exercise capacity. (148-152) One study by Golomb *et al* reported that, compared with placebo, 6 months treatment with a modest dose of simvastatin or pravastatin had an adverse effect on a cumulative measure of energy and fatigue. (153)

HMG-CoA reductase inhibitors block the synthesis of co-enzyme Q_{10} which is recognized component of mitochondrial ATP production. (154) There has been much interest in the potential role of coenzyme Q_{10} as a therapeutic agent in heart failure. (155-157) It has even been proposed that treatment with ubiquinone (co-enzyme Q10) should be included in guidelines for congestive heart failure (158); however, few studies have looked at the association between statin use, co-enzyme Q10 levels and fatigue in patients with heart failure (159-161) and they have conflicting results. While two of the studies support the idea that supplementation with ubiquinone (co-enzyme Q10) is beneficial for symptom reduction in patients with heart failure (159, 161), these studies have been small (n=50 and 79) and the associations have been either weak (161) or the authors have failed to adequately analyze their data (i.e. presenting descriptive results without statistical testing of modeling). (159) One other study found no association between treatment with co-enzyme Q10 and exercise capacity in patients with congestive heart failure (160), although the authors did not look specifically at fatigue but rather exercise capacity.

2.3.5 Discussion

Although a number of studies have been published looking to identify predictors of fatigue in heart failure patients and fatigue as a prognostic tool, the results are conflicting. Most of the studies are small and underpowered to detect an association between fatigue and clinical outcomes and very few look at objective measures. The paper by Evangelista *et al* (73) is the most widely cited, and although it is well written with robust statistical analyses and includes thorough demographic and clinically relevant covariates, it has a small sample size and does not include information on potentially important laboratory values like NT-proBNP, electrolyte levels or thyroid hormone levels. Smith (99, 100, 126, 131, 162, 163) and Falk (95, 96, 164, 165) are the two most prolific authors looking at the role of fatigue in patients with heart failure but their focus has mostly been on the impact of symptoms on quality of life and not on the correlates of fatigue or its prognostic value. Although all the publications

included in this review clearly state their objectives and methods, most of them rely on subjective data (i.e. quality of life, depression, social support or emotional distress) and are not supported by objective data (i.e. laboratory of haemodynamic measures).

An association between younger age and worse health related quality of life (measured with the MLHFQ) in patients with heart failure has been documented; female sex was also an independent predictor or worse quality of life in this study. (166) It is also well known that depression and fatigue are closely linked. Having said this, it has been documented that both the prevalence and the incidence of major depression double after 70-85 years of age (167-169); however, an elderly person is slightly less likely than someone who is middle-aged to report symptoms of depression. (170) This could mean that older age might influence how patients experience and report symptoms of heart failure, making them less likely to report them. In other words, depression could be confounding the association between age and fatigue. Moreover, cultural differences in the experience of symptoms have been documented (171, 172)

Evidence supporting the concept that statins have a deleterious effect on fatigue in patients with heart failure is scarce. Similarly, the evidence-base supporting the benefit of treatment with co-enzyme Q10 on fatigue severity in patients with heart failure is weak.

Table 2-1 Evidence table for published literature relating to fatigue and heart failure

Author Year of publication	N	Objectives	Method Used to Measure Fatigue	Factors Associated with Fatigue
Lipkin 1986 (138)	25	To evaluate the response to exercise in patients with heart failure and determine what metabolic, haemodynamic and ventilator changes correlate to symptoms.	Reason for stopping exercise test (fatigue vs. dyspnoea)	Inversely related to maximal cardiac output during exercise.
Friedman 1995 (130)	57	Examine the contribution of physical and psychological factors to the variance in fatigue.	Cohen-Hoberman Inventory of Physical Symptoms.	Shortness of breath
Tiesinga 2001 (102)	138	To test the sensitivity, specificity, and usefulness of the Dutch Fatigue Scale (DUFS), which is based on NANDA's defining characteristics of fatigue.	The Dutch Exertion Fatigue Scale	Women with heart failure report more fatigue than men
Shah 2002(139)	201	Evaluate the association between symptoms and changes in hemodynamic variables on pulmonary-artery catheterization.	Yale Dyspnoea-Fatigue Index	No correlation between reduction in filling pressures/ increase in cardiac contractility and symptoms
Ekman 2002 (94)	158	Describe and compare the experience of fatigue in a group of elderly women and men with severe chronic heart failure.	Fatigue Interview Schedule	Women report more fatigue than men
Falk 2006 (96)	93	Describe the fatigue experience and its relationship to haemoglobin (Hb) concentration and to evaluate its effect on health-related quality of life in a hospitalised CHF population.	Multidimensional Fatigue Inventory Scale	Lower Haemoglobin levels (<=125 g/L) Higher NYHA
Smith 2007 (131)	136	To examine the role of clinical and psychological characteristics as predictors of fatigue in HF.	Dutch Exertion Fatigue Scale	Decreased exercise capacity, dyspnoea, hypertension, depressive symptoms, type-D personality, sleep problems
Evangelista 2008 (73)	150	Determine the prevalence of fatigue and identify its demographic, clinical, and psychological correlates.	Profile of Mood States-Fatigue	Lower maximal workload, lower physical and emotional health scores, and depression
Smith 2008 (163)	506	Examine the effect of the stage of ischemic heart disease and type-D personality on fatigue and depressive symptoms and whether the effect of type-D personality on these symptoms is moderated by ischemic heart disease stage.	The Maastricht Questionnaire(173)	Type-D personality is an independent predictor of fatigue.

Stephen 2008 (91)	53	Describe fatigue and the relationships among fatigue intensity, self-reported functional status, and quality of life in older adults with stable heart failure.	Profile of Mood States fatigue subscale	Marital status-married
Falk 2009 (95)	112	Examine the association between fatigue, depression and symptom distress and to explore the relationships between individual symptoms and the dimensions of fatigue in patients with CHF.	Multidimensional Fatigue Inventory Scale	Increased Emotional and symptom distress Depression
Fink 2009 (97)	87	Determine the psychometric properties of 2 fatigue questionnaires in patients with HF, compare fatigue in patients with HF to published scores of healthy adults and patients with cancer undergoing treatment, and identify the physiological and psychosocial correlates of fatigue in HF	Fatigue Symptom Inventory (174) and the Fatigue subscale scores on the Profile of Mood States.	Depressed mood, reduced physical functioning, lower haemoglobin (below 11.0 mg/dL)
Smith 2009 (126)	387	Examine the factors associated with changes in fatigue in chronic heart failure and determine their prognostic impact.	Dutch Exertion Fatigue Scale	Lower LVEF, not having a biventricular pacemaker, use of beta-blockers, and cognitive affective depressive symptoms.
Albert 2010 (71)	276	Examine prevalence of signs and symptoms relative to demographics, care setting, and functional class.	Self reported through checklist	Higher NYHA Hospitalised patients report more fatigue
Chen 2010 (93)	105	Examine the level of fatigue perceived by patients with heart failure and to explore the potential factors influencing fatigue.	Piper fatigue scale (PFS)	Higher NYHA class, increased symptomatic distress, depression, anxiety and appraisal support by health care providers (not family).
Tang 2010 (101)	107	Examine the associations among age, gender, NYHA, EF, beta-blocker use, Haemoglobin, depression and fatigue in patients with HF and determine the contribution of physiological and psychological factors to the variance in HF patients' fatigue.	Fatigue Visual Analogue Scale Tang Fatigue Rating Scale	Higher NYHA, depression and lower LVEF
Smith 2010 (100)	310	To identify distinct trajectories of fatigue over a 12-month period and to examine their impact on mortality in chronic heart failure.	The Dutch Exertion Fatigue Scale	Female gender, older age, physical inactivity, diabetes mellitus, co-morbidities, higher NYHA class, impaired exercise capacity, and

				use psychotropic medication
Austin 2011 (92)	200	Report on patterns and severity of fatigue in surviving patients in a 5-year heart failure programme.	Question 13 of the Living with Heart Failure Questionnaire (University of Minnesota MLHF)	Increased impairment in QoL measured with MLHF questionnaire.
Bunevicius 2012 (175)	83	Evaluate the possible associations of fatigue and exercise capacity with function of adrenal and thyroid axis in patients with coronary artery disease	The Dutch Exertion Fatigue Scale	Low thyroid hormone concentrations and low cortisol levels associated with fatigue
Fink 2012 (125)	59	To examine the relationship among fatigue, cytokines and projected mortality and elucidate the biological and clinical correlates of fatigue	Profile of Mood States fatigue subscale	NYHA, depression, poor sleep quality
Guglin 2012(137)	433	Evaluate if there is a correlation between haemodynamic, echocardiographic and laboratory data and presenting symptoms of heart failure	4 point Likert scale	Positive correlation to pulmonary artery pressures
Redeker 2012 (176)	173	Evaluate nocturia severity and nocturia-related differences in sleep, daytime symptoms and functional performance among patients with stable HF.	The global fatigue score of the Multidimensional Assessment of Fatigue scale (MAF)	Presence of nocturia was associated with increased fatigue
Riegel 2012 (177)	280	Explore the correlates of fatigue in patients with HF as a secondary objective	Items from the Kansas City Cardiomyopathy Questionnaire (15)	Worse sleep quality score and worse functional class
Comin-Colet 2013(178)	552	Evaluate the effect of iron deficiency and/or anaemia on health-related quality of life in patients with HF	Living with Heart Failure Questionnaire (University of Minnesota MLHF)	Iron deficiency was significantly associated with physical aspects of the questionnaire (including fatigue)
Eckhardt 2014 (179)	102	Describe fatigue in patients with HF and determine if specific demographic, physiological or psychological variables were correlated to fatigue, and if fatigue is associated with health-related quality of life.	Fatigue Symptom inventory	Depressive symptoms were the only predictors of fatigue

3 Dyspnoea in heart failure

3.1 Search Strategies

The electronic database MEDLINE was searched (from 1946 to July week 1 2015), limited to human subjects and English language. Relevant MeSH terms were identified. Terms and keywords were combined according to the search criteria and to the requirements of the database. Hand searching the bibliographies of relevant studies identified no further publications.

Heart failure was defined in the same way as detailed in Chapter 2.

Dyspnoea was defined using MeSH terms “Dyspnea”, “Dyspnoea”, “Paroxysmal Dyspnoea” and “Paroxysmal Dyspnea”, and the following keywords: dyspnea, dyspnoea, shortness of breath, breath shortness and breathlessness.

Search strategies and terms were discussed with and approved by the College Librarian for the School of Medicine (Ms Heather Worlledge). I screened titles and abstracts to identify relevant studies. All relevant publications with a focus on heart failure that looked at individual symptoms were included in this literature review. Detailed search strategies can be found in Appendix 2.

Search strategies described above were applied to EMBASE (OVID) and resulted in 20803 additional potential publications. A preliminary scan of titles and abstracts of the first 3,000 publications proved unsuccessful in identifying additional relevant publications for the purpose of this literature review so the search was limited to MEDLINE for the final document.

3.2 Aims

The aims of this review were to: 1) Identify the demographic characteristics associated with dyspnoea in patients with heart failure; 2) Determine whether dyspnoea (and change in dyspnoea over time) is associated with worse morbidity and mortality in patients with heart failure. A secondary aim was to identify literature describing the aetiology of dyspnoea in heart failure.

3.3 Results

3810 studies were identified in the MEDLINE (OVID) search.

3.3.1 Aetiology of dyspnoea in heart failure

Dyspnoea has been defined in a consensus statement by the American Thoracic Society as a "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity". (180, 181) It is a common and complex symptom that accompanies many disorders and diseases and is derived from multiple pathophysiological sources, rather than from a single one. (182) Although dyspnoea on exertion can be normal, it is considered pathological when it occurs with a level of activity that should usually be well tolerated. (183)

Dyspnoea occurs when there is a mismatch between the feedback from the central respiratory centres and the efferent motor signals to respiratory muscles. (184-186) Traditionally, it was thought that symptoms were derived from haemodynamic changes in heart failure that lead to an increased left ventricular pressure to maintain cardiac output by the Frank-Starling principle, leading to stiff lungs or apparent alveolar fluid overload, but now it is well known that the degree of left ventricular dysfunction is not closely related to symptoms, a mechanism often referred to as the "central hypothesis" for the origin of symptoms. (81, 84, 113) The precise mechanisms of why heart failure causes dyspnoea are not thoroughly understood and it has become widely accepted that generalised changes in muscle bulk, metabolism, endurance, and blood flow may all contribute to the origin of dyspnoea. (106, 187)

As mentioned in chapter 1, a new term of bendopnea has been introduced to describe dyspnoea when bending forward in patients with heart failure (26), and while orthopnoea has been best correlated to elevated left ventricular pressures (not dyspnoea on exertion) (188) so has bendopnea been associated with high PCWP supporting the concept that both symptoms have the same underlying pathophysiology. Orthopnoea, nocturnal paroxysmal dyspnoea and bendopnea are more specific to heart failure, but are also less common than exertional dyspnoea. (5) The focus of my thesis is on dyspnoea on exertion.

The frequent coexistence of dyspnoea and fatigue and the weak association between dyspnoea relief and improvement of haemodynamic parameters support the notion that structural abnormalities of skeletal muscle may be involved in the generation of dyspnoea.

3.3.2 Correlates of dyspnoea

I identified 12 publications looking at the correlates of dyspnoea in patients with heart failure. Reviews, editorials and meta-analyses were not considered for this section, only studies that analysed individual symptoms in patients with heart failure with reduced ejection fraction were included. Three publications (27, 137, 189) determined that dyspnoea was not associated or was weakly correlated to haemodynamic measures like pulmonary artery pressures or pulmonary capillary wedge pressures, while Solomonica *et al* (190) found that improved pulmonary capillary wedge pressure (OR 1.80, 95% CI 1.22-2.65) and mean pulmonary artery pressure (OR 2.98, 95% CI, 1.91-4.66) were associated with improvement of dyspnoea at rest. Other variables associated with dyspnoea relief are opioid use (191, 192), higher respiratory rate, higher haemoglobin levels, higher serum sodium levels and history of peripheral artery disease. (193, 194)

Several other studies looked at the relationship between pulmonary/respiratory function and dyspnoea. Bronchodilator use showed benefit in alleviating dyspnoea in patients with concomitant airway obstruction (Borg score 0.7 ± 1.2 pre-bronchodilator use versus 0.9 ± 1.3, p = 0.002 post-bronchodilator use) (195); however, two earlier studies (196, 197) showed that dyspnoea had no association with spirometric measures or measures of airway obstruction. Inspiratory muscle training nonetheless proved beneficial in two small studies. (198, 199) Another factor which has shown to have inconclusive associations with dyspnoea is NT-proBNP level, where one research group (193) showed a correlation with dyspnoea while another failed to do so (200). The paper that provides evidence for an association of dyspnoea with NT-proBNP levels report an increase of 5% in the odds of reporting relief in dyspnoea with a doubling of NT-proBNP levels (95% CI 1.01-1.08, p<0.01), which is rather counter-intuitive as one would assume that higher NT-proBNP levels represent a worse health status; the authors fail to provide an explanation or speculate as to the reasons for this finding. Although the confidence interval is narrow, and the p value is small, the

authors do not provide information on interactions, if any were performed. This finding could either be a spurious finding or could be influenced by confounding factors, like weight or renal function, which can affect NT-proBNP levels. Another possible explanation for this association between increased NT-proBNP levels and a higher likelihood of reporting symptom relief could be due the biological effects of natriuretic peptides, which promote diuresis, vasodilation and inhibition of renin and aldosterone secretion. (201)

Table 3-1 presents a summary of the publications I found to be relevant in identifying the correlates of dyspnoea in patients with heart failure. I present the objectives of each study, the number of patients included in each one, the method used to measure dyspnoea and the relevant findings.

3.3.3 Prognostic value of dyspnoea

A secondary analysis from the PROTECT trial (Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal FuncTion)(202) which included 1998 patients identified early dyspnoea relief (as defined by moderately or markedly better dyspnoea at both 24 and 48 hours from randomisation) as a significant independent predictor for lower mortality at both 14 and 30 days (HR at 14 days 0.28, 95% CI 0.15-0.50; HR 30 days 0.35, 95% CI 0.22-0.55). It is important to note that PROTECT included patients with dyspnoea at rest or minimal activity and looked at patients who were hospitalised for acute heart failure.

As mentioned in section 2.3.3, in a secondary analysis of The Carvedilol or Metoprolol European Trial (COMET) dyspnoea correlated significantly with mortality (1.14 per unit increase in dyspnoea: 95% CI 1.04–1.26; p=0.01) and hospitalisation due to worsening HF (1.09 per unit increase in dyspnoea: 95% CI 1.02–1.17; p=0.02). (86)

Moser *et al* (203) hypothesised that patients who reported greater variability in their symptom severity would have more difficulty recognising worsening symptoms and would in consequence have worse outcome. In their study they followed 71 patients with heart failure and asked them to record their heart

failure symptoms daily for 30 days and were followed-up for an average of one year. They found that high variability in daily ratings of dyspnoea was associated with higher risk of the composite outcome of heart failure hospitalisation or death when compared to a stable symptom pattern (OR 4.09, 95% CI 1.16-14.39). The authors determined high or low symptom variability patterns by averaging the daily ratings and determining the standard deviation for each patient, subsequently classifying them. Nonetheless, the authors failed to adjust for average symptom severity, comparing only the groups who had some variation. The results would have been more robust if they could show that symptom variability was associated with outcome independently from average dyspnoea levels.

In 2005, a very large retrospective cohort study (n=74,580) from the United States identified dyspnoea on exertion as an independently significant predictor for 30-day rehospitalisation, stating that this symptom was the primary clinical variable associated with rehospitalisation. (204) They report that having no dyspnoea was associated with a 45% lower risk of being re-hospitalised within 30 days of the index hospitalisation when compared to having dyspnoea at rest (HR 0.55, 95% CI 0.51-0.60). In this study, Madigan *et al* speculate that the dyspnoea patients reporting during home health-care visits could be influenced by both the disease process and deconditioning associated with inactivity. Although the authors identify the reason for rehospitalisation as cardiac related in 42% of the cases, they also report that 32% of the re-hospitalisations had a secondary diagnosis of COPD, which could contribute heavily to the sensation of dyspnoea. (8, 205)

A small study (n=58) performed in Brazil by Weber *et al* identified higher baseline levels of dyspnoea (as self-reported with a 5-point Likert scale) to be independently associated with hospitalisation due to cardiovascular causes, even after adjusting for NYHA class and NT-proBNP. However, the authors fail to describe if and how adverse events (including hospitalisations) were adjudicated. Additionally, the sample was selected from a pre-transplant clinic, which might be more representative of a “sicker” population rather than the majority of heart failure patients. (206)

A retrospective study including 134 individuals with heart failure by KM Anderson published in 2014 identified dyspnoea as a significant predictor for 60-day

hospital readmission. The author, however, fails to describe how dyspnoea was measured or if it was dyspnoea at rest or on exertion, simply stating that demographic data and patient history were obtained from medical records. (207)

More recently, Mentz *et al* (208) performed analyses on an American registry for acute decompensated heart failure, a large cohort that they linked to Medicare files (48616 individuals). The authors identified dyspnoea at rest (on admission for acute heart failure) compared to dyspnoea with moderate activity as an independent predictor for increased 30-day mortality and HF readmission (all-cause mortality HR 1.89, 95 % CI 1.60-2.24; HF readmission within 30 days HR 1.35, 95% CI 1.14-1.59). The excluded patients who had no record of dyspnoea on admission or who reported no dyspnoea, effectively eliminating data on over 23,000 subjects, they also excluded patients with an elective hospital admission.

In late 2008, a study comparing fatigue vs. dyspnoea as the reason for stopping exercise testing in 271 patients with chronic heart failure found that there was no difference in adverse outcome (death) at 36 months follow-up when comparing the two symptoms (HR 1.02, 95% CI 0.63-1.64). The authors conclude that symptoms experienced by patients with chronic heart failure with no concomitant pulmonary disease during exercise testing do not provide additional prognostic information over other indicators such as NYHA class or peak oxygen consumption (209), although previous, larger studies have shown differently. For example, a study published in 2005 that analysed data from 17991 patients who underwent stress testing determined that dyspnoea was associated with a significant increase in the risk of death due to cardiac causes (HR 1.9, 95% CI 1.5-2.4)(210). Another group of seemingly healthy males who underwent exercise testing that was followed-up for 26 years published in 2014 found that after adjusting for other important covariates (age, smoking, total cholesterol, systolic blood pressure, blood glucose and physical fitness), people stopping due to difficulty breathing had a 1.55 fold increase (95 % CI 1.10-2.18) in the risk of dying from coronary heart disease when compared to stopping due to fatigue. (211) Similarly, Chase et al found that patients who stopped exercise testing due to dyspnoea were more than 2 times more likely to have a cardiac related event than those who stopped due to fatigue (HR 2.1, 95% CI 1.1-4.0), sample size was 183 men and women and follow-up time was 2 years. (144)

3.3.4 Discussion

I found a very weak evidence base for correlates of dyspnoea in patients with heart failure. Most of the literature identified what is *not* associated with dyspnoea (i.e. haemodynamic measures, pulmonary function), which gets us one step closer to effectively identifying the pathophysiological process underlying dyspnoea, by eliminating potential mechanisms. Nevertheless, eliminating causes does not provide evidence of what is effectively responsible for dyspnoea in patients with heart failure and more importantly the potential role of dyspnoea as a predictor of outcome remains unclear. Few studies look at correlates of dyspnoea on exertion, most focus on variables associated with dyspnoea relief and few studies look at dyspnoea in a non-acute setting, which is the focus of this thesis.

Although dyspnoea is recognised widely as a pivotal symptom of the disease, and is commonly associated with outcome, the pathophysiology underlying this complex symptom is still poorly understood. Additionally, most studies looking at the importance of dyspnoea as a predictor of outcome focus on acute heart failure in a hospital setting, while the majority of patients living with this devastating disease are ambulatory and live with exertional dyspnoea that limits their activities on a daily basis and has an important influence on their quality of life.

Table 3-1 Evidence table for published literature relating to dyspnoea and heart failure

Author Year of publication	N	Objectives	Method Used to Measure Dyspnoea	Factors Associated with Dyspnoea
Lipkin 1986 (138)	25	To evaluate the response to exercise in patients with heart failure and determine what metabolic, haemodynamic and ventilator changes correlate to symptoms.	Reason for stopping exercise test (fatigue vs. dyspnea)	Associated with a rapid rise in plasma lactate concentration and fall in arterial pH.
Evans 1996(196)	37	Examine if airway obstruction and bronchial hyper-responsiveness contribute to dyspnoea and reduce exercise capacity in patients with heart failure	Borg score	No relationship between measures of airway obstruction and dyspnoea on exertion
Russell 1998(189)	71	Identify factors responsible for the symptom of dyspnoea in patients with heart failure	10-point Likert scale	No correlation with rest or exercise haemodynamic, spirometric or metabolic variables.
Laoutaris 2004(199)	35	To investigate the effect of inspiratory muscle training on exertional dyspnoea in patients with chronic heart failure.	Borg score	Inspiratory muscle training for 10 weeks was associated with alleviated dyspnoea
Witte 2004(212)	120	To examine the effect of aspirin on the ventilatory response to exercise in a group of patients with chronic heart failure	10-pont Likert scale	Aspirin had no effect on dyspnoea on exertion
Drazner 2008(27)	194	Determine if estimated hemodynamics from history and physical examination reflect invasive measurements and predict outcomes in advanced heart failure.	Data obtained from CRF where dyspnoea was recorded as: at rest, walking in a room or walking less than a block.	Dyspnoea on exertion was not associated with hemodynamic measures.
Bosnak-Guclu 2011(198)	36	Investigate the effects of inspiratory muscle training on dyspnoea in heart failure patients	Modified Medical Research council dyspnoea scale	Inspiratory muscle training decreases the perception of dyspnoea
Eckman 2011(213)	72	Investigate if lowering breathing rate with the help of a respiratory modulation device could improve symptoms in patients with chronic heart failure	5-point Likert scale	Device guided respiratory modulation did not improve symptoms compared to

				those who only listened to music.
Guglin 2012(137)	433	Investigate the haemodynamic, echocardiographic and laboratory correlations to various heart failure symptoms.	Presence or absence of dyspnoea on admission, discharge and 3-month follow-up.	Weak correlation with haemodynamic measurements of pulmonary artery pressures during systole and diastole. Inverse relation to systemic systolic and diastolic pressures and right and left atrial size. Inversely correlated to serum creatinine, albumin, sodium, total bilirubin, haemobglobin and haematocrit.
Minasian 2012(195)	116	Evaluate the effect of maximal bronchodilation with combined inhaled salbutamol and ipratropium bromide on pulmonary function and dyspnoea in patients with chronic heart failure.	Borg dyspnoea score	Bronchodilators were associated with improved dyspnoea.
Gomutbutra 2013 (191)	115	Describe the management of moderate-to-severe dyspnoea in palliative care patients	Self reporting of moderate-to-severe dyspnoea on a four-point categorical scale	The combination of opioids and benzodiazepines was associated with an improvement
Kociol 2013(200)	308	Investigate the relationship between markers of decongestion and dyspnoea relief in patients hospitalised for acute decompensated heart failure.	Dyspnoea visual analogue scale	Weight loss, fluid loss and NT-proBNP reductions were poorly correlated with dyspnoea relief.
Mentz 2013(193)	7141	Examine the characteristics of acute HF patients associated with moderate or marked dyspnoea relief at 6 h following initiation of nesiritide.	7-point Likert scale	Higher respiratory rate age, lower sodium levels, presence of oedema on chest radiograph, higher NT-proBNP, higher BNP, NYHA class I, higher

				systolic blood pressure, lower BUN
Oxberry 2013(192)	35	Assess the longer-term effect of oral opioids on dyspnoea due to CHF.	0-10 numerical rating scale and modified Borg score	Long term opioid use (3 months) was associated with dyspnoea relief.
Solomonica 2013 (190)	233	Examine the relationship between hemodynamic measures during treatment ant dyspnoea improvement.	Dyspnoea at rest assessed with a self-reported 7-point Likert scale.	Improvement of PCWP and mean pulmonary artery pressure was associated with improvement of dyspnoea at rest.
Pang 2014 (214)	524	Determine predictors of early dyspnoea improvement for three different commonly used scales in patients with acute heart failure.	5-point Likert scale, 10 cm visual analogue scale and 7-point relative Likert scale	Peripheral vascular disease, longer dyspnoea onset time and having new onset heart failure was associated with dyspnoea improvement if using the 7-point Likert scale. Baseline dyspnoea was associated with dyspnoea improvement if measured with the visual analogue scale or the 5-point Likert scale.
Mentz 2015(208)	48616	To describe the characteristics of patients hospitalized for acute HF according to dyspnoea severity and to examine associations among dyspnoea severity, outcomes and costs.	Self reported dyspnoea on exertion as obtained from medical records	Advanced chronic kidney disease and systolic blood pressure ≥140 was associated with dyspnoea at rest vs. dyspnoea with moderate activity.

Aims and Objectives

Aims

Following the results of the literature review, the following aims were developed for this thesis:

- Identify the factors associated with symptoms of fatigue and dyspnoea in heart failure patients.

- Describe the relationship between these two symptoms of heart failure and cardiovascular outcomes.

- Identify the baseline characteristics associated with change in symptoms over time.

- Describe the relationship between change in symptoms and cardiovascular outcomes.

The following objectives were formed from these overarching aims

Objectives

- To describe the prevalence and severity of fatigue and dyspnoea at time of randomisation in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)

- To describe the baseline characteristics of CORONA participants according to fatigue and dyspnoea severity at time of randomisation.

- To determine which baseline characteristics are independently associated with symptom severity at time of randomisation in CORONA.

- To examine how symptom severity at time of randomisation is independently associated with cardiovascular outcomes in CORONA.

- To determine which baseline characteristics are independently associated with change in symptom severity from randomisation to 6 months follow-up in CORONA.

- To determine in CORONA whether change in symptom severity from randomisation to 6 months follow-up is associated with cardiovascular outcomes after 6 months.

- Study any impact that statin use has on symptom severity over time in the CORONA population.

- To describe the prevalence fatigue and dyspnoea on effort at time of randomisation in the Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARDIGM-HF).

- To describe the baseline characteristics of PARDIGM-HF participants according to presence of fatigue and dyspnoea on effort at time of randomisation.

- To determine which baseline characteristics are independently associated with symptom presence at time of randomisation in PARADIGM-HF.

- Examine how the presence of symptoms on effort at time of randomisation is independently associated with cardiovascular outcomes in PARADIGM-HF.

4 Methods

4.1 Data Source

The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) was a multicentre, randomised, double-blind, placebo-controlled study which enrolled a total of 5011 patients aged ≥ 60 years with symptomatic (NYHA class II-IV), systolic (LVEF ≤ 40% but no more than 35% in patients with NYHA class II) heart failure. Patients were randomised to receive 10 mg of rosuvastatin or matching placebo once daily.

The exclusion criteria included: previous statin-induced myopathy or hypersensitivity reaction; decompensated heart failure or a need for inotropic therapy; myocardial infarction within the past 6 months; unstable angina or stroke within the past 3 months; percutaneous coronary intervention (PCI), coronary-artery bypass grafting, or the implantation of a cardioverter–defibrillator or biventricular pacemaker within the past 3 months or a planned implantation of such a device; previous or planned heart transplantation; clinically significant, uncorrected primary valvular heart disease or a malfunctioning prosthetic valve; hypertrophic cardiomyopathy; acute endomyocarditis or myocarditis, pericardial disease, or systemic disease (e.g., amyloidosis); acute or chronic liver disease; levels of alanine aminotransferase or thyrotropin of more than 2 times the upper limit of the normal range; a serum creatinine level of more than 2.5 mg per decilitre (221 μmol per litre); chronic muscle disease or an unexplained creatine kinase level of more than 2.5 times the upper limit of the normal range; previous treatment with cyclosporine; any other condition that would substantially reduce life expectancy or limit compliance with the protocol; or the receipt of less than 80% of dispensed placebo tablets during the run-in period. (1, 2)

The ethics committee at each of the participating hospitals approved the trial, and patients provided written informed consent. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The median follow up was 32.8 months. Secondary outcomes included death from any cause, any coronary event, death from cardiovascular causes, and the number of hospitalisations. Compared with placebo, rosuvastatin did not reduce the primary outcome of composite of death from cardiovascular

causes, nonfatal myocardial infarction, and nonfatal stroke, analysed according to the time to the first event (HR 0.92; 95% CI 0.83 to 1.02; P = 0.12) or death from any cause (HR 0.95 in the rosuvastatin group 95% CI, 0.86 to 1.05; P=0.31). (2)

Symptoms were measured at baseline (randomisation visit), 6 weeks after randomisation, and 3 monthly thereafter in this trial population (1) Investigators were asked to evaluate symptoms using the following statement: "State symptoms during the past few days. Tick lowest level of physical activity causing symptoms".

Fatigue *"during the past few days"* was measured using a five-point exertion scale (0 none, 1 heavy exertion, 2 moderate exertion, 3 slight exertion, 4 rest), recorded by the investigator. Dyspnoea *"during the past few days"* was measured using a four-point exertion scale (1 heavy exertion, 2 moderate exertion, 3 slight exertion, 4 rest); a four- rather than five-point scale was used for dyspnoea because the presence of dyspnoea at baseline was an inclusion criterion for CORONA. The questionnaire for symptom severity was developed for the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)(31) and later used for CORONA.

The scale used in CORONA to measure symptom severity is not validated for heart failure, although simple Likert scales are commonly used to measure symptoms in a wide spectrum of diseases. For this reason I will look at the relationship between NYHA class and symptom severity at baseline as an early step in my analyses.

The focus of my analyses in CORONA will be on patients with LVEF ≤35% (n=3830) because patients with a LVEF between 35% and 40% had to be in NYHA class III or IV (i.e. could not be in NYHA class II). By excluding patients with LVEF>35% I avoid NYHA class acting as a surrogate for LVEF, hence I am able to include both of them in the multivariate model.

Additionally, I will examine symptoms on effort in The Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). PARADIGM-HF was a large, multicentre, randomised, double blind, parallel group, active-controlled, two-arm, event-

driven trial which compared LCZ696 and enalapril in patients with chronic symptomatic heart failure with reduced ejection fraction published in 2014. (3)

The design and inclusion/exclusion criteria for the PARADIGM-HF trial have been described in detail elsewhere. (3, 215-217) Briefly, patients had to be consenting adults with symptomatic heart failure (NYHA class II-IV) and LVEF≤40%. If there was a heart failure hospitalisation in the prior year, then BNP should be above or equal to 100 pg/mL or NT-proBNP≥400 pg/ml; if there was no history of hospitalisation due to worsening heart failure, then BNP had to be greater or equal to 150pg/mL or NT-proBNP≥600 pg/mL. Patients had to be on ACE-inhibitor or ARB therapy with a stable dose for the prior 4 weeks to screening equivalent to enalapril ≥10mg/day. They also had to be on a beta-blocker with a stable dose for the prior 4 weeks. Exclusion criteria included symptomatic hypotension, systolic blood pressure less than 100 mmHg at screening or <95 at randomisation, eGFR<30 mL/min/1.73 m^2, reduction in eFGR>35% from screening to randomisation, potassium >5.2 mmol/L at screening or >5.4 mmol/L at randomisation, history of angioedema, or a history of unacceptable side effects with ACE-inhibitors or ARBs.

PARADIGM-HF had a single-blind run-in period where all patients were treated with enalapril 10 mg PO BID for two weeks then held for a day, then they were treated with an angiotensin receptor neprilysin inhibitor (ARNI) at 100 mg PO BID then 200 mg PO BID for 4-6 weeks. 8399 patients were randomised to either ARNI LCZ696 (sacubitril/valsartan) 200 mg PO BID or enalapril 10 mg PO BID (the goal dose from the Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure trial [SOLVD]). Doses were adjusted for tolerability. Patients were followed-up every 2-8 weeks the first 4 months and then every 4 months.

Median follow-up was of 27 months; the trial was stopped following a positive interval efficacy analysis. The ARNI group had a reduction in the primary outcome of CV mortality or HF hospitalisation (21.8% vs. 26.5%; NNT 21) as well as each of the individual components. Additionally, the ARNI group had a significant reduction in all-cause mortality (17.0% vs. 19.8%; NNT 36). (3)

The Ethics Committee of each of the 1043 participating institutions (in 47 countries) approved the protocol, and all patients gave written, informed consent.

Dyspnoea and fatigue on effort in PARADIGM-HF were recorded in every visit as "present" or "absent". I will analyse symptoms at randomisation.

4.2 Statistical Analyses

Data were analysed in several ways to comply with the objectives of this thesis. I examined prevalence and severity of fatigue and dyspnoea by using traditional descriptive statistics. I also analysed baseline characteristics (at randomisation visit) according to fatigue and dyspnoea severity or presence/absence of symptoms, reporting means and standard deviations for continuous variables (medians and interquartile ranges for variables that were not normally distributed) and percentages for categorical variables and comparing across symptom groups by running a test for trend or chi^2 to obtain a p value.

A logarithmic transformation of NT-proBNP was made for CORONA, as values tend to have a very wide range (going from single digits to thousands), additionally such a transformation will be consistent with comparable medical literature and ease interpretation. For PARADIGM-HF, continuous variables were dichotomised to allow for non-linear relationships with outcomes.

Given the possibility of an issue with co-linearity between NYHA class and symptom severity, a Spearman's rank correlation coefficient (218) was calculated to investigate if both variables (NYHA class and symptom severity) could be included in multivariable analyses. For fatigue, the correlation coefficient was of 0.54 and for dyspnoea it was 0.65, both showing a moderate positive correlation (219), but not sufficient to warrant exclusion of NYHA class from the multivariable model. The stronger positive correlation between NYHA and dyspnoea than between NYHA class and fatigue could be a reflection of how NYHA class is assigned by clinicians, where there seems to be a tendency to interrogate (and assign functional class based on this) more about dyspnoea than other symptoms.

For CORONA, I then used ordered logistic regression (220) to examine which baseline characteristics were independently associated with symptom severity at baseline. Ordered logistic regression and the assumptions underlying it are described in detail later in this chapter.

I also looked at how symptoms are related to the risk of various events using Cox proportional hazards regression (221). I later examined in CORONA change in symptom severity from baseline to the 6-month visit, classifying patients as showing a decrease (reduction in score), an increase (an increase in score) or no change (unchanged score) in symptoms and analysed the relationship between change in symptoms and subsequent clinical outcomes using Cox regression.

Finally. I examined the effect of a rosuvastatin treatment for six months on symptom severity in CORONA.

A more detailed description of the method employed will be given in each relevant results section.

In all analyses from CORONA, Group 1 (i.e. no/slight symptoms on exertion) was used as the reference group for the symptom groups. In PARADIGM-HF, no symptoms on effort is the reference group.

Unless stated otherwise, analyses were performed on a complete case scenario where only patients with complete observations for all variables were included in the analyses. Patients with missing observations were excluded for the main analyses; however to address the issue of missing data I will report on analyses based on averaging across 10 imputed data sets (following the multiple imputation technique). The rationale and process of multiple imputation is described in section 4.2.4 below.

Additionally, I ran all the analyses on the entire cohort from CORONA (i.e. patients with the entire spectrum of LVEF; n=5011). Results for the sensitivity analyses on the entire spectrum of LVEF and imputed data will be presented separately in Appendix 5.

All analyses were carried out using Stata (version 12 or 14 Stata Corporation, College Station, Texas, USA). P values are two tailed and a significance level of

1% was used ($p \leq 0.01$). 95% confidence intervals were calculated. Interpretation of the results is based on both p values and confidence intervals and their relationship and whether they are consistent with available literature.

4.2.1 Ordered logistic regression

4.2.1.1 Introduction to the proportional odds model

I will analyse the association between baseline characteristics and symptom severity at randomisation visit. Symptom severity was recorded using a Likert scale, which graded symptom severity in an ordered fashion (see section 4.1). The outcome of interest (symptom severity) is, strictly speaking, a categorical variable, so some type of logistic regression would be in order for such purposes.

When examining the dependence of an outcome variable on one or more independent variables, the scale of measurement of the response variable usually determines the method. (222, 223) This scale can be nominal (yes/no; cause of death), ordinal (with specific ranking) or interval (includes both ranking and distance between intervals). (223, 224) Standard logistic regression is applicable only to binary response variables (yes/no);(222, 224) and multinomial logistic regression -although adequate for analysing a polytomous outcome variable- would ignore the ranking of response variable. (222) A number of variations of logistic/multinomial regression models have been developed for analysing ordinal response variables, any such model is called an ordered regression model. (220) There are several ordinal logistic regression models, the most popular of them is the constrained cumulative logit model called "proportional odds model" (POM). (224, 225) The choice between models can be made on empirical grounds, dependent on model fit. (220) I have chosen the POM for the same reason for which it is most commonly used in medical literature; it allows for the effect of a covariate on the response variable to be quantified by a single regression coefficient, thus allowing a single odds ratio to be calculated, simplifying the interpretation and presentation of results. (224, 225)

The POM makes assumptions about the nature of the relationship between the response variable and the prognostic factors. If the data do not fulfil the

assumptions, the results of a regression applied to them can be misleading or have no meaning at all. (222, 224, 225)

The following sections will focus on the logic behind the proportional odds model and the assumptions linked to it.

4.2.1.2 Proportional odds model

To be able to extend the logistic regression model to allow for ordinal response variables instead of binary response variables, modelling of cumulative logits is common. For example, when the outcomes of Y are ordinal and are assigned the values 0,1,……,*k*, cumulative probabilities can be defined by

Equation 1 Cumulative probabilities

$$C_{ij}=\Pr(Y\geq j \mid X_i),\ i=1,\ldots.,n,\ j=1,\ldots.,k,$$

allowing a logistic model to be written as

Equation 2 Proportional odds model

$$\ln\left(\frac{C_{ij}}{1-C_{ij}}\right)=\alpha_j+X_i'\boldsymbol{\beta},\ i=1,\ldots.,n,\ j=1,\ldots.,k,$$

where $\alpha_1>\alpha_2>\ldots>\alpha_k$. j indexes the k possible cumulative probabilities obtained from using k cut-offs to dichotomise Y. The regression coefficient β_1 for the lth explanatory variable X_1 is the log-odds ratio for the Y by X_l association, controlling for the remaining explanatory variables. Since β_1 does not depend on j, the model assumes that the relationship between X_l and a dichotomised Y does not depend on j, the point at which the dichotomisation is made. This assumption of identical odds ratios across the k cut-offs is called the proportional odds assumption. (224, 226)

4.2.1.3 Proportional odds assumption

This assumption states that the relationship between each pair of outcome groups is the same. That is, the coefficients that describe the relationship between the lowest versus all higher categories of the dependant variable are the same as the coefficients for the next lowest category versus all higher categories. In other words, the correlation between an independent variable and a dependent variable does not change for the categories in the dependent

variable, and the parameter estimations do not change for different cut-off points. The fulfilment of this assumption allows for a single coefficient to present results. If this were not the case, one would need different sets of coefficients to describe the relationship between each pair of outcome groups. (220, 224, 226)

If the data fail to satisfy the proportional odds assumption a valid approach is to analyse such data by fitting a partial proportional odds model (222, 226), which is an extension of the ordinal logistic regression models that allows non-proportional odds for a subset of the explanatory variables. (226, 227) This will give a single coefficient for explanatory variables that fulfil the proportional odds assumption, regardless of the number levels in the outcome variable, and will allow separate coefficients for comparing different levels of the outcome variable for those explanatory variables that fail to fulfil the proportional odds assumption. In other words, an ordered logistic regression is fitted when assumptions are fulfilled, and a partial proportional odds regression is run when the proportional odds assumption is not fulfilled.

The proportional odds model was used to model the effect of available baseline covariates and their effect on severity of symptoms at baseline. It is important to note that the purpose of my thesis is not to build a prognostic model for symptom severity, but to identify which baseline demographic and medical characteristics are associated with and would independently predict worse symptoms at baseline. This was done to try and identify if fatigue and dyspnoea have the same predictors and in this manner try to clarify if these two symptoms have the same origin. The adjusted analyses used a previously published CORONA risk-model for total mortality as this model has been developed for this specific trial population. (228)

Proportional odds assumption was tested by fitting a partial proportional odds model and comparing coefficients and confidence intervals in the different models. (227) When the assumption was not met, separate odds ratios are reported for the relationship between each group of symptoms and the covariate of interest compared to the reference group. This was achieved by using a user-written program in Stata that fits generalised ordered logit models for ordinal dependent variables (called ‘gologit2’) which allows three cases of the generalised model: the proportional odds model, the partial proportional odds

model and the logistic regression model. This program automatically identifies the partial proportional odds model that best fits the data when used in combination with the *autofit* option. (229)

4.2.2 Cox Regression

Cox regression is a commonly used method to analyse the survival experience of a cohort. It studies the time elapsing between two events, time is a numeric variable like any other but a specific feature of a time variable is that its observations may be censored.

Survival analysis is preoccupied with following subjects over time and observing at which point in time they experience an event of interest. It is common that the study does not span long enough to observe the event for all subjects in the study, which could be due to several reasons, usually unrelated to the study. This is called administrative or right censoring and it means that the information is incomplete because the subject did not have an event *during the time that the subject was part of the study. (230)*

Typically, the effect of an intervention such as a new pharmacological compound that is thought to modify an outcome of interest is examined on a basis of time to outcome. I am interested in the association between a variable (in this case symptom severity at baseline) and an event of interest (e.g. heart failure hospitalisation). However, during follow up more than one type of event can occur. While one event is usually chosen as the event of interest, the occurrence of another event would prevent the occurrence of the event of interest (e.g. death prevents a subject experiencing heart failure hospitalisation). Survival analysis treats these competing events as censored observations and assumes independence of the time to event and the censoring distributions. One way to deal with the competing risks problem is to define a composite endpoint that includes a clinical outcome such as death. (221, 231). I analysed this cohort using traditional proportional hazards Cox regression and using composite outcomes.

The assumptions underlying Cox regression are detailed below.

4.2.2.1 Linearity assumption

As with all regression models, Cox regression considers a log-linear effect of numeric covariates (equivalent to proportional odds assumption mentioned above). This means that one unit's increase in a numeric covariate x_j should have the same effect whatever the value of x_j and whatever the values of the other covariates (if no interaction effects are included). (221) This assumption was assessed by categorising the continuous variables and estimating a separate effect for each group, then plotting the median for each group against it's coefficient and assessing the line to see if I got a fairly linear trend for the estimates (see Appendix 3). Another valid approach to assess linearity would be to include a spline transformation or a quadratic transformation of the continuous variable and testing the null that the coefficients are equal to zero. I did this in cases where the plots and/or Wald test left doubt about the linearity assumption.

4.2.2.2 Proportional hazards assumption

The other assumption in Cox regression is the proportional hazards assumption. This means that the survival functions for two strata must have hazard functions that are proportional over time; in other words, the relative hazard must be constant. This assumption was assessed using Schoenfeld residuals by testing the null hypothesis of a zero slope in a generalised linear model. (232, 233) I also tested this assumption by building log-log plots and assessing if the plotted lines were reasonably parallel.

I tested the prognostic value of each symptom relative to the composite outcome of cardiovascular death or hospital stay due to worsening HF, using Cox proportional hazard regression models. Cardiovascular death or hospital stay due to worsening HF rather than the pre-specified primary outcome of CORONA was used in the present analysis as it better reflects disease-specific morbidity and mortality related to HF (and the primary endpoint of CORONA was recommended by regulatory authorities to reflect the treatment intervention used [e.g. a statin]). (234, 235)

As mentioned earlier, the adjusted analyses used a previously published CORONA risk-model for total mortality. (228) The prognostically significant variables in that model were: age, sex, NYHA class, LVEF, body mass index (BMI), systolic

blood pressure, heart rate, smoking, MI, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter (AF), stroke, intermittent claudication, pacemaker and ICD implantations, apoA-1, apoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, and log NT-proBNP (228); with symptom level at baseline included. The model was run twice, once for dyspnoea and another time for fatigue to avoid collinearity issues between the two symptoms.

Kaplan-Meier cumulative event curves are presented by symptom category and compared with log-rank tests. Similar analyses were carried out that examined the relationship between change in symptoms (baseline to 6 months) and subsequent clinical outcomes (from 6 months to the end of the study).

A more detailed description of each component of the analyses will be given in relevant chapters.

4.2.3 Multinomial logistic regression

As stated in the aims and objectives, I am interested in identifying which baseline characteristics independently predict change in symptom severity over 6 months. To achieve this, I will use multinomial logistic regression, which is an extension of logistic regression used when the dependent variable consists of several categories that are not ordinal, it is concerned with modelling the probabilities of different possible outcomes of a categorically distributed dependent variable. With this type of analysis, the log odds of the outcomes are modelled as a linear combination of the predictor variables. (236, 237)

4.2.4 Multiple imputation

Multiple imputation is a tool used to deal with missing data. Missing data refers to observations and measurements that should have been recorded but for some reason were not. This missing data may derive from an array of reasons, like dropouts, refusal to answer certain questions, error while measuring or collecting data, among others.

Rubin described the missing data mechanism in 1976 when he and his colleagues defined the classification system that is still in use today. These mechanisms

detailed below describe the relationship between measured variables and the probability of missing data (238-240):

- Missing completely at random (MCAR), where the probability that data are missing does not depend observed or unobserved data. That is, the probability of being missing is the same for all cases. The missing data values can be considered a simple random sample from the original data set. An example would be if a laboratory sample was accidentally dropped. This is a strong assumption that is often unrealistic.

- Missing at random (MAR), where the probability that data are missing depends on the values of the observed data, but does not depend on the values of the missing data. Under this assumption, the missing data values do not contain any additional information about the mechanism of missing data. For example, blood pressure would be missing at random if older individuals are more likely to have blood pressure recorded- and age is observed. This mechanism of missing data is more general and realistic and methods that deal with missing data usually start from this assumption.

- Missing not at random (MNAR), where the probability that the data are missing may also depend on the values of the unobserved data. For example, people with high blood pressure are more like to have their blood pressure recorded than other individuals of the same age. This is the most common situation.

The best practice would be to avoid missing data, but this is rarely possible. Commonly in medical literature analyses are run on complete case scenarios only, this however will lead to the loss of information in the incomplete cases. This approach will ignore any possible difference between the complete cases and the incomplete cases leading to a substantial reduction of effective sample size, which in turn will lead to a potential misinterpretation of the results form multivariate analyses. Additionally, complete case analyses makes the assumption that data are missing completely at random, which is often not the case. (238, 240)

Another approach to dealing with missing data is to consider some sort of imputation, or the practice of "filling in" missing data with plausible values like a mean or a regression coefficient. However, this should be done with caution; if one imputes an observed variable mean for the variable's missing values, this would preserve the sample mean but would distort the covariance matrix. On the other hand, imputing predicted values from regression models tends to inflate observed correlations. More importantly, treating imputed data as if it were "real" in estimation and inference can lead to misleading test results and p values, since they fail to reflect the uncertainty due to the missing data.

Multiple imputation replaces the missing value with two or more plausible values by generating $M>1$ copies of the data set where the missing data simulated according to a fixed imputation model. Each of the simulated complete data sets in then analysed using a chosen method (commonly regression) and the results are then combined. (241)

To put it in other words, let's assume that we have only two variables in a data set: x_1 which is observed only in some units, and x_2 which is observed for each unit. Multiple imputation will use the data from units where both x_1 and x_2 are observed to learn about the relationship between the two variables. Then, it will use this relationship to create M complete data sets by drawing the missing observations from $(x_1|x_2)$. Finally, the results are pooled to run the chosen analyses.

Multiple imputation will be valid under the assumption that data is MAR or MCAR. (240)

The method I chose to impute the data with was using chained equations, which uses a sequence of univariate imputation methods with fully conditional specifications; that is, it includes all variables in the prediction except the one that is being imputed. In other words, it uses the already imputed data to predict the missing values, adding a small perturbation to each prediction to consider uncertainty surrounding said missing values, and then reruns the analyses using those same imputed data to predict other missing values. (242-244) For this thesis, I created 10 data sets using linear regression if the missing value was from a continuous variable or logistic regression if the missing value

was from a binary variable. All missing observations were imputed. Results for analyses on imputed data are presented Appendix 4.

Results

In the following chapters I will present results from analyses performed surrounding this thesis. I will first report findings from CORONA, including previously published results from visit prior to randomisation, followed by descriptive statistics for randomisation visit and results from multiple analyses performed on the CORONA cohort at this time point. I will then present results from PARADIGM-HF in the same manner as for CORONA.

5 Symptoms as predictors of outcome: visit prior to randomisation

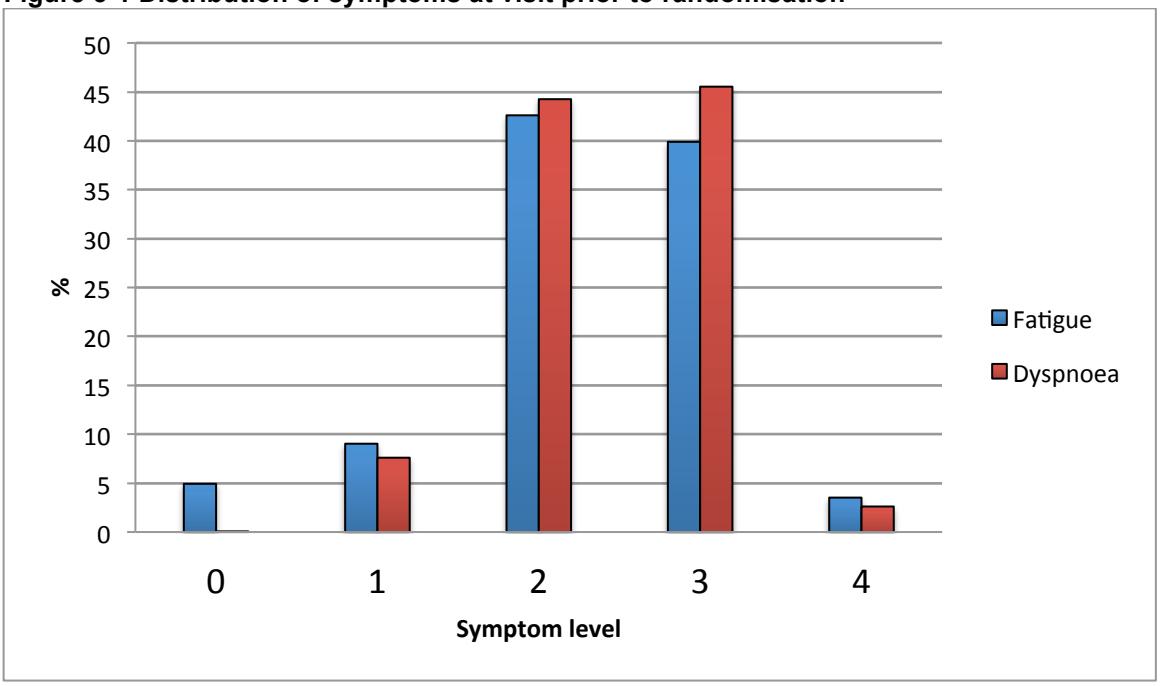
I have previously published results from analyses (85) looking at the association of symptoms at visit prior to randomisation (on average one month prior to randomisation) and outcomes. This time-point was chosen for these analyses because in CORONA, NT-proBNP was measured at the visit prior to randomisation. In said published paper, I analysed how symptom severity related to NT-proBNP tertiles, and choosing the same analysis time point was paramount for this purpose. I present a summary of the relevant findings from the published paper next.

5.1 Distribution of symptoms at visit 2

All of the 3830 patients with LVEF≤35% had an observation for fatigue, 3641 (95%) reported some level of fatigue on exertion, and most of them (86%) reported high symptom severity (from moderate exertion to symptoms at rest); 1663 (43%) patients reported the highest symptom severity (group 3: fatigue on slight exertion or at rest).

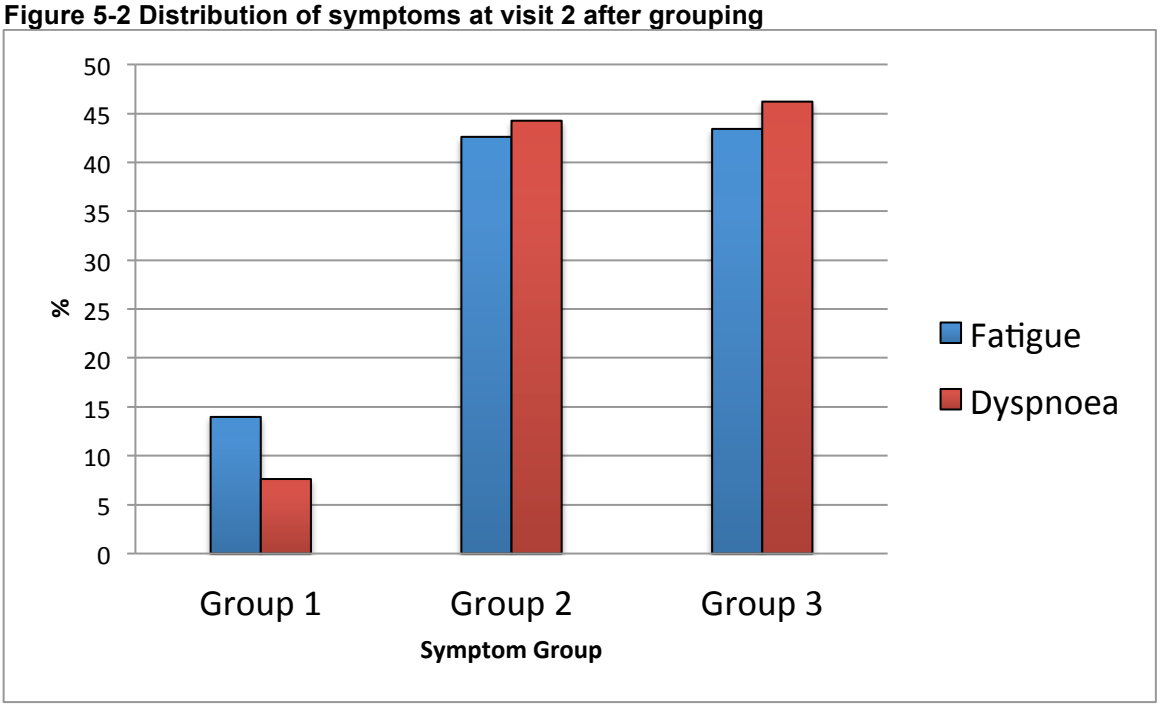
For dyspnoea 3528 patients (92%) reported dyspnoea from moderate exertion to dyspnoea at rest, and 48% (n=1843) reported the highest symptom severity with dyspnoea on slight exertion or at rest. Figure 5-1

Figure 5-1 Distribution of symptoms at visit prior to randomisation



To achieve sufficient numbers in each severity class, patients were grouped into 3 categories: fatigue score 0-1 (n= 535 [14%]), 2 (n=1,632 [43%]) and 3-4 (n= 1663 [43%]); dyspnoea score 0/1 (n=292 [8%]), 2 (n=1,695 [44%]), and 3-4(n=1843 [48%]). Figure 5-2

Figure 5-2 Distribution of symptoms at visit 2 after grouping



For the sake of practicality, I will only present now the results from multivariate analyses. Details of unadjusted results and baseline characteristics according to symptom severity at visit 2 can be found in published paper. (85)

Briefly, after adjustment for other prognostically significant covariates, fatigue on slight exertion or rest was only predictive of heart hospitalisation when compared to no fatigue or fatigue on heavy exertion (HR 1.57, 95% CI 1.15-2.14), while dyspnoea on slight exertion or at rest was predictive of both cardiovascular death and heart failure hospitalisation (CV death: HR 1.80, 95% CI 1.15-2.81; HF hospitalisation: HR 1.72, 95CI 1.12-2.62). Table 5-1

Table 5-1 Hazard ratio for symptom severity and clinical outcomes: Multivariable analysis on symptoms from visit 2

	Fatigue				Dyspnoea			
	2 vs. 1		**3 vs. 1**		**2 vs. 1**		**3 vs. 1**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Cardiovascular death or heart failure hospitalisation	1.12 (0.89, 1.41)	0.34	1.28 (1.00, 1.64)	0.05	1.14 (0.84, 1.55)	0.41	1.49 (1.07, 2.08)	0.02
Cardiovascular death	1.02 (0.76, 1.36)	0.92	1.13 (0.82, 1.54)	0.46	1.32 (0.87, 2.02)	0.19	1.80 (1.15, 2.81)	0.01
Heart failure hospitalisation	1.29 (0.96, 1.74)	0.10	1.57 (1.15, 2.14)	0.01	1.22 (0.82, 1.82)	0.32	1.72 (1.12, 2.62)	0.01
All-cause death	1.06 (0.82, 1.38)	0.45	1.17 (0.89, 1.55)	0.26	1.37 (0.96, 1.97)	0.09	1.60 (1.08, 2.37)	0.02

Adjusted for: Age, sex, New York Heart Association, left ventricular ejection fraction, body mass index kg/m^2, systolic blood pressure, heart rate, smoking, myocardial infarction, angina pectoris, coronary artery bypass graft, percutaneous coronary intervention, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter, stroke, intermittent claudication, pacemaker, implanted cardioverter defibrillator, apoA-1, apoB, creatinine, alanine aminotransferase, creatine kinase, triglycerides, C reactive protein, high density lipoproteins, low density lipoprotein, estimated glomerular filtration rate.

CV = cardiovascular; HF= heart failure

5.2 Symptoms visit 2 vs. visit 3

Because I wanted to analyse symptoms from randomisation visit for the main analysis on this thesis (as outcomes are considered from randomisation onwards), I examined how symptoms were different from visit 2 to visit 3. Briefly, a total of 3176 patients (83%) reported same level of fatigue at visit 2 and visit 3. Of the 653 patients who reported different levels of fatigue in visit 2 and 3, 291 (44.6%) report a decrease in fatigue while 362 (55.4%) report an increase. Table 5-2

Table 5-2 Cross tabulation between fatigue visit 2 (published paper) and fatigue visit 3 (thesis): LVEF≤.35%

Fatigue	Visit 3					
Visit 2	0	1	2	3	4	Total
0	145 (3.8%)	12 (0.3%)	20 (1.0%)	10 (0.3%)	2 (0.1%)	189 (5%)
1	23 (0.6%)	250 (6.5%)	62 (1.6%)	10 (0.3%)	1 (0.03%)	346 (9.0%)
2	30 (0.8%)	64 (1.7%)	1,389 (36.3%)	142 (3.7%)	7 (0.2%)	1,632 (42.6%)
3	7 (0.2%)	18 (0.5%)	167 (4.4%)	1,310 (34.2%)	25 (0.7%)	1,527 (39.9%)
4	3 (0.1%)	0 (0.0%)	9 (0.2%)	41 (1.1%)	82 (2.1%)	135 (3.5%)
Total	208 (5.4%)	344 (9.0%)	1,647 (43.0%)	1,513 (39.5%)	117 (3.1%)	3,829 (100%)

There were 117 overall CV death/HF hospitalisation composite outcomes in the patients who report a decrease in fatigue over the course of one month, while there were 145 events in those who report an increase. There were overall 262 composite primary outcomes in the patients that report different levels of fatigue between visits 2 and 3, 17% of the total 1568 composite events in patients with LVEF≤35%.

For the other outcomes analysed, 152 had a CV death (961 total CV deaths in patients with LVEF≤35%), with 71 in the patients reporting decrease in fatigue and 81 in the group reporting an increase in fatigue. 182 had a hospitalisation due to worsening heart failure (out of 1040), with 76 being in the group reporting a decrease in symptom severity and 106 in those reporting an increase. 209 patients with all cause death (out of 1205), with 93 of them being in the group reporting a decrease in fatigue and 116 in those reporting an increase in fatigue. Table 5-3

Table 5-3 Clinical outcomes according to change in fatigue severity from visit 2 to visit 3

	Fatigue		
	Unchanged	**Decrease**	**Increase**
	(n=3176)	**(n=291)**	**(n=362)**
n (%)			
Cardiovascular death or heart failure hospitalisation	448/858 (41.1)	41/76 (40.2)	39/106 (40.1)
Cardiovascular death	809 (25.5)	71 (24.4)	81 (22.4)
Heart failure hospitalisation	858 (27.0)	76 (26.1)	106 (29.3)
All-cause death	996 (31.4)	93 (32.0)	116 (32.0)

A total of 3299 patients (86.4%) reported the same level of dyspnoea at visit 2 and visit 3. Of the 531 patients who reported different levels of dyspnoea in visit 2 and 3, 204 (38.4%) reported a decrease in dyspnoea and 327 (61.6%) reported an increase in dyspnoea severity. Table 5-4

Table 5-4 Cross tabulation between dyspnoea visit 2 (published paper) and dyspnoea visit 3 (thesis): LVEF≤.35%

Dyspnoea	Visit 3					
Visit 2	0	1	2	3	4	Total
0	1 (0.03%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.03%)
1	0 (0.0%)	238 (6.2%)	45 (1.2%)	7 (0.2%)	1 (0.03%)	291 (7.6%)
2	0 (0.0%)	81 (2.1%)	1,482 (38.7%)	126 (3.3%)	6 (0.2%)	1,695 (44.3%)
3	0 (0.0%)	18 (0.5%)	190 (5.0%)	1,516 (39.6%)	19 (0.5%)	1,743 (45.5%)
4	0 (0.0%)	0 (0.0%)	5 (0.1%)	33 (0.9%)	62 (1.6%)	100 (2.6%)
Total	1 (0.03%)	337 (8.8%)	1,722 (45.0%)	1,682 (43.9%)	88 (2.3%)	3,830 (100%)

Of those who reported an increase in dyspnoea severity from visit 2 to visit 3, 141 a CV death/HF hospitalisation, 89 had a CV death, 96 had a heart failure hospitalisation and 110 had an all cause death during the course of the trial.

Of the 204 patients who reported a decrease in dyspnoea severity from visit 2 to visit 3, 82 had a composite outcome of CV death/HF hospitalisation, 45 had a CV

death, 61 a hospitalisation due to worsening heart failure and 64 an all cause death during the course of the trial. Table 5-5

Table 5-5 Clinical outcomes according to change in dyspnoea severity from visit 2 to visit 3

	Dyspnoea		
	Unchanged	**Decrease**	**Increase**
	(n=3299)	**(n=204)**	**(n=327)**
n (%)			
Cardiovascular death or heart failure hospitalisation	462/883 (40.8)	21/61 (40.2)	45/96 (43.1)
Cardiovascular death	827 (25.1)	45 (22.1)	89 (27.2)
Heart failure hospitalisation	883 (26.8)	61 (29.9)	96 (29.4)
All-cause death	1031 (31.3)	64 (31.4)	110 (33.6)

5.3 Summary of results and discussion

Fatigue and dyspnoea were both strongly associated with the composite outcome of CV death or heart failure hospitalisation, an association that was maintained after adjusted for other prognostic variables including LVEF, NT-proBNP and NYHA class. Although after adjustment the association between fatigue and fatal outcomes (both CV death and all-cause mortality) was no longer statistically significant, the association with heart failure hospitalisation endured. Dyspnoea at visit prior to randomisation remained predictive of all outcomes in multivariate analyses.

Symptoms between visit 2 and visit 3 differed substantially, with up to 17% of the patients reporting different levels of symptoms between the two visits which were only 1 month apart. Nonetheless, the proportion of patients experiencing adverse events was similar across the groups (Table 5-3 andTable 5-5).

6 Descriptive statistics randomisation visit: CORONA

In this chapter I will present baseline characteristics and summary statistics according to dyspnoea and fatigue severity in CORONA at randomisation visit.

6.1 Distribution of symptoms

Of the 5011 patients randomised to CORONA, 5010 (99.98%) had some level dyspnoea on exertion at baseline (which was an inclusion criterion). It is possible that a mistake was made while recording dyspnoea, as this patient who reported no dyspnoea on exertion should not have been randomised. This patient was treated as having mild dyspnoea on exertion (Group 1). 5010 patients had an observation for fatigue on exertion at baseline.

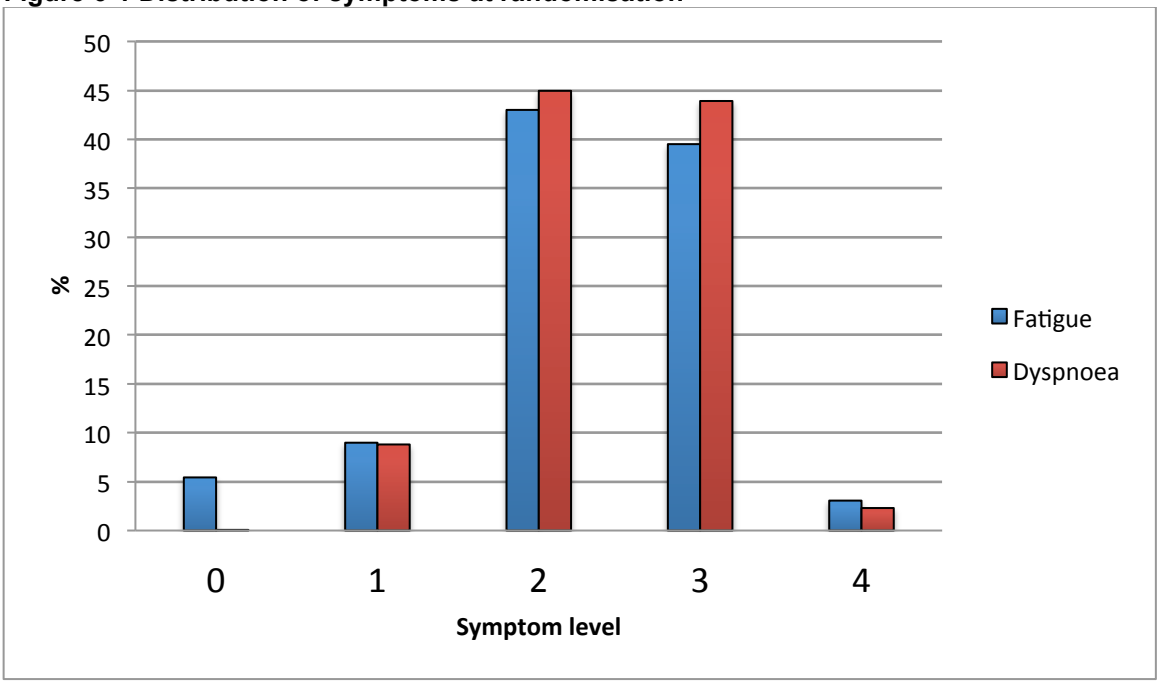
Data on the predictor variables included in the model were missing in 1% or less of patients except for NT-proBNP which was missing in 28% of the patients (27% for entire spectrum of LVEF).

As discussed in chapter 4, my focus on CORONA will be on patients with LVEF≤35%, so from now on, all results refer to this cohort; however, for the sake of completeness, all analyses were run on the entire population randomised in CORONA (results will presented in supplementary material). Of the 5011 patients randomised, 3830 (76%) had a baseline LVEF≤35%; of these 3830 patients, 3829 (99.9%) had a baseline measure for fatigue and all of them had a baseline observation for dyspnoea.

Of these 3829 patients with an observation for fatigue, 3621 (95%) reported some level of fatigue on exertion, and most of them (85%) reported high symptom severity (from moderate exertion to symptoms at rest); 1630 (42%) patients reported the highest symptom severity (group 3: fatigue on slight exertion or at rest).

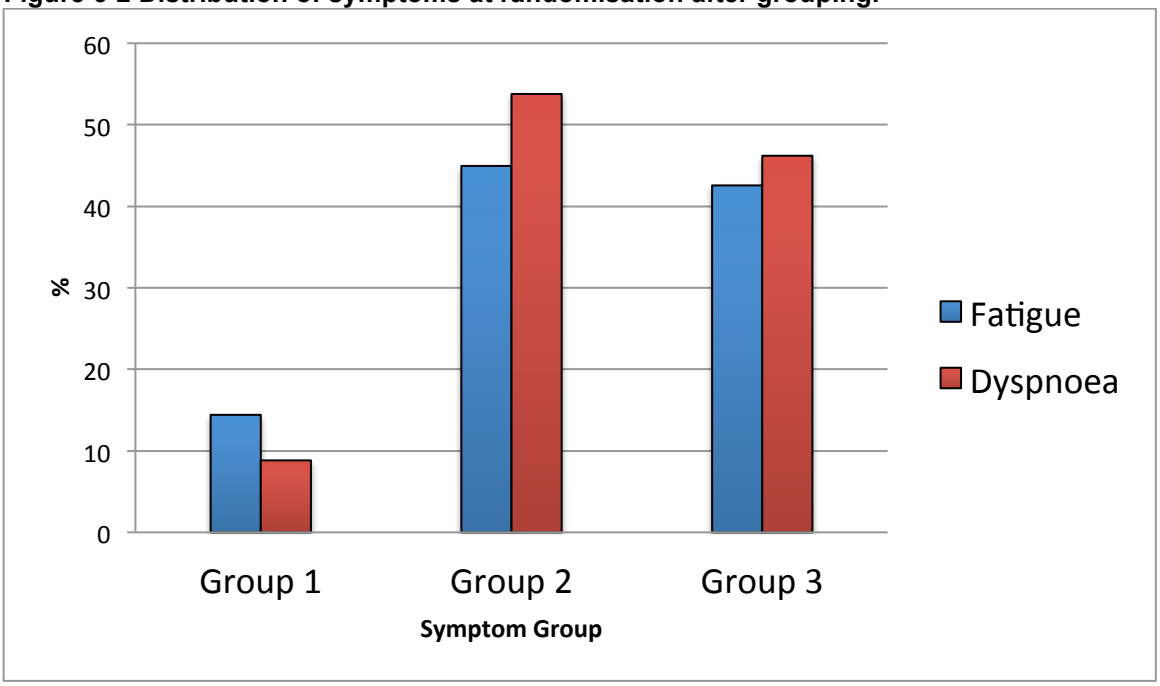
Dyspnoea showed a similar pattern, although some level of dyspnoea was an inclusion criterion. 3492 patients (91%) reported dyspnoea from moderate exertion to dyspnoea at rest, and 46% (n=1170) reported the highest symptom severity with dyspnoea on slight exertion or at rest. Figure 6-1

Figure 6-1 Distribution of symptoms at randomisation



To achieve sufficient numbers in each severity class, patients were grouped into 3 categories: fatigue score 0-1 (n= 552 [14%]), 2 (n=1,647 [43%]) and 3-4 (n= 1630 [43%]); dyspnoea score 0/1 (n=383 [9%]), 2 (n=1,722 [45%]), and 3-4(n=1770 [46%]). Figure 6-2

Figure 6-2 Distribution of symptoms at randomisation after grouping.



Overall, 2743 (72%) of the patients reported the same baseline severity of fatigue and dyspnoea, 725 (19%) reported greater dyspnoea than fatigue and 361 (9%) greater fatigue than dyspnoea. 75% (n=2881)of the patients fall on the diagonal. Table 6-1

Table 6-1 Cross-tabulation between symptoms at baseline

	Dyspnoea			
Fatigue	0/1	2	3/4	Total
0/1	233 (6.1%)	253 (6.6%)	66 (1.7%)	552 (14.4%)
2	77 (2.0%)	1257 (32.8%)	313 (8.2%)	1647 (43.0%)
3/4	28 (1.0%)	211 (5.5%)	1391 (36.3%)	1630 (42.6%)
Total	338 (8.8%)	1721 (45.0%)	1770 (46.2%)	3829 (100%)[2]

[2] Percentages in brackets represent cell percentages (i.e. 3829 is the denominator).

Tables 6-2 and 6-3 show the distribution of fatigue and dyspnoea within each NHYA class.

Table 6-2 Tabulation between fatigue and NYHA class at baseline

Fatigue status	**NYHA class at baseline**			
	II	III	IV	Total
0	153 (73.6%)	52 (25%)	3 (1.4%)	208
1	299 (86.9%)	44 (12.8%)	1 (0.3%)	344
2	1143 (69.4%)	499 (30.3%)	5 (0.3%)	1647
3	203 (13.4%)	1290 (85.3%)	20 (1.3%)	1513
4	30 (25.6%)	57 (48.7%)	30 (25.6%)	117
Total	1829 (47.7%)	1942 (50.7%)	59 (1.5%)	3829

Table 6-3 Tabulation between dyspnoea and NYHA class at baseline

Dyspnoea status	**NYHA class at baseline**			
	II	III	IV	Total
0	1 (100%)	0 (0.0%)	0 (0.0%)	1
1	312 (92.6%)	25 (7.4%)	0 (0.0%)	337
2	1328 (77.1%)	392 (22.8	2 (0.1%)	1722
3	177 (10.5%)	1487 (88.41%)	18 (1.1%)	1682
4	11 (12.5%)	38 (43.2%)	39 (44.3%)	88
Total	1829 (47.8%)	1942 (50.7%)	59 (1.5%)	3830

6.2 Baseline characteristics according to symptom severity at randomisation

Baseline characteristics by symptom severity are summarised in Table 6-4. In summary, patients with higher levels of fatigue (i.e. fatigue on slight exertion or at rest) were more likely to be female (26% vs. 15% for no fatigue/heavy exertion and 19% for moderate fatigue), and to have lower systolic blood pressure than patients with lower levels of fatigue (127 mm/Hg vs. 129 mm/Hg). They also had, on average, higher heart rates (73 bpm vs. 69 bpm fatigue 0/1 and 71 bpm fatigue 2) and were more likely to be in NYHA functional class III or IV (86% vs. 18% fatigue 0/1 and 31% fatigue 2) and had a longer history with heart failure (4.5 years vs. 3.8 years group 1 and 4.2 years for group 2). Patients with greater fatigue more frequently had a history of myocardial infarction (63% vs. 51% fatigue 1/61% fatigue 2), angina (76% vs. 61%/70%), hypertension (65% vs. 51%/59%), diabetes (32% vs. 23%/28%), atrial fibrillation (27% vs. 16%/22%), intermittent claudication (15% vs. 12%/11%) or stroke (15% vs. 8%/11%), lower levels of lipids (for cholesterol a mean of 5.3 mmol/L vs. 5.4 mmol/L; LDL 3.5 mmol/L vs. 3.6 mmol/L), ubiquinone (0.7 mmol/L vs. 0.8 mmol/L) and eGFR (55 ml/min/1.73m^2 vs. 57 ml/min/1.73m^2)and higher levels of NT-proBNP (233 pmol/L vs. 145pmol/L for group 1 and 185 pmol/L in group 2) and hs-CRP (4 mg/L vs. 2.8 mg/L group 1 and 3.3 mg/L group 2). They were more likely to be treated with diuretics (92% vs. 82%/86%), MRAs (49% vs. 31%/35%) and digitalis (40% vs. 24%/32%). They were less likely to smoke (8% vs. 13%/9%).

Patients with higher levels of dyspnoea (i.e. dyspnoea at rest or slight exertion) presented with a generally similar pattern, although there was no association between level of dyspnoea and smoking status. They were slightly older on average (74 years vs. 72/73 years) had higher creatinine levels (118 mg/dL vs. 116 mg/dL) and were more likely to have an implanted pacemaker (14% vs. 8%/11%).

Table 6-4 Baseline characteristics

	All patients (n=3830)	Fatigue 0/1 (n=552)	Fatigue 2 (n=1647)	Fatigue 3/4 (n=1630)	p value	Dyspnoea 1 (n=338)	Dyspnoea 2 (n=1722)	Dyspnoea 3/4 (n=1770)	p value
Age	73.0 ± 7.1	72.73 ± 6.89	72.72 ± 7.01	73.36 ± 7.29	0.015	72.22 ± 7.09	72.57 ± 6.95	73.55 ± 7.25	<0.001
Female	810 (21.2%)	81 (14.7%)	307 (18.6%)	422 (25.9%)	<0.001	52 (15.4%)	326 (18.9%)	432 (24.4%)	<0.001
Race									
Caucasian	4939 (98.6%)	544 (98.6%)	1623 (98.5%)	1601 (98.2%)		334 (98.8%)	1696 (98.5%)	1738 (98.2%)	
Black	13 (0.3%)	2 (0.4%)	5 (0.3%)	4 (0.2%)		1 (0.3%)	6 (0.3%)	5 (0.3%)	
Asian	38 (0.8%)	3 (0.5%)	11 (0.7%)	20 (1.2%)		3 (0.9%)	10 (0.6%)	21 (1.2%)	
Other	21 (0.4%)	3 (0.5%)	8 (0.5%)	5 (0.3%)	0.484	0 (0.0%)	10 (0.6%)	6 (0.3%)	0.336
NYHA III/IV	2001 (52.3%)	100 (18.1%)	504 (30.6%)	1397 (85.7%)	<0.001	25 (7.4%)	394 (22.9%)	1582 (89.4%)	<0.001
LVEF (%)	28.6 ± 5.7	28.34 ± 5.92	28.76 ± 5.56	28.45 ± 5.71	0.791	28.31 ± 5.88	28.76 ± 5.58	28.42 ± 5.73	0.462
Systolic BP mm/Hg	128.5 ± 16.9	129.4 ± 17.3	129.7± 16.6	127.1 ± 16.9	<0.001	129.3 ± 16.4	129.7 ± 16.9	127.29 ± 16.9	<0.001
Heart Rate bpm	71.8 ± 11.3	69.4 ± 10.6	71.2 ± 11.5	73.1 ± 11.2	<0.001	68.8 ± 11.1	70.65 ± 11.1	73.40 ± 11.4	<0.001

BMI kg/m2	26.9 ± 4.4	26.6 ± 4.0	27.1 ± 4.5	26.9 ± 4.5	0.298	26.4 ± 4.0	27.0± 4.4	27.0 ± 4.5	0.077
BMI <25 kg/m^2	1324 (34.7%)	206 (37.5%)	547 (33.4%)	571 (35.8%)		132 (39.2%)	590 (34.4%)	602 (34.7%)	
BMI ≥25 and <30 kg/m^2	1665 (46.3%)	243 (44.2%)	716 (43.7%)	706 (43.0%)		144 (42.7%)	738 (43.1%)	783 (43.1%)	
BMI ≥30 kg/m^2	830 (21.7%)	101 (18.4%)	377 (23.0%)	377 (23.0%)	0.4563	61 (18.1%)	386 (22.5%)	383 (21.7%)	0.194
Years with heart failure	4.3 ± 4.7	3.83 ± 4.75	4.20 ± 4.62	4.54 ± 4.77	0.001	3.66 ± 4.55	4.11 ± 4.62	4.58 ± 4.81	<0.001
Current Smoker	430 (8.6%)	70 (12.7%)	146 (8.9%)	133 (8.2%)	0.0047	36 (10.7%)	153 (8.9%)	160 (9.0%)	0.570
	Past Medical History								
MI	2311 (60.3%)	284 (51.4%)	998 (60.6%)	1028 (63.1%)	<0.001	168 (49.7%)	1029 (59.8%)	1114 (62.9%)	<0.001
Angina	2728 (71.2%)	336 (60.9%)	1154 (70.1%)	1237 (75.9%)	<0.001	193 (57.1%)	1212 (70.4%)	1323 (74.7%)	<0.001
CABG/PCI	1052 (27.5%)	156 (28.3%)	485 (29.4%)	411 (25.2%)	0.033	84 (24.9%)	518 (30.1%)	450 (25.4%)	0.123
Hypertension	2308 (60.3%)	280 (50.7%)	972 (59.0%)	1055 (64.7%)	<0.001	174 (51.5%)	1018 (59.1%)	1116 (63.1%)	<0.001
Diabetes	1109 (29.0%)	129 (23.4%)	456 (27.7%)	523 (32.1%)	<0.001	72 (21.3%)	457 (26.5%)	580 (32.8%)	<0.001
Baseline atrial fibrillation/ flutter	895 (23.4%)	89 (16.1%)	362 (22.0%)	444 (27.2%)	<0.001	62 (18.3%)	343 (19.9%)	490 (27.7%)	<0.001

Stroke	478 (12.5%)	46 (8.3%)	181 (11.0%)	251 (15.4%)	<0.001	33 (9.8%)	191 (11.1%)	254 (14.4%)	0.001
Intermittent Claudication	496 (13.0%)	67 (12.1%)	182 (11.1%)	247 (15.2%)	0.006	35 (10.4%)	198 (11.5%)	263 (14.9%)	0.001
Pacemaker	454 (11.9%)	62 (11.2%)	182 (11.1%)	210 (12.9%)	0.150	26 (7.7%)	182 (10.6%)	246 (13.9%)	<0.001
ICD	122 (3.2%)	24 (4.3%)	52 (3.2%)	46 (2.8%)	0.105	10 (3.0%)	59 (3.4%)	53 (3.0%)	0.707
	Laboratory measurements								
Cholesterol (mmol/L)	5.34 ± 1.07	5.45 ± 1.05	5.36 ± 1.03	5.28 ± 1.12	<0.001	5.44 ± 1.05	5.41 ± 1.03	5.25 ± 1.11	<0.001
ApoB:ApoA-1 ratio	0.87 ± 0.25	0.86 ± 0.24	0.86 ± 0.24	0.88 ± 0.26	0.017	0.85 ± 0.24	0.87 ± 0.24	0.88 ± 0.26	0.140
ApoB (g/L)	1.27 ± 0.30	1.28 ± 0.29	1.27 ± 0.29	1.26 ± 0.31	0.171	1.27 ± 0.29	1.28 ± 0.29	1.25 ± 0.31	0.021
ApoA-1 (g/L)	1.50 ± 0.28	1.52 ± 0.28	1.51 ± 0.28	1.47 ± 0.28	<0.001	1.53 ± 0.27	1.51 ± 0.28	1.47 ± 0.28	<0.001
TSH (mIU/L)	2.19 ± 4.02	2.07 ± 2.68	2.12 ± 4.47	2.35 ± 4.84	0.113	1.88 ± 1.40	2.20 ± 4.62	2.28 ± 4.60	0.176
ALT (IU/L)	17.64 ± 39.96	18.02 ± 27.00	17.02 ± 31.44	17.94 ± 49.45	0.831	19.62 ± 31.38	16.77 ± 29.80	18.11 ± 49.02	0.919
LDL (mmol/L)	3.5 ± 0.9	3.61 ± 0.91	3.55 ± 0.91	3.49 ± 0.96	0.006	3.62 ± 0.92	3.59 ± 0.90	3.46 ± 0.95	<0.001
Creatine Kinase IU/L (median/IQR)	54.3 [33.0, 65.0]	50.0 [35.5, 70.5]	48.0 [34.0, 67.0]	41.0 [30.0, 60.0]	<0.001	50.0 [34.0, 74.0]	48.0 [34.0, 67.0]	42.0 [31.0, 61.0]	<0.001

Creatinine (µmol/L)	116.8 ± 28.3	115.5 ± 26.2	116.0 ± 27.7	118.0 ± 29.6	0.026	115.30± 27.0	115.7 ± 27.2	118.1 ± 29.6	0.010
NT-proBNP--pmol/litre (median)	193.8 [88.7, 406.4]	144.5 [74.1, 293.2]	184.7 [77.7, 374.1]	233.1 [107.1, 484.2]	<0.001	144.9 [78.5, 311.6]	174.1 [75.9, 356.2]	233.9 [106.7, 477.5]	<0.001
hs-CRP mg/litre (median)	3.5 [1.6, 7.4]	2.8 [1.3, 6.2]	3.3 [1.5, 6.8]	4.0 [1.8, 8.6]	<0.001	2.4 [1.2, 5.6]	3.3 [1.5, 6.7]	4.0 [1.8, 8.6]	<0.001
Co-enzyme Q_{10} (mmol/L)	0.7 [0.6, 1.0]	0.8 [0.6, 1.0]	0.8 [0.6, 1.0]	0.7 [0.5, 0.9]	<0.001	0.7 [0.6, 1.0]	0.8 [0.6, 1.0]	0.7 [0.5, 1.0]	0.012
Estimated GFR ml/min/1.73m^2	55.8 ± 15.4	57.0± 15.04	56.6 ± 15.3	54.7 ± 15.6	<0.001	57.2 ± 15.0	56.8 ± 15.1	54.7 ± 15.7	<0.001

	Medication								
Loop/thiazide diuretics	3364 (87.8%)	453 (82.1%)	1418 (86.1%)	1492 (91.5%)	<0.001	267 (79.0%)	1473 (85.5%)	1624 (91.8%)	<0.001
ACE inhibitor or ARB	3548 (92.6%)	523 (94.7%)	1523 (92.5%)	1501 (92.1%)	0.069	314 (92.9%)	1608 (93.4%)	1626 (91.9%)	0.160
MRAs	1154 (40.6%)	171 (31.0%)	582 (35.3%)	800 (49.1%)	<0.001	118 (34.9%)	570 (33.1%)	866 (48.9%)	<0.001
Digitalis	1305 (34.1%)	131 (23.7%)	530 (32.2%)	644 (39.5%)	<0.001	81 (24.0%)	523 (30.4%)	701 (39.6%)	<0.001
Anticoagulant	1433 (37.4%)	203 (36.8%)	623 (37.8%)	607 (37.2%)	0.979	130 (38.5%)	637 (37.0%)	666 (37.6%)	0.991
Beta-blockers	2847 (74.3%)	409 (74.1%)	1250 (75.9%)	1187 (72.8%)	0.220	252 (74.6%)	1308 (76.0%)	1287 (72.7%)	0.089
Nitrate	1,131 (29.5%)	120 (21.7%)	457 (27.7%)	554 (34.0%)	<0.001	65 (19.2%)	452 (26.2%)	614 (34.7%)	<0.001
Insulin	303 (7.9%)	35 (6.3%)	122 (7.4%)	146 (9.0%)	0.028	19 (5.6%)	125 (7.3%)	159 (9.0%)	0.013
Antiarrhythmic	479 (12.5%)	60 (10.9%)	193 (11.7%)	226 (13.9%)	0.030	41 (12.1%)	204 (11.8%)	234 (13.2%)	0.289

LVEF – left ventricular ejection fraction, NYHA – New York Heart Association functional class, BMI – body mass index BP – blood pressure, CABG/PCI – coronary artery bypass grafting/ percutaneous coronary intervention, ICD – implantable cardioverter defibrillator, LDL – low density lipoprotein, NT-proBNP – N-terminal of the prohormone brain natriuretic peptide, hs-CRP – high-sensitivity C-reactive protein, TSH – thyroid stimulating hormone, ACE – angiotensin converting enzyme, ARB – angiotensin II receptor blocker, MRA – Mineralocorticoid receptor antagonist.
Mean and standard deviation (SD) for continuous variables and percentage for categorical variables are presented.

6.3 Summary of results

I found both symptoms to be highly prevalent in this population. I found that 95% of the patients reported some level of fatigue, with 99% reporting some level of dyspnoea (although dyspnoea was an inclusion criterion as mentioned earlier). Most patients reported moderate to severe symptoms, which coincides with NYHA classification and provides some construct validity (245) to the scale used to measure symptoms in this clinical trial. While I found some level of discrepancy between NYHA class and symptom severity, it is important to keep in mind that NYHA class measures *any* symptom to assign a class, and I am only looking at fatigue and dyspnoea, it is possible that NYHA class was assigned considering chest pain, palpitations or any other symptom, which could explain why some patients (fatigue 87 [2%] and dyspnoea 49 [1%]) have symptoms at rest (fatigue or dyspnoea 4) while still being classified as NYHA class II or III.

Results for univariate analyses looking at the correlates of symptoms will be discussed in the following chapter.

7 Correlates of symptoms in CORONA: randomisation visit

In this chapter I will present the results of analyses examining which patient characteristics are associated with dyspnoea and fatigue and whether the magnitude of the associations between such characteristics and fatigue and dyspnoea are similar or different.

7.1 Background

The classic description of heart failure is a syndrome caused by cardiac dysfunction and characterised by two prototypal symptoms, namely dyspnoea and fatigue. (246) However, the cause of these symptoms, particularly fatigue, remains unclear and little is known about their prevalence, severity and predictors. (76, 79, 80, 82, 83) It has even been suggested that both symptoms might be different manifestations of the same pathophysiological process. (76, 80, 84) However, in two separate studies each symptom has been shown to predict outcome independently of the other, suggesting they might be biologically distinct. (85, 86)

7.2 Methods

Baseline characteristics are presented by symptom group at baseline, with mean and standard deviation (SD) for continuous variables and percentage for categorical variables. Baseline characteristics were compared across groups using a test for trend (see Table 6-4).

Linearity of the association between covariates and outcome was assessed in several ways (visually, using a Wald test and including spline transformations or quadratic terms) and was satisfied for all continuous covariates (see 4.2.2.1 for rationale).

The selected variables were fitted into a generalized ordered logistic regression model for ordinal dependent variables. A partial proportional odds regression was run for variables that did not fulfil the proportional odds assumption (225, 229) (see section 4.2.1.3).

A detailed description of the ordered logistic regression model (or proportional odds model) and the underlying assumptions can be found in the Methods chapter (Section 4.2.1).

Most baseline characteristics were included in the model; some were excluded to avoid collinearity (i.e. multiple lipid indicators). Hence the final model included the following covariates: age, sex, LVEF, NYHA class, weight status as per baseline BMI (i.e. obese, overweight), systolic blood pressure, baseline heart rate, years with heart failure, history of myocardial infarction, history of diabetes, history of stroke, hypertension, history of angina, baseline atrial fibrillation/flutter, intermittent claudication, history of CABG or PCI, pacemaker, implantable cardioverter defibrillator; or treatment with a mineralocorticoid receptor antagonist, loop/thiazide diuretic, beta-blocker, nitrate, insulin, antiarrhythmic drug, ACE-inhibitor or ARB, digoxin, anticoagulant, thyroid stimulating hormone, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein, alanine aminotransferase, creatine kinase, creatinine and low-density lipoprotein. A logarithmic transformation of NT-proBNP was performed (see section 4.2). Baseline body mass index was categorized to ease interpretation and comply with the WHO criteria (247).

I also tested the null hypothesis of equivalence between the odds ratio for fatigue and the odds ratio for dyspnoea using a Wald test: (H_0: $OR_{fatigue}=OR_{dyspnoea}$).

7.3 Results from randomisation visit

7.3.1.1 Unadjusted outcomes

Baseline characteristics, including co-morbidities and concomitant drug treatments are summarised in Table 6-4.

Correlates with both fatigue and dyspnoea: Patients with higher levels of fatigue or dyspnoea (i.e. symptoms on slight exertion or at rest) were more likely to be female (fatigue 26%; dyspnoea 24%); to have a history of myocardial infarction (fatigue and dyspnoea both 63), angina (fatigue 76%; dyspnoea 75%), stroke (fatigue 15%; dyspnoea 14%), intermittent claudication (15% for both fatigue and dyspnoea group 3) and diabetes (32%/33%); to be in atrial fibrillation/flutter (fatigue 27%; dyspnoea 28%) and NYHA functional class III or IV (fatigue 86%; dyspnoea 89%); and have a longer history of HF (fatigue 4.5 years; dyspnoea 4.6 years). They were also more likely to have a lower systolic blood pressure (fatigue and dyspnoea 127 mm/Hg) and lower levels of creatine kinase (fatigue 41 IU/L; dyspnoea 42 IU/L), cholesterol (fatigue 5.4 mmol/L; dyspnoea 5.3 mmol/L), Apo-lipoprotein A-1 levels (both 1.47 mg/L) and estimated glomerular filtration rates (both 54.7 ml/min/1.73m^2), but a higher heart rate (73 bpm for both) and NT-proBNP (fatigue 233 pmol/L; dyspnoea 234 pmol/L) and hsCRP levels (both 4 mg/L). More symptomatic patients were more likely to be treated with diuretics (both 92%), digitalis (both 40%), mineralocorticoid receptor antagonists (49% both) or nitrates (fatigue 34%; dyspnoea 35%).

Correlates with fatigue only: Patients with lower levels of fatigue were more likely to be current smokers (13% vs. 8%), while more symptomatic patients had lower levels of co-enzyme Q_{10} (0.7 mmol/L vs. 0.8 mmol/L).

Correlates with dyspnoea only: Prior pacemaker implantation (14% in patients with dyspnoea on slight exertion or rest vs. 11% in those with moderate dyspnoea and 10% in those with dyspnoea on heavy exertion) was associated with dyspnoea but not fatigue. Patients with more severe dyspnoea had, higher creatinine levels (mean of 118 mg/dL vs. mean of 115 mg/dL on those with mild or moderate dyspnoea).

7.3.1.2 Multivariable analyses

2724 (71%) patients were included in the complete case analysis, with missing NT-proBNP values being the main reason for missing data in the regressions. Results are summarised in Table 7-1.

Correlates with both fatigue and dyspnoea: History of myocardial infarction was associated with a higher baseline level of both fatigue (OR 1.85, 95 CI 1.46-2.36, p value <0.01 for moderate vs. no/slight fatigue) and dyspnoea (OR 1.39, 95% CI 1.15-1.69, p value<0.01), as was history of angina (fatigue OR 1.57 95% CI 1.23-2.01, p value <0.01; dyspnoea OR 1.64, 95% CI 1.22-2.20, p value <0.01: moderate symptoms versus no/slight symptoms on exertion). Higher NYHA functional class (the higher NYHA class the stronger the association with symptom severity for both symptoms; p value <0.001 for all levels and both symptoms) and use of a mineralocorticoid receptor antagonist (MRA) (fatigue OR 1.42, 95% CI 1.19-1.69; dyspnoea OR 1.33, 95% CI 1.10-1.61: p value <0.01 for both) were associated with worse symptom severity.

Correlates with fatigue only: Female sex was significantly associated with fatigue (OR 1.54, 95% CI 1.24-1.91, p value<0.01) as well as a history of hypertension (OR 1.38, 95% CI 1.16-1.65, p value<0.01).

Correlates with dyspnoea only: being overweight or obese at baseline was associated with dyspnoea only (overweight OR 1.34, 95% CI 1.09-1.65; obese [moderate vs. slight dyspnoea] OR 1.89, 95% CI 1.25-2.84; p value<0.01 for both of them) but not with fatigue.

Differences in correlates of fatigue and dyspnoea: Although the two symptoms vary slightly in their correlates, no clear difference is seen when testing the null hypothesis that the odds ratio for fatigue is equal to the odds ratio for dyspnoea. This is true for all predictors except NYHA functional class, where this seems to be a stronger predictor for dyspnoea than it is for fatigue.

Table 7-1 Multivariable analyses:

	Fatigue		Dyspnoea		Equality test for OR fatigue vs. OR dyspnoea
Variable	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**P value**
Age p/10 years	1.02 (0.90, 1.15)	0.806	1.15 (1.00, 1.32)	0.043	0.056
Female	1.54 (1.24, 1.91)	<0.001	1.31 (1.03, 1.60)	0.025	0.391
LVEF	1.96 (0.49, 8.60)	0.370	1.04 (0.20, 5.32)	0.170	0.429
NYHA III/IV*					
**fatigue/dyspnoea 2 vs. 1*	5.02 (3.80, 6.63)	<0.001	13.45 (8.22, 22.03)	<0.001	<0.001
**fatigue/dyspnoea 3 vs.1*	13.14 (10.69, 16.16)	<0.001	29.86 (23.68, 37.64)	<0.001	<0.001
Overweight	1.13 (0.94, 1.37)	0.196	1.34 (1.09, 1.65)	0.006	0.193
Obese*					
**fatigue/dyspnoea 2 vs. 1*	1.46 (1.06, 2.03)	0.022	1.89 (1.25, 2.84)	0.002	0.139
**fatigue/dyspnoea 3 vs. 1*	0.98 (0.75, 1.27)	0.862	1.14 (0.86, 1.53)	0.361	0.055
Systolic BP p/10 mmHg	0.96 (0.91, 1.01)	0.151	0.98 (0.93, 1.04)	0.509	0.343
Heart rate p/10 beats/min	1.04 (0.96, 1.12)	0.373	1.11 (1.02, 1.21)	0.017	0.171
Years w/heart failure	1.00 (0.99, 1.02)	0.649	1.00 (0.98, 1.02)	0.933	0.579
Myocardial Infarction			1.39 (1.15, 1.69)	0.001	
**fatigue 2 vs. 1*	1.85 (1.46, 2.36)	<0.001			0.606
**fatigue 3 vs. 1*	1.30 (1.06, 1.58)	0.010			0.537
History of Diabetes	1.07 (0.87, 1.31)	0.526	1.20 (0.95, 1.51)	0.118	0.209
Stroke	1.36 (1.06, 1.74)	0.017	0.98 (0.75, 1.29)	0.890	0.039
Hypertension	1.38 (1.16, 1.65)	<0.001	1.13 (0.93, 1.37)	0.229	0.105
History of angina*					
**fatigue/dyspnoea 2 vs. 1*	1.57 (1.23, 2.01)	<0.001	1.64 (1.22, 2.20)	0.001	0.834
**fatigue/dyspnoea 3 vs. 1*	1.17 (0.94, 1.45)	0.163	1.05 (0.83, 1.34)	0.681	0.522
Baseline atrial fibrillation/flutter*			1.13 (0.87, 1.46)	0.375	
**fatigue 2 vs. 1*	1.46 (1.04, 2.06)	0.029			0.421
**fatigue 3 vs. 1*	1.00 (0.78, 1.29)	0.980			0.402
Intermittent Claudication	1.15 (0.91, 1.47)	0.245	1.06 (0.82, 1.39)	0.644	0.722
CABG/PCI	0.90 (0.74, 1.08)	0.259	0.95 (0.77, 1.17)	0.602	0.449

Pacemaker	0.88 (0.68, 1.13)	0.312	1.16 (0.87, 1.54)	0.325	0.111
ICD	0.75 (0.48, 1.16)	0.197	0.84 (0.52, 1.35)	0.462	0.429
MRAs*	1.42 (1.19, 1.69)	<0.001	1.33 (1.10, 1.61)	0.004	0.415
Loop/thiazide	1.05 (0.81, 1.35)	0.727	1.02 (0.77, 1.36)	0.874	0.996
Beta-blocker	1.12 (0.93, 1.36)	0.238	1.11 (0.90, 1.37)	0.341	0.755
Nitrate	1.04 (0.87, 1.26)	0.649	1.20 (0.97, 1.48)	0.092	0.150
Insulin	0.86 (0.61, 1.21)	0.377	0.82 (0.56, 1.21)	0.323	0.956
Antiarrhythmic	1.06 (0.82, 1.37)	0.653	0.89 (0.68, 1.18)	0.436	0.058
ACE inhibitor or ARB	0.90 (0.66, 1.24)	0.524	1.00 (0.70, 1.43)	0.991	0.179
Digoxin	1.23 (1.02, 1.48)	0.031	1.15 (0.94, 1.43)	0.166	0.552
Anticoagulant	0.88 (0.73, 1.07)	0.201	0.91 (0.74, 1.13)	0.391	0.546
TSH mIU/L	1.00 (0.98, 1.02)	0.756	1.00 (0.98, 1.01)	0.623	0.303
Log(NT-proBNP)	1.09 (1.00, 1.01)	0.045	1.04 (0.95, 1.13)	0.442	0.295
hs-CRP mg/litre	1.00 (1.00, 1.01)	0.128	1.00 (1.00, 1.01)	0.445	0.894
alanine transaminase IU/L	1.00 (1.00, 1.01)	0.442	1.00 (1.00, 1.01)	0.379	0.786
Creatine kinase p/50	0.86 (0.82,1.02)	0.093	0.93 (0.82, 1.05)	0.249	0.514
Creatinine mg/dL	1.00 (0.99, 1.00)	0.078	1.00 (0.99, 1.00)	0.035	0.334
Low density lipoprotein mmol/L	0.99 (0.90, 1.08)	0.779	0.96 (0.87, 1.06)	0.415	0.525

*Did not fulfil proportional odds (PO) assumption

LVEF – left ventricular ejection fraction, NYHA – New York Heart Association functional class, BP –blood pressure, CABG/PCI – coronary artery bypass grafting/ percutaneous coronary intervention, ICD – implantable cardioverter defibrillator, MRA – Mineralocorticoid receptor antagonists, ACE – angiotensin converting enzyme, ARB – angiotensin II receptor blocker, TSH – thyroid stimulating hormone, NT-proBNP – N-terminal of the prohormone brain natriuretic peptide, CRP – – high-sensitivity C-reactive protein.

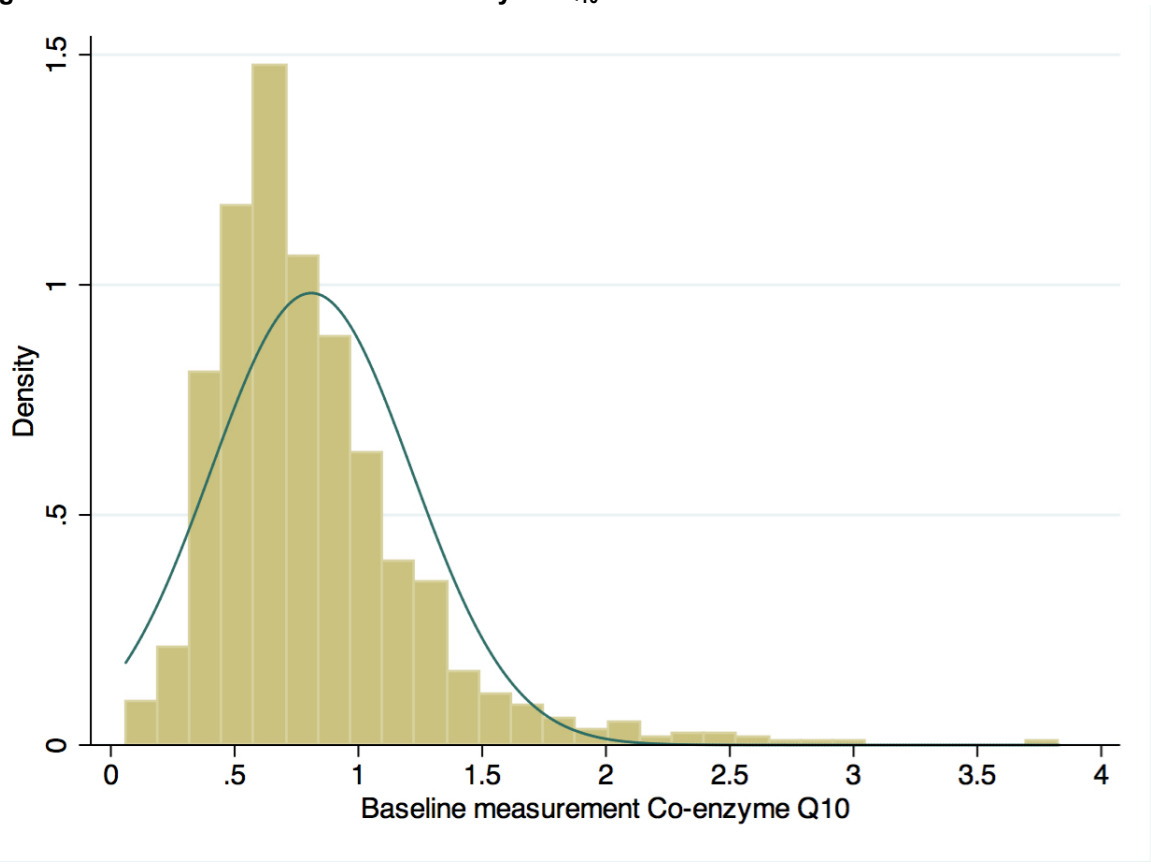
7.3.1.3 Model including co-enzyme Q_{10}

Given the controversy surrounding the role of ubiquinone as a potential treatment for reduction in symptom severity in patients with heart failure, I decided to include serum co-enzyme Q_{10} levels as a covariate in the model to analyse if there was any association between them and symptom severity at baseline. The results are shown next.

Of the 3830 patients analysed, 980 (25%) had a baseline coenzyme Q10 value and 678 were included in the multivariate model described above (the others were excluded mostly due to missing NT-proBNP values).

A histogram of baseline co-enzyme Q_{10} can be seen below.

Figure 7-1 Distribution of baseline co-enzyme Q_{10}



The distribution of co-enzyme Q_{10} across symptom group can be seen in TablesTable 7-2 andTable 7-3. P values were obtained by performing a Kruskal Wallis test. Both median and mean values of co-enzyme Q_{10} are lower in the high symptom group for both fatigue and dyspnoea, lending some support to the notion that co-enzyme Q_{10} could be a potential treatment target for improving symptoms. (158, 160, 248)

Table 7-2 Distribution of co-enzyme Q_{10} across fatigue groups

Fatigue	n	Mean	SD	Median	p25	p75	p
0/1	250	0.83	0.40	0.76	0.59	0.98	
2	397	0.85	0.43	0.77	0.58	1.03	
3/4	333	0.74	0.37	0.67	0.51	0.89	
Total	980	0.81	0.41	0.73	0.56	0.97	<0.001

Table 7-3 Distribution of co-enzyme Q_{10} across dyspnoea groups

Dyspnoea	n	Mean	SD	Median	p25	p75	p
0/1	143	0.80	0.36	0.72	0.57	0.97	
2	443	0.85	0.42	0.76	0.60	1.00	
3/4	394	0.77	0.40	0.68	0.51	0.96	
Total	980	0.81	0.41	0.73	0.56	0.97	0.003

Results of the multivariate model including co-enzyme Q_{10} are summarised in Table 7-4 below. Co-enzyme Q_{10} was not significantly associated with fatigue or dyspnoea on exertion. It could be argued however that a tendency can be seen where co-enzyme Q_{10} is associated with fatigue as the effect size is rather large (OR 0.60, 95% CI 0.38-0.93) and the p value is small (p=0.02). For this reason I decided to run an equality test (in the same manner as the preceding section) between the odds ratio for fatigue and the one for dyspnoea, getting a non-significant test result (p value=0.34 for the null hypothesis of ORfatigue=ORdyspnoea for co-enzyme Q_{10}).

Table 7-4 Multivariable analyses including co-enzyme Q10

	Fatigue		Dyspnoea	
Variable	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Age p/10 years	1.10 (0.87, 1.40)	0.424	1.27 (0.87, 1.66)	0.077
Female	1.99 (1.29, 3.07)	0.002	2.16 (1.31, 3.58)	0.003
LVEF	1.15 (0.09, 15.28)	0.916	0.36 (0.02, 5.95)	0.474
NYHA III/IV*				
**fatigue/dyspnoea 2 vs. 1*	3.22 (2.10, 14.94)	<0.001	10.97 (5.38, 22.40)	<0.001
**fatigue/dyspnoea 3 vs.1*	5.63 (3.79, 8.38)	<0.001	22.91 (14.46, 36.29)	<0.001
Overweight*			1.45 (0.97, 2.16)	0.067
**fatigue 2 vs. 1*	0.69 (0.45, 1.05)	0.082		
**fatigue 3 vs.1*	1.11 (0.73, 1.67)	0.628		
Obese*	0.77 (0.50, 1.20)	0.253		
**dyspnoea 2 vs. 1*			1.57 (0.81, 3.04)	0.180
**dyspnoea 3 vs.1*			0.71 (0.40, 1.26)	0.240
Systolic BP p/10 mmHg	0.96 (0.87, 1.05)	0.370	1.09 (0.98, 1.21)	0.124
Heart rate p/10 beats/min*			1.07 (0.90, 1.27)	0.460
**fatigue 2 vs. 1*	1.28 (1.05, 1.54)	0.013		
**fatigue 3 vs.1*	0.91(0.77, 1.10)	0.350		
Years w/heart failure	1.04 (1.01, 1.07)	0.019	1.00 (0.96, 1.03)	0.795
Myocardial Infarction	1.43 (1.01, 2.03)	0.044	1.70 (1.15, 2.05)	0.008
History of Diabetes	0.91 (0.60, 1.36)	0.631	1.09 (0.68, 1.75)	0.710

Stroke	1.69 (0.98, 2.92)	0.060	1.24 (0.67, 2.31)	0.490
Hypertension	1.09 (0.79, 1.52)	0.593	1.11 (0.77, 1.60)	0.577
History of angina	0.99 (0.69, 1.43)	0.972	0.79 (0.53, 1.19)	0.269
Baseline atrial fibrillation/flutter	1.09 (0.67, 1.77)	0.717	0.99 (0.57, 1.71)	0.972
Intermittent Claudication	1.07 (0.67, 1.71)	0.769	0.71 (0.43, 1.17)	0.181
CABG/PCI	1.25 (0.88, 1.76)	0.207	1.86 (1.26, 1.75)	0.002
Pacemaker	1.23 (0.77, 1.97)	0.382	1.06 (0.63, 1.77)	0.824
ICD	0.74 (0.36, 1.52)	0.593	0.75(0.34, 1.65)	0.476
MRAs*	1.21 (0.85, 1.73)	0.281	1.07 0.72, 1.59)	0.725
Loop/thiazide	0.72 (0.47, 1.12)	0.149	0.89 (0.55, 1.46)	0.661
Beta-blocker*			0.92 (0.61, 1.40)	0.705
**fatigue 2 vs. 1*	1.62 (1.05, 2.49)	0.030		
**fatigue 3 vs.1*	0.88 (0.57, 1.34)	0.553		
Nitrate	1.00 (0.69, 1.88)	0.995	1.02 (0.68, 1.54)	0.910
Insulin	1.44 (0.73, 2.83)	0.296	1.84 (0.80, 4.24)	0.151
Antiarrhythmic	1.22 (0.70, 2.13)	0.490	0.65 (0.36, 1.18)	0.159
ACE inhibitor or ARB	0.92 (0.51, 1.67)	0.785	0.91 (0.47, 1.03)	0.067
Digoxin	1.55 (1.07, 2.24)	0.020	1.30 (0.85, 1.97)	0.224
Anticoagulant	0.74 (0.52, 1.05)	0.097	0.70 (0.47, 1.03)	0.067
TSH mIU/L	0.94 (0.87, 1.02)	0.144	1.00 (0.94, 1.07)	0.878
Log(NT-proBNP)*	1.03 (0.87, 1.21)	0.748		
**dyspnoea 2 vs. 1*			0.87 (0.69, 1.09)	0.232
**dyspnoea 3 vs. 1*			1.41 (1.15, 1.74)	0.001
hs-CRP mg/litre			1.01 (0.99, 1.02)	0.320
**fatigue 2 vs. 1*	1.00 (0.98, 1.02)	0.905		
**fatigue 3 vs.1*	1.02 (1.01, 1.03)	0.004		
Alanine transaminase IU/L	1.00 (0.99, 1.01)	0.555	1.00 (0.99, 1.01)	0.983
Creatine kinase p/50 IU/L	0.83 (0.67, 1.03)	0.097	1.03 (.82, 1.30)	0.772
Creatinine mg/dL	1.00 (0.99, 1.01)	0.863	1.00 (0.99, 1.00)	0.580
Low density lipoprotein mmol/L	1.01 (0.84, 1.22)	0.890	0.87 (0.71, 1.07)	0.196
Co-enzyme Q10 mmol/L	0.60 (0.39, 0.93)	0.023	0.93 (0.57, 1.53)	0.784

*Did not fulfil proportional odds (PO) assumption

LVEF – left ventricular ejection fraction, NYHA – New York Heart Association functional class, BP –blood pressure, CABG/PCI – coronary artery bypass grafting/ percutaneous coronary intervention, ICD – implantable cardioverter defibrillator, MRA – Mineralocorticoid receptor antagonists, ACE – angiotensin converting enzyme, ARB – angiotensin II receptor blocker, TSH – thyroid stimulating hormone, NT-proBNP – N-terminal of the prohormone brain natriuretic peptide, CRP – – high-sensitivity C-reactive protein.

7.4 Summary of results and discussion

I found that a limited number of variables (history of hypertension and coronary heart disease; NYHA functional class; and use of mineralocorticoid receptor antagonists) were independently associated with both fatigue and dyspnoea, with no variables clearly associated with only one of these symptoms. The lack of association with ejection fraction or NT-proBNP suggests that "peripheral" rather than "central" mechanisms may explain the origin of both symptoms.

Beta-blocker use has been linked to fatigue (249, 250) and two case series (albeit they had no control group) (251, 252) and early clinical trials in patients with acute myocardial infarction (253, 254) have found an association between

beta blocker use and fatigue. I conversely found no association between beta-blocker use and symptoms. This could be due to the fact that beta-blocker use was almost ubiquitous (74% of patients in CORONA reported use of beta blockers). A quantitative review of randomized trials (255) that tested beta-blockers in myocardial infarction, heart failure, and hypertension published in 2002 found that the conventional wisdom that beta-blocker therapy is associated with a substantial risk of suffering fatigue is not supported by data from clinical trials. In their analysis, beta-blockers were associated with a small significant annual increase in risk of reported fatigue (18 per 1000 patients; 95% CI, 5-30), equivalent to 1 additional report of fatigue for every 57 patients treated per year with beta-blockers. Hjalmarson *et al* examined the effects of metoprolol succinate on symptoms and quality of life among patients in the MERIT-HF trial and found that it had an overall beneficial effect on patient well being, they report only a 0.3% net increase in fatigue between metoprolol succinate and placebo. (256) Another more recent study looking at the correlates of fatigue in patients who had a stroke (257) found no association between fatigue and beta-blocker use. The risk of fatigue with beta-blocker use should be put in the context of the documented benefits of these medications.

My results show that co-enzyme Q_{10} was not a significant correlate of fatigue, however it is very important to note that a lot of information was lost due to missing data on said covariate. Although the results do not change with imputation for missing data, findings from such analyses should be interpreted cautiously due to the strong assumptions underlying imputation methods (specifically that the data are missing at random), which are probably not fulfilled as the missing values of co-enzyme Q_{10} are missing according to centre (i.e. some centres did not measure co-enzyme Q_{10} levels as centres had to be near a laboratory because samples were sent fresh on ice).

8 Symptoms as predictors of outcome: CORONA randomisation visit

In this chapter I will present the results of analyses examining the association between symptom severity at baseline and the risk of a number of cardiovascular outcomes after adjustment for other risk factors in CORONA. The relationship is examined using traditional methods of survival analyses. As a result, I aim to determine if higher symptom burden at baseline is associated with a higher risk of certain cardiovascular outcomes. I will compare how two of the pivotal symptoms of heart failure (i.e. fatigue and dyspnoea) relate to such outcomes to examine if there is difference between them.

8.1 Methods

I tested the prognostic value of each symptom in relation to the composite outcome of cardiovascular death or hospitalisation due to worsening heart failure (heart failure) using Cox proportional-hazard regression models (described in Methods chapter). Cardiovascular death or hospitalisation due to worsening heart failure (rather than the pre-specified primary outcome of CORONA) was used in the present analysis as it better reflects the disease-specific morbidity and mortality related to heart failure (and the primary endpoint of CORONA was recommended by regulatory authorities to reflect the treatment intervention used i.e. a statin). (234, 235) Other outcomes analysed were the components of the composite (cardiovascular death and heart failure) . As mentioned in section 4.2.2, the adjusted analyses used a previously published CORONA risk model for all cause mortality. The covariates included were: age, sex, NYHA class, LVEF, body mass index (BMI), systolic blood pressure, heart rate, smoking, MI, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter (AF), stroke, intermittent claudication, pacemaker and ICD implantations, apoA-1, apoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, and log NT-proBNP. (228) A logarithmic transformation of NT-proBNP was performed. Linearity and proportional hazard assumptions were assessed for all continuous model covariates.

Kaplan-Meier cumulative event curves are presented by symptom category and compared with log-rank tests.

8.2 Results

Of the 3830 patients analysed, 1568 (40.9%) had a heart failure hospitalisation or cardiovascular death with a median survival time of 389 days (IQR 163.5-690). 961 (25.1%) patients had a cardiovascular death with a median survival time of 507 days (IQR 240-793). 1040 patients were hospitalised due to worsening heart failure; median "survival" time was of 349 days (IQR 134-664). (see Table 8-1) For the 2262 patients who did not have a CV death or heart failure hospitalisation, median survival time was of 1071 days (IQR 914-1176).

8.2.1 Unadjusted outcomes

Patients with a higher symptom severity were significantly more likely to die from any cause (fatigue group 3 n=618 [38%] vs. group 1 n=136 [24%], HR 1.72, 95% CI 1.43-2.07; dyspnoea group 3 n=662 [37%] vs. group 1 n=77 [23%], HR 1.81, 95% CI 1.43-2.29) and from cardiovascular causes (fatigue group 3 n=503 [31%] vs. group 1 n=109 [20%] HR 1.75, 95% CI 1.42-2.15; dyspnoea group 3 n=540 [31%] vs. group 1 n=63 [19%], HR 1.81, 95% CI 1.39-2.35). Those with greater symptom severity were also more likely to be hospitalized for worsening heart failure (fatigue group 3 n=554 [34%] vs. group 1 n=109 [20%], HR 2.07, 95% CI 1.68-2.54; dyspnoea group 3 n=611 [35%] vs. group 1 n=49 [15%], HR 2.88, 95% CI 2.16-3.86); log rank $p<0.01$ for all outcomes (see Table 8-1 and Table 8-2: Figure 8-1 and Figure 8-2).

Table 8-1 Clinical outcomes according to baseline symptom severity

	Fatigue			Dyspnoea		
	0/1	**2**	**3/4**	**1**	**2**	**3/4**
	(n=552)	**(n=1647)**	**(n=1630)**	**(n=338)**	**(n=1722)**	**(n=1770)**
n (%)						
Cardiovascular death or heart failure hospitalisation	67/109 (31.9)	207/377 (35.5)	254/554 (49.6)	47/49 (28.4)	216/380 (34.6)	265/611 (49.5)
Cardiovascular death	109 (19.8)	349 (21.2)	503 (30.9)	63 (18.6)	358 (20.8)	540 (30.5)
Heart failure hospitalisation	109 (19.8)	377 (22.9)	554 (34.0)	49 (14.5)	380 (22.1)	611 (34.5)
All-cause death	136 (24.6)	451 (27.4)	618 (37.9)	77 (22.8)	466 (27.1)	662 (37.4)

Table 8-2 Hazard ratio for symptom severity and clinical outcomes: Unadjusted analysis

	Fatigue				Dyspnoea			
	2 vs. 1		3 vs. 1		2 vs. 1		3 vs. 1	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular death or heart failure hospitalisation	1.16 (0.98, 1.37)	0.079	1.87 (1.59, 2.20)	<0.001	1.28 (1.03, 1.59)	0.024	2.12 (1.71, 2.62)	<0.001
Cardiovascular death	1.10 (0.89, 1.36)	0.393	1.75 (1.42, 2.15)	<0.001	1.14 (0.87, 1.48)	0.353	1.81 (1.39, 2.35)	<0.001
Heart failure hospitalisation	1.21 (0.98, 1.50)	0.080	2.07 (1.68, 2.54)	<0.001	1.60 (1.19, 2.16)	0.002	2.88 (2.16, 3.86)	<0.001
All-cause death	1.14 (0.94, 1.38)	0.188	1.72 (1.43, 2.07)	<0.001	1.21 (0.95, 1.54)	0.128	1.81 (1.43, 2.29)	<0.001

Figure 8-1 Kaplan Meier curves for outcomes according to fatigue severity

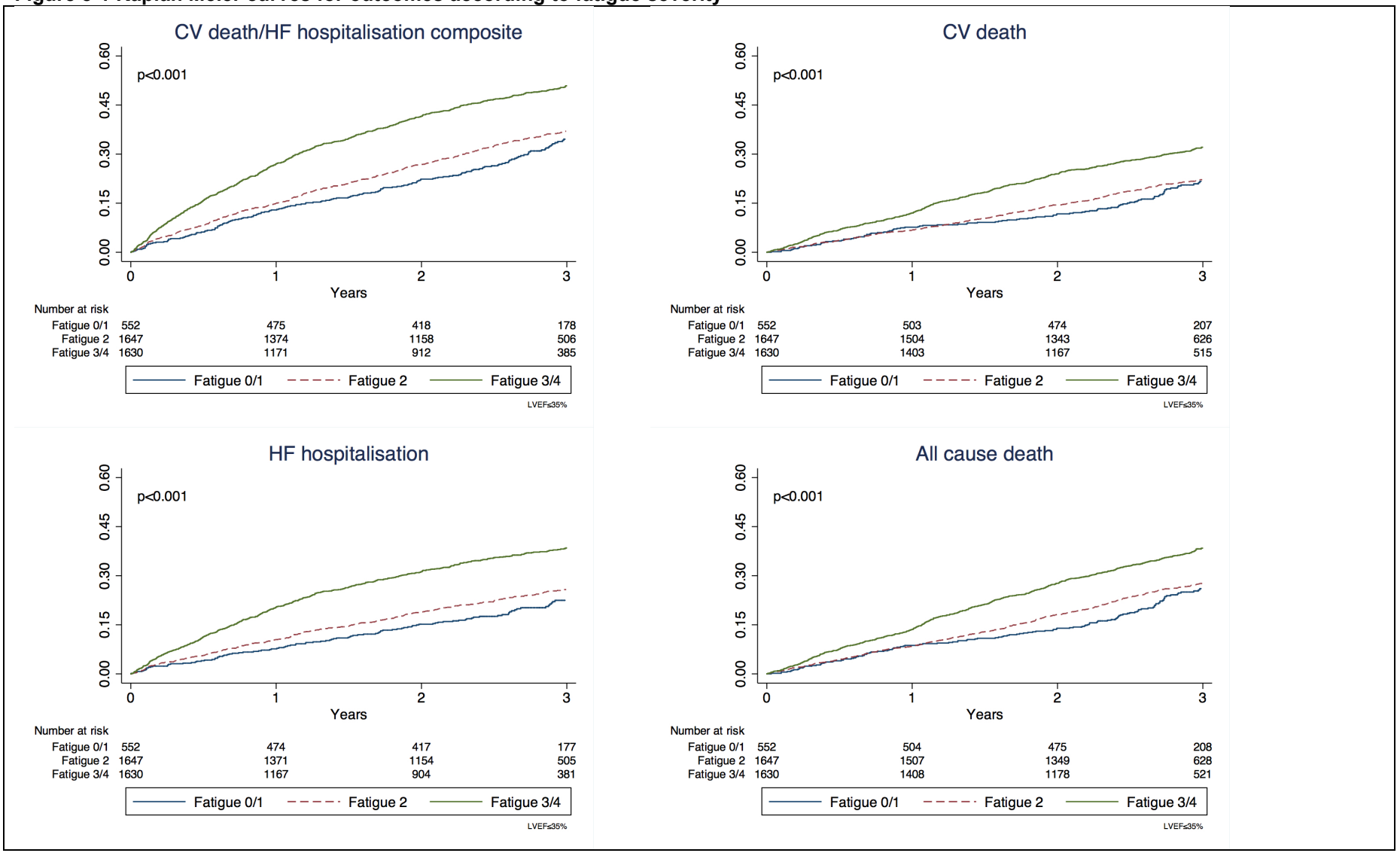
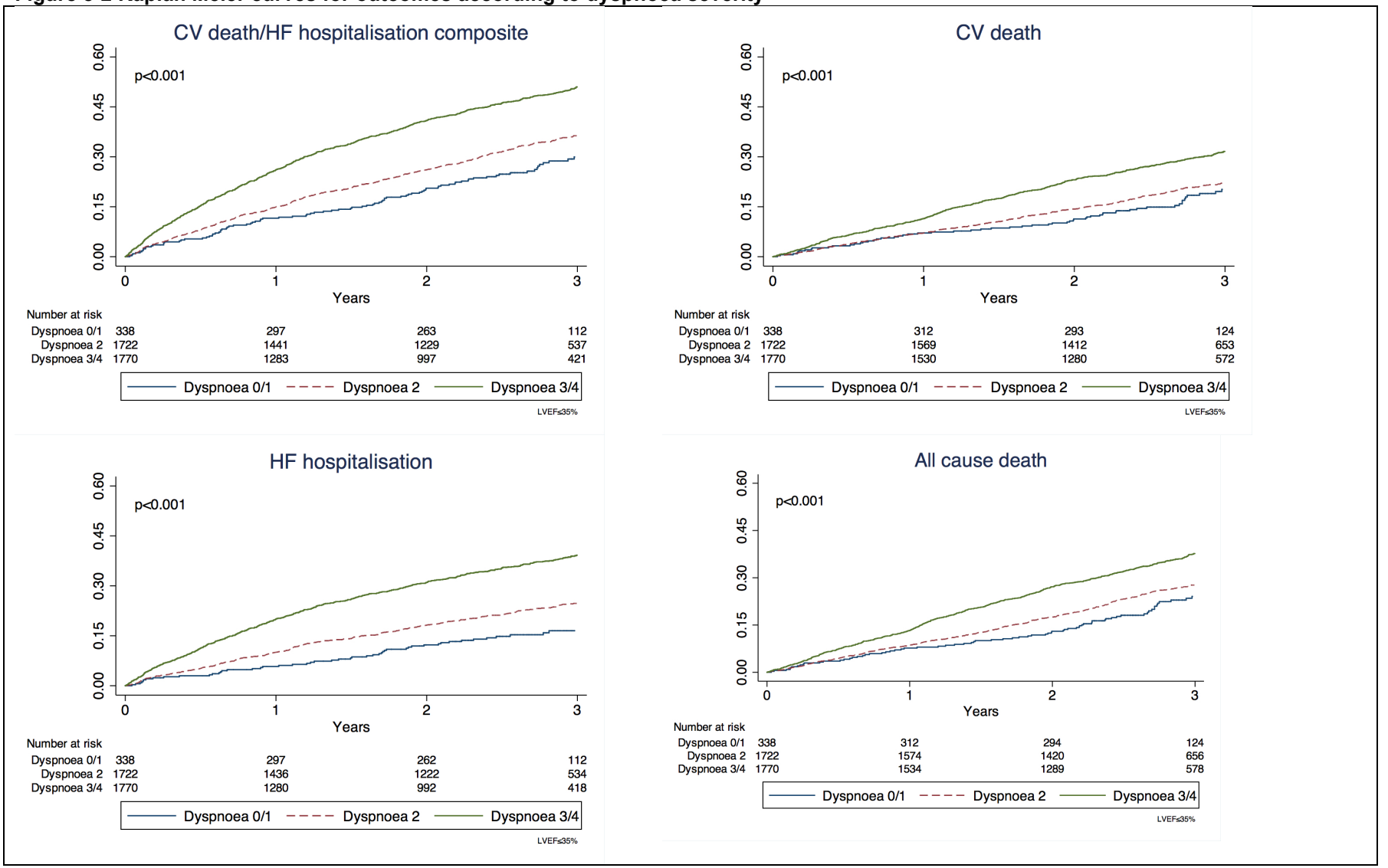


Figure 8-2 Kaplan Meier curves for outcomes according to dyspnoea severity



8.2.2 Adjusted outcomes

Adjustment for the other variables associated with worse clinical outcomes listed in the Methods section of this chapter weakened the relationship between symptom severity and all outcomes. (Group 3 vs. Group 1): fatigue - cardiovascular death HR 1.06 (95% CI 0.79, 1.41), p=0.72 and heart failure hospitalisation HR 1.10 (0.84, 1.44), p= 0.50; dyspnoea - cardiovascular death HR 1.13 (0.78, 1.64) p=0.52 and heart failure hospitalisation HR 1.35 (0.93, 1.95), p=0.11. A total of 2718 (71%) patients were included in the complete-case analyses, with missing NT-proBNP values being the main reason for missing data in the regression, as stated previously (1112 patients had missing NT-proBNP values). (Table 8-3)

Table 8-3 Hazard ratio for symptom severity and clinical outcomes: Multivariable analysis

	Fatigue				Dyspnoea			
	2 vs. 1		3 vs. 1		2 vs. 1		3 vs. 1	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular death or heart failure hospitalisation	0.98 (0.80, 1.21)	0.884	1.10 (0.88, 1.38)	0.401	1.05 (0.81, 1.36)	0.719	1.09 (0.82, 1.45)	0.547
Cardiovascular death	0.94 (0.72, 1.23)	0.674	1.06 (0.79, 1.41)	0.719	1.09 (0.78, 1.52)	0.609	1.13 (0.78, 1.64)	0.516
Heart failure hospitalisation	0.99 (0.76, 1.28)	0.925	1.10 (0.84, 1.44)	0.496	1.19 (0.85, 1.67)	0.317	1.35 (0.93, 1.95)	0.113
All-cause death	1.05 (0.83, 1.34)	0.671	1.11 (0.86, 1.45)	0.422	1.21 (0.90, 1.64)	0.214	1.18 (0.84, 1.65)	0.333

Adjusted for: age, sex, NYHA class, LVEF, body mass index (BMI), systolic blood pressure, heart rate, smoking, MI, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter (AF), stroke, intermittent claudication, pacemaker and ICD implantation, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, and log NT-proBNP.

8.2.2.1 Including randomised treatment

My analysis was of the relationship between fatigue and dyspnoea at baseline (before randomisation to placebo or rosuvastatin) and outcomes, which would not have been confounded by treatment group allocation. Whether or not rosuvastatin affected fatigue after randomisation is not directly relevant to this analysis. However, an effect of rosuvastatin could be relevant to my analysis of the relationship between *change* in fatigue from baseline and subsequent outcomes, which will be analysed in Chapter 9. Creatine kinase was measured as a safety outcome in CORONA and showed no increase with rosuvastatin. Consequently, I do not think that statin therapy confounded analysis of the association between fatigue and clinical outcomes, nevertheless, including randomised treatment in the multivariable adjustment made little difference to the findings as can be seen from Table 8-4 below.

Table 8-4 Hazard ratio for symptom severity and clinical outcomes including randomised treatment

	Fatigue				Dyspnoea			
	2 vs. 1		3 vs. 1		2 vs. 1		3 vs. 1	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular death or heart failure hospitalisation	0.98 (0.80, 1.21)	0.879	1.09 (0.87, 1.37)	0.428	1.05 (0.81, 1.36	0.711	1.08 (0.81, 1.44)	0.598
Cardiovascular death	0.94 (0.72, 1.23)	0.674	1.06 (0.79, 1.42)	0.717	1.09 (0.78, 1.53)	0.608	1.13 (0.78, 1.64)	0.514
Heart failure hospitalisation	0.98 (0.76, 1.27)	0.907	1.09 (0.83, 1.43)	0.541	1.19 (0.85, 1.67)	0.315	1.33 (0.92, 1.92)	0.135
All-cause death	1.05 (0.83, 1.34)	0.670	1.11 (0.86, 1.45)	0.424	1.21 (0.90, 1.64)	0.214	1.18 (0.84, 1.65)	0.337

Adjusted for: age, sex, NYHA class, LVEF, body mass index (BMI), systolic blood pressure, heart rate, smoking, MI, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter (AF), stroke, intermittent claudication, pacemaker and ICD implantation, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, log NT-proBNP, and *randomised treatment*

8.2.2.2 Parsimonious model

To address a potential problem of over-fitting the model, I decided to run a model including only the top 10 predictive variables (based on chi-square) to the adjusted model (covariates selected from CORONA model with death and heart failure hospitalisation as outcome). Running this more parsimonious model made no difference to my overall results: (Group 3 vs. Group 1): fatigue-cardiovascular death HR 1.15 (95% CI 0.86, 1.52), p=0.34; dyspnoea- cardiovascular death HR 1.21 (0.84, 1.75), p=0.31: fatigue- heart failure hospitalisation HR 1.13 (0.86, 1.48), p=0.37; dyspnoea- heart failure hospitalisation HR 1.44 (1.00, 2.08), p=0.05. See Table 8-5.

Table 8-5 Hazard ratio for symptom severity and clinical outcomes for 10 strongest predictors

	Fatigue				Dyspnoea			
	2 vs. 1		3 vs. 1		2 vs. 1		3 vs. 1	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular death or heart failure hospitalisation	1.02 (0.83, 1.25)	0.874	1.15 (0.93, 1.44)	0.202	1.09 (0.85, 1.42)	0.483	1.16 (0.88, 1.55)	0.294
Cardiovascular death	0.98 (0.75, 1.28)	0.892	1.15 (0.86, 1.52)	0.344	1.13 (0.81, 1.58)	0.469	1.21 (0.84, 1.75)	0.307
Heart failure hospitalisation	1.02 (0.78, 1.31)	0.903	1.13 (0.86, 1.48)	0.371	1.25 (0.89, 1.76)	0.193	1.44 (1.00, 2.08)	0.051
All-cause death	1.08 (0.85, 1.36)	0.526	1.18 (0.92, 1.52)	0.200	1.25 (0.92, 1.68)	0.152	1.24 (0.89, 1.73)	0.197

Adjusted for: age, sex, NYHA class, LVEF, heart rate, diabetes, baseline atrial fibrillation/flutter (AF), randomised treatment, ApoA-1, and log NT-proBNP (covariates selected from CORONA model with death and heart failure hospitalisation as outcome: 10 strongest predictors selected on a basis of chi-square)

8.2.3 Summary of results and discussion

I found that the baseline level of symptoms was strongly associated with heart failure hospitalisation and fatal outcomes. However, this association was lost after adjustment for other well-known prognostic variables, including NYHA class, LVEF and NT-proBNP. This remains true for all the sensitivity analyses performed on symptoms from randomisation visit. Including randomised treatment or running a more parsimonious model did not change the results.

Additionally, my findings from randomisation visit contradict those from the studies that I found which looked at fatigue and dyspnoea at baseline independently from NYHA class (see sections 2.3.3 and 3.3.3). In COMET (258) fatigue was associated with heart failure hospitalisation in multivariate analyses, and dyspnoea was associated with both death and hospitalisation. Madigan *et al* (204) found that dyspnoea on index hospitalisation for heart failure was associated with an increased risk for re-hospitalisation; they did include NT-proBNP in their multivariate analyses and did not investigate fatigue.

As can be seen in Chapter 5, my previously published work (85) looking at the same cohort of patients at a different time point showed slightly different results. So why did I get different results? Firstly, in such paper I chose to analyse the visit prior to randomisation (which is the main analysis time point in this thesis) for the reasons mentioned earlier in section 5.2. As I have shown, symptoms differed substantially between these two visits, and there were a large number of events in those patients who reported different levels of symptoms between these two visits. Secondly, and most importantly, although the hazard ratios vary slightly between analyses from the two time points, the point estimates generally go in the same direction and are of similar magnitude, and the 95% confidence intervals overlap. In recent years, emphasis has been put onto presenting confidence intervals and giving them due notice, as even precise p values convey no information about the sizes or directions of the differences between two groups (non-significant p value will only indicate that there as no difference between groups, or that the sample size was too small to detect a difference). (259) Confidence intervals cover a wide range of plausible population means, with the best estimate of the true effect being more likely to be near the middle of the confidence interval. (260, 261) This does not exclude

values in the extremes of the confidence intervals; it just makes them less likely. In this way, confidence intervals provide a range of possibilities for the true population value, rather than an “arbitrary dichotomy based solely on statistical significance” as Altman (260) points out. Actually, this year, a scientific journal passed a motion to ban p values from their publications, arguing that reporting such statistics support “lower-quality research”. (262)

Having said that, it is also important to note that for the published paper a significance level of 5% was considered, while for this thesis a 1% significance level is considered

9 Change in symptom severity and clinical outcomes

In this chapter I will examine change in symptom severity from baseline to 6 month visit in CORONA, classifying patients as showing a decrease (reduction in score), an increase (an increase in score) or no change (unchanged score) in symptoms. I will analyse the relationship between change in symptoms and subsequent clinical outcomes.

9.1 Background

It is well known that patients with heart failure frequently report worsening of symptoms for hours/days before presenting to hospital. (130, 263-265) Similarly, the prognostic importance of NYHA classification is well known and as well as the prognostic significance of signs and symptoms combined. (5, 266-268) However, the relationship between individual symptoms (as opposed to NYHA class which envelopes all symptoms without discriminating among them in the overall classification-see 1.2.1) and particularly change in symptom severity and clinical outcomes has seldom been analysed. (18, 85, 258)

The association between symptom severity at baseline and outcomes has been reported in chapter 5; in this chapter the focus will be twofold. First, I will analyse which baseline characteristics are associated with change in symptoms at 6 months and then I will analyse the relationship between change in symptoms (baseline to 6 months) and subsequent clinical outcomes (from 6 months to end of study).

9.2 Methods

The data source and CORONA trial have been described in chapter 4, as well as the scale and methods used to measure symptom severity. Symptoms in CORONA were measured at baseline, 6 weeks and 12 weeks after randomisation and every three months thereafter.

I examined change in symptoms from baseline to the 6-month visit by classifying patients as showing a decrease (reduction in score), an increase (an increase in score) or no change (unchanged score) in symptoms. Baseline characteristics are

presented according to change in symptom severity (i.e. unchanged, decrease or increase) and were compared using a chi^2 test for categorical variables or ANOVA for continuous variables (a Kruskall Wallis test was used when the assumption of normality was not met). To analyse the correlates of change in symptoms I used a multinomial logistic regression. The multivariate model was adjusted for age, sex, LVEF, NYHA class, weight status as per baseline BMI (i.e. obese, overweight), systolic blood pressure, baseline heart rate, years with heart failure, history of myocardial infarction, history of diabetes, history of stroke, hypertension, history of angina, baseline atrial fibrillation/flutter, intermittent claudication, history of CABG or PCI, pacemaker, implantable cardioverter defibrillator, treatment with a mineralocorticoid receptor antagonist, loop/thiazide diuretic, beta-blocker, nitrate, insulin, antiarrhythmic drug, ACE-inhibitor or ARB, digoxin, anticoagulant, thyroid stimulating hormone, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein, alanine aminotransferase, creatine kinase, creatinine and low-density lipoprotein and baseline symptom severity. Baseline symptom severity was added to the multivariate model to ensure that the results would be independent of average symptom levels. A logarithmic transformation of NT-proBNP was performed (see 4.2 for rationale). Baseline body mass index was categorized to ease interpretation and to fit with the usual World Health Organization classification. (247)

I tested the prognostic value of each category of change in symptom severity in relation to the composite outcome of cardiovascular death or hospitalisation due to worsening heart failure using Cox proportional-hazard regression models (described in Methods chapter). As in a previous chapter, other outcomes analysed were the components of the composite (cardiovascular death and heart failure hospitalisation individually) and all-cause death.

The multivariate analysis was adjusted for: age, sex, NYHA class, LVEF, body mass index (BMI), systolic blood pressure, heart rate, smoking, MI, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter (AF), stroke, intermittent claudication, pacemaker and ICD implantations, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, and log NT-proBNP. (228) The

group with unchanged symptom status was used as reference. (See section 8.1 for rationale)

Additionally, I investigated how time between visits was associated with change in symptom severity over time. That is, I wanted to figure out if greater time between visits was associated with a higher likelihood of reporting some change, either an increase or decrease, in symptom severity.

Only patients with a follow-up observation for symptom status at 6 months were included in the model. Of the 3830 patients who had a LVEF≤35% at baseline, 282 (7%) did not have a 6-month visit; of these 282 patients 216 (77%) died before visit 6. Given that such a large proportion of patients who did not have a 6-month visit died, the interpretation of the results must be interpreted cautiously as the prognostic relevance of change in symptom severity only reflects the association between this change in a cohort of survivors.

9.2.1 Predictors of change in symptom severity

9.2.1.1 Unadjusted outcomes

Of the 3830 patients in this analysis, 3547 (93%) had both a baseline and 6-month measure of fatigue and 3548 (93%) had a 6-month measure for dyspnoea. Of these 3547, 625 (17.6%) reported a decrease, 459 (12.9%) an increase and 2463 (69.4%) no change in fatigue over that period. Of the 3548 patients who had a 6-month measure for dyspnoea, 2507 (70.7%) reported no change, 667 (18.8%) reported a decrease and 374 (10.5%) reported an increase in dyspnoea over that period. (Table 9-1)

Table 9-1 Cross-tabulation between change in symptoms at 6 months

	Dyspnoea			
Fatigue	**Unchanged**	**Decrease**	**Increase**	**Total**
Unchanged	2107 (59.4%)	231 (6.5%)	125 (3.5%)	2463 (69.4%)
Decrease	203 (5.7%)	397 (11.2%)	25 (0.7%)	625 (17.6%)
Increase	197 (5.5%)	39 (1.1%)	223 (6.3%)	459 (12.9%)
Total	2507 (70.7%)	667 (18.8%)	373 (10.5%)	3547

Most of the patients reported no change in symptom severity after 6 months, however of the 459 patients who reported worse fatigue at 6 months than at baseline, 85 (2% of the 3547 patients who had an observation for 6 months) reported a worsening of 2 or more categories (e.g. going from 0 to 2, or from 1 to 3 or higher) – see Table 9-2.

Table 9-2 Cross tabulation between fatigue level at baseline and 6-month visit

	Fatigue at 6-month visit					
Fatigue at Baseline	**0**	**1**	**2**	**3**	**4**	**Total**
0	124 (3.5%)	21 (0.6%)	31 (0.9%)	13 (0.4%)	5 (0.1%)	194 (5.5%)
1	27 (0.8%)	195 (5.5%)	85 (2.4%)	18 (0.5%)	5 (0.1%)	330 (9.3%)
2	39 (1.1%)	133 (3.8%)	1,150 (32.4%)	219 (6.2%)	13 (0.4%)	1,554 (43.8%)
3	21 (0.6%)	39 (1.1%)	308 (8.7%)	949 (26.8%)	49 (1.4%)	1,366 (38.5%)
4	5 (0.1%)	11 (0.3%)	14 (0.4%)	28 (0.8%)	45 (1.3%)	103 (2.9%)
Total	216 (6.1%)	399 (11.3%)	1,588 (44.8%)	1,227 (34.6%)	117 (3.3%)	3,547

For dyspnoea, 374 (11%) patients reported worsening dyspnoea after 6 months, with 23 (<1% of the total 3548) worsening 2 or more categories - see Table 9-3.

Table 9-3 Cross tabulation between dyspnoea level at baseline and 6-month visit

	Dyspnoea at 6-month visit					
Dyspnoea at Baseline	**0**	**1**	**2**	**3**	**4**	**Total**
0	1 (0.03%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.03%)
1	18 (0.5%)	208 (5.9%)	80 (2.3%)	14 (0.4%)	3 (0.1%)	323 (9.1%)
2	15 (0.4%)	163 (4.6%)	1214 (34.2%)	221 (6.2%)	6 (0.2%)	1619 (45.6%)
3	17 (0.5%)	37 (1.0%)	367 (10.3%)	1057 (29.8%)	50 (1.4%)	1528 (43.1%)
4	0 (0.0%)	8 (0.2%)	9 (0.3%)	33 (0.9%)	27 (0.8%)	77 (2.2%)
Total	51 (1.4%)	416 (11.7%)	1670 (47.1%)	1325 37.3%)	86 (2.4%)	3,548

Correlates of change in fatigue and dyspnoea: People in the lower symptom severity groups (no symptoms or on heavy exertion) were more likely to report an increase in symptom severity at 6 months (38.8% vs.13% no change or 4.3% a decrease), likewise, patients who were on higher NYHA class at baseline were more likely to report a decrease (51.1%) or no change (57.9%) in symptom

severity at 6 months. Lower systolic blood pressure was associated with an increase in both fatigue and dyspnoea at 6 months (p value <0.01 for both).

Correlates of change in fatigue: People who did reported some change in fatigue severity were more likely to be treated with digitalis (31.9% no change vs. 37.3% decrease or 36.6% increase), while people who had a no change or an increase in fatigue severity were more likely to be treated with nitrates (22.1% vs. 31% no change or 28.5% increase).

Correlates of change dyspnoea: Patients who reported no change in fatigue severity were more likely to have a past history of angina (73.1% vs. 66.1% decrease or 69% increase) while history of intermittent claudication was associated with an increase (17.9% vs. 12% no change or 12.3% decrease) in dyspnoea.

Baseline characteristics according to change in symptom severity are summarised in Table 9-4 below.

Table 9-4 Baseline characteristics according to change in symptom severity.

	All patients (n=3548)	Change in fatigue				Change in dyspnoea			
		Unchanged (n=2463)	Decrease (n=625)	Increase (n=429)	P value	Unchanged (n=2507)	Decrease (n=667)	Increase (n=374)	P value
Group 1		319 (13.0%)	27 (4.3%)	178 (38.8%)		209 (8.3%)	18 (2.7%)	97 (25.9%)	
Group 2		1150 (46.7%)	172 (27.5%)	232 (50.5%)		1214 (48.4%)	178 (26.7%)	227 (60.7%)	
Group 3		994 (40.4%)	426 (68.2%)	49 (10.7%)	<0.0001	1084 (43.2%)	471 (70.6%)	50 (13.4%)	<0.0001
Age	72.94 ± 7.10	72.94 ± 7.15	72.48 ± 6.91	73.57 ± 7.04	0.0454	72.90 ± 7.16	72.66 ± 7.00	73.71 ± 6.86	0.0635
Female	757 (21.3%)	526 (21.4%)	137 (21.9%)	94 (20.5%)	0.8487	548 (21.9%)	132 (19.8%)	77 (20.6%)	0.4765
Race									
	3492 (98.4%)								
Caucasian	11 (0.3%)	2427 (98.5%)	610 (97.6%)	455 (99.1%)		2470 (98.5%)	653 (97.9%)	369 (98.7%)	
Black	31 (0.9%)	7 (0.3%)	3 (0.5%)	0 (0.0%)		6 (0.2%)	3 (0.4%)	2 (0.5%)	
Asian	14 (0.4%)	19 (0.8%)	9 (1.4%)	3 (0.7%)		20 (0.8%)	8 (1.2%)	3 (0.8%)	
Other		10 (0.4%)	3 (0.5%)	1 (0.2%)	0.4739	11 (0.4%)	3 (0.4%)	0 (0.0%)	0.6624
NYHA III/IV	1813 (51.1%)	1258 (51.1%)	362 (57.9%)	193 (42.0%)	0.0001	1250 (49.9%)	421 (63.1%)	142 (38.0%)	0.0001
LVEF (%)	28.67 ± 5.63	28.78 ± 5.62	28.57 ± 5.63	28.22 ± 5.68	0.1356	28.77 ± 5.56	28.60 ± 5.89	28.10 ± 5.64	0.0916
Systolic BP mm/Hg	124.23 ± 17.49	129.55 ± 16.60	127.21 ± 16.70	127.55 ± 17.45	0.0014	129.64 ± 16.52	127.05 ± 16.71	126.98 ± 18.03	0.0001
Heart Rate bpm	74.66 ± 10.97	71.41 ± 11.31	71.45 ± 11.05	72.23 ± 11.82	0.3617	71.55 ± 11.20	71.52 ± 11.42	71.35 ± 12.09	0.9523
BMI kg/m^2	26.14 ± 4.44	27.04 ± 4.38	26.92 ± 4.57	26.83 ± 4.40	0.5928	27.06 ± 4.37	26.93 ± 4.57	26.66 ± 4.41	0.2389
BMI<25 kg/m^2	1324 (34.7%)	206 (37.5%)	547 (33.4%)	571 (35.1%)		132 (39.2%)	590 (34.4%)	602 (34.0%)	
BMI ≥25 and <30 kg/m^2	1665 (43.6%)	243 (44.2%)	716 (43.7%)	706 (43/4%)		144 (42.7%)	738 (43.1%)	783 (44.3%)	
BMI ≥30 kg/m^2	830 (21.7%)	101 (18.4%)	377 (23.0%)	351 (21.6%)	0.1794	61 (18.1%)	386 (22.5%)	383 (21.7%)	0.2773
Years with heart failure	4.79 ± 5.28	4.28 ± 4.62	4.29 ± 4.83	4.08 ± 4.63	0.6913	4.26 ± 4.59	4.19 ± 4.83	4.30 ± 4.81	0.9293
Current Smoker	28 (9.9%)	228 (9.3%)	53 (8.5%)	40 (8.7%)	0.8035	227 (9.1%)	66 (9.9%)	28 (7.5%)	0.4296
MI	179 (63.5%)	1518 (61.6%)	350 (56.0%)	263 (57.3%)	0.0158	1539 (61.4%)	373 (55.9%)	220 (58.8%)	0.0327

Angina	196 (69.5%)	1792 (72.8%)	422 (67.5%)	317 (69.1%)	0.0179	1833 (73.1%)	441 (66.1%)	258 (69.0%)	0.0010
CABG/PCI	65 (23.0%)	661 (26.8%)	186 (29.8%)	140 (30.5%)	0.1354	680 (27.1%)	194 (29.1%)	113 (30.2%)	0.3322
Hypertension	167 (59.2%)	1488 (60.4%)	388 (62.1%)	264 (57.5%)	0.3126	1512 (60.3%)	409 (61.3%)	220 (58.8%)	0.7307
Diabetes	103 (36.5%)	687 (27.9%)	187 (29.9%)	131 (28.5%)	0.6005	697 (27.8%)	191 (28.6%)	118 (31.6%)	0.3193
Baseline atrial fibrillation/ flutter	74 (26.2%)	557 (22.6%)	154 (24.6%)	110 (24.0%)	0.5096	572 (22.8%)	164 (24.6%)	85 (22.7%)	0.6158
Stroke	46 (16.3%)	297 (12.1%)	86 (13.8%)	49 (10.7%)	0.2917	290 (11.6%)	90 (13.5%)	52 (13.9%)	0.2238
Intermittent Claudication	46 (16.3%)	301 (12.2%)	81 (13.0%)	68 (14.8%)	0.3010	301 (12.0%)	82 (12.3%)	67 (17.9%)	0.0056
Pacemaker	26 (9.2%)	311 (12.6%)	67 (10.7%)	50 (10.9%)	0.3023	289 (11.5%)	92 (13.8%)	47 (12.6%)	0.2660
ICD	8 (2.8%)	76 (3.1%)	25 (4.0%)	13 (2.8%)	0.4523	75 (3.0%)	26 (3.9%)	13 (3.5%)	0.4760
Cholesterol mmol/litre	5.06 ± 1.24	5.37 ± 1.06	5.33 ± 1.00	5.34 ± 1.10	0.5799	5.38 ± 1.06	5.30 ± 1.01	5.32 ± 1.10	0.1868
ApoB:ApoA-1 ratio	0.87 ± 0.27	0.87 ± 0.24	0.88 ± 0.25	0.87 ± 0.24	0.8710	0.87 ± 0.24	0.87 ± 0.25	0.87 ± 0.25	0.9441
ApoB g/L	1.21 ± 0.32	1.28 ± 0.30	1.26 ± 0.28	1.26 ± 0.30	0.3901	1.28 ± 0.30	1.25 ± 0.29	1.26 ± 0.30	0.1248
ApoA-1 g/L	1.43 ± 0.31	1.50 ± 0.27	1.49 ± 0.29	1.49 ± 0.29	0.5006	1.51 ± 0.27	1.49 ± 0.29	1.49 ± 0.30	0.3489
TSH mIU/L	2.53 ± 3.00	2.17 ± 4.05	2.32 ± 6.99	2.07 ± 1.88	0.6376	2.24 ± 5.20	2.02 ± 2.23	2.11 ± 1.76	0.5004
ALT IU/L	19.16 ± 67.41	17.71 ± 41.75	15.84 ± 11.56	18.12 ± 28.03	0.4766	17.67 ± 40.84	16.89 ± 22.64	17.66 ± 29.05	0.8860
LDL mmol/L	3.29 ± 1.01	3.56 ± 0.93	3.55 ± 0.87	3.52 ± 0.94	0.6752	3.57 ± 0.93	3.51 ± 0.89	3.52 ± 0.94	0.1921
Creatinine µmol/L	122.81 ± 31.45	116.20 ± 27.92	115.78 ± 27.83	117.55 ± 28.77	0.5586	115.71 ± 27.88	116.49 ± 27.98	120.02 ± 28.88	0.0210
NT-proBNP-- pmol/litre (median	386.9 [181.2, 847.8]	183.5 [82.5, 374.4]	195.4 [88.0, 383.5]	198.1 [99.0, 426.6]	0.0721	172.8 [79.7, 359.7]	214.3 [93.8, 413.5]	245.6 [125.0, 438.5]	0.0001
hs- CRP mg/litre (median)	5.7 [2.4, 13.7]	3.2 [1.5, 6.7]	3.7 [1.6, 8.0]	3.7 [1.6, 7.9]	0.0336	3.3 [1.6, 7.0]	3.4 [1.5, 7.5]	3.7 [1.5, 7.3]	0.6365
Co-enzyme Q_{10} mmol/L (median)	0.7 [0.5, 0.9]	0.8 [0.6, 1.0]	0.7 [0.5, 0.9]	0.7 [0.6, 1.0]	0.0753	0.8 [0.6, 1.0]	0.7 [0.5, 0.9]	0.7 [0.6, 1.0]	0.0085
Creatine Kinase UI/L (median)	39.5 [28.0, 60.0]	46.0 [33.0, 66.0]	44.0 [32.0, 60.0]	43.0 [32.0, 61.0]	0.0394	46.0 [33.0, 66.0]	43.0 [32.0, 60.0]	45.0 [32.0, 62.0]	0.0297
eGFR ml/min/1.73m^2	53.95 ± 15.39	55.93 ± 15.43	56.64 ± 15.19	55.45 ± 15.32	0.4204	56.19 ± 15.31	56.45 ± 15.36	53.90 ± 15.63	0.0187
Loop/thiazide diuretics	264 (93.6%)	2146 (87.1%)	542 (86.7%)	411 (89.5%)	0.3117	2178 (86.9%)	583 (87.4%)	339 (90.6%)	0.1235

ACE inhibitor or ARB	248 (87.9%)	2293 (93.1%)	580 (92.8%)	426 (92.8%)	0.9514	2322 (92.6%)	622 (93.3%)	356 (95.2%)	0.1852
MRAs	123 (43.6%)	978 (39.7%)	261 (41.8%)	191 (41.6%)	0.5377	1006 (40.1%)	265 (39.7%)	160 (42.8%)	0.584
Digitalis	118 (41.8%)	786 (31.9%)	233 (37.3%)	168 (36.6%)	0.0124	824 (32.9%)	239 (35.8%)	124 (33.2%)	0.3506
Anticoagulant	104 (36.9%)	924 (37.5%)	224 (35.8%)	181 (39.4%)	0.4804	925 (36.9%)	256 (38.4%)	148 (39.6%)	0.5238
Beta-blockers	189 (67.0%)	1866 (75.8%)	464 (74.2%)	327 (71.2%)	0.1117	1898 (75.7%)	488 (73.2%)	272 (72.7%)	0.2369
Nitrate	98 (34.8%)	764 (31.0%)	138 (22.1%)	131 (28.5%)	0.0001	761 (30.4%)	169 (25.3%)	103 (27.5%)	0.0313
Insulin	32 (11.3%)	185 (7.5%)	46 (7.4%)	40 (8.7%)	0.6445	189 (7.5%)	50 (7.5%)	32 (8.6%)	0.7785
Antiarrhythmic	46 (16.3%)	305 (12.4%)	70 (11.2%)	58 (12.6%)	0.6902	307 (12.2%)	80 (12.0%)	46 (12.3%)	0.9828

LVEF – left ventricular ejection fraction, NYHA – New York Heart Association functional class, BP –blood pressure, CABG/PCI – coronary artery bypass grafting/ percutaneous coronary intervention, ICD – implantable cardioverter defibrillator, MRA – Mineralocorticoid receptor antagonists, ACE – angiotensin converting enzyme, ARB – angiotensin II receptor blocker, TSH – thyroid stimulating hormone, NT-proBNP – N-terminal of the prohormone brain natriuretic peptide, CRP – – high-sensitivity C-reactive protein.
Mean and standard deviation (SD) for continuous variables (median and interquartile range [IQR] when appropriate) and percentage for categorical variables are presented.

Descriptive statistics for number of days from randomisation to the 6-month visit according to change in symptom severity are summarised in Table 9-5 and Table 9-6. There was no difference in the time between visits (randomisation and 6 months) among those who reported an increase, decrease or unchanged symptom severity.

Table 9-5 Days from randomisation to visit 6 according to change in fatigue

	Mean	SD	Median	P25	P75
No change	181.5	10.2	182	176	184
Decrease	181.2	12.2	182	175	184
Increase	182.9	13.4	182	177	187

Table 9-6 Days from randomisation to visit 6 according to change in dyspnoea

	Mean	SD	Median	P25	P75
No change	181.6	10.7	182	176	184
Decrease	181.3	11.1	182	176	184
Increase	182.9	12.8	182	177	186

9.2.1.2 Adjusted outcomes

Correlates of change of both fatigue and dyspnoea (see Tables Table 9-7 *and* Table 9-8*)*: Higher symptom severity at baseline was strongly associated with a higher risk of reporting a decrease of symptom severity at 6 months (fatigue: group 2 vs. 1 RR 2.02, 95% CI 1.23-3.25; 3 vs. 1 RR 11.01, 95% CI 6.35-19.05; dyspnoea: group 2 vs. 1 RR 1.23, 95% CI 1.22-4.07; 3 vs. 1 RR 11.49, 95% CI 5.97-22.07), with the opposite being true with higher symptom severity at baseline was associated with a lower risk of reporting an increase in symptoms after 6 months. History of angina at baseline was significantly associated with a lower risk of reporting a decrease in symptoms (fatigue RR 0.72, 95% CI 0.56-0.92; dyspnoea RR 0.63, 95% CI 0.50-0.80; p value <0.01 for both). History of coronary intervention (CABG/PCI) was associated with decrease in symptom severity (fatigue RR 1.47, 95% CI 1.13-1.90; dyspnoea RR 1.42, 95% CI 1.11-1.81). On the other hand, intermittent claudication was associated with a higher risk of reporting an increase in symptoms (fatigue RR 1.68. 95% CI 1.17-2.42; dyspnoea RR 2.18, 95% CI 1.50-3.16). Similarly, NYHA III/IV at baseline was associated with a higher risk of reporting worse symptoms at 6 months (fatigue RR 1.63, 95% CI 1.20-2.20; dyspnoea 1.86, 95% CI 1.29-2.67), as well as higher NT-proBNP values (fatigue RR 1.20, 95% CI 1.02-1.86; dyspnoea RR 1.32, 95% CI 1.12-1.54)

*Correlates of change in fatigue (*see Table 9-7*):* Higher systolic blood pressures were associated with a 12% lower risk for higher fatigue over 6 months. Patients on treatment with digitalis were more likely to report a decrease in fatigue over 6 months (RR 1.38, 95% CI 1.07-1.76, p value=0.01).

Table 9-7 Correlates of change in fatigue severity

	Decrease in fatigue			Increase in fatigue		
	RR	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
Fatigue 2 vs. 1	2.06	1.23, 3.45	0.006	0.26	0.19, 0.36	<0.001
Fatigue 3 vs. 1	11.01	6.35, 19.05	<0.001	0.04	0.02, 0.06	<0.001
Age	0.98	0.97, 1.00	0.032	1.01	0.99, 1.03	0.203
Female	0.91	0.69, 1.21	0.521	1.06	0.75, 1.50	0.738
LVEF %	0.31	0.04, 2.27	0.248	0.48	0.05, 4.92	0.536
NYHA III/IV	0.45	0.33, 0.61	<0.001	1.63	1.20, 2.20	0.002
Overweight	0.84	0.64, 1.09	0.183	1.24	0.91, 1.69	0.167
Obese	0.97	0.70, 1.33	0.834	1.14	0.77, 1.69	0.510
Systolic BP p/10 mmHg	0.93	0.86, 1.00	0.045	0.88	0.80, 0.96	0.003
Heart rate p/10 beats/min	0.97	0.88, 1.08	0.618	1.13	1.00, 1.28	0.053
Years w/heart failure	0.99	0.97, 1.02	0.489	1.00	0.98, 1.03	0.816
Myocardial Infarction	0.78	0.62, 0.99	0.044	0.84	0.63, 1.12	0.231
History of Diabetes	1.21	0.92, 1.58	0.167	0.99	0.71, 1.39	0.958
Stroke	1.10	0.80, 1.51	0.573	1.04	0.69, 1.58	0.847
Hypertension*	1.09	0.85, 1.39	0.493	1.17	0.88, 1.56	0.274
Baseline atrial fibrillation/flutter	0.94	0.68, 1.28	0.687	0.81	0.55, 1.19	0.285
History of angina*	0.72	0.56, 0.92	0.010	1.05	0.78, 1.42	0.731
Intermittent Claudication	0.96	0.69, 1.33	0.784	1.68	1.17, 2.42	0.005
CABG/PCI	1.47	1.13, 1.90	0.004	1.13	0.83, 1.54	0.426
Pacemaker	0.78	0.54, 1.11	0.169	0.64	0.42, 0.97	0.037
ICD	1.26	0.69, 1.33	0.449	0.53	0.24, 1.20	0.128
MRAs*	0.93	0.73, 1.17	0.527	1.23	0.93, 1.63	0.138
Loop/thiazide	0.85	0.60, 1.22	0.382	1.25	0.81, 1.94	0.315
Beta-blocker	0.90	0.69, 1.17	0.422	0.73	0.54, 0.99	0.046
Nitrate	0.67	0.51, 0.87	0.003	0.98	0.72, 1.33	0.889
Insulin	0.84	0.52, 1.35	0.480	1.23	0.72, 2.13	0.446
Antiarrhythmic	0.83	0.57, 1.21	0.328	1.30	0.87, 1.96	0.198
ACE inhibitor or ARB	0.81	0.53, 1.25	0.346	0.90	0.72, 1.33	0.889
Digoxin	1.38	1.07, 1.76	0.012	1.38	1.02, 1.86	0.035
Anticoagulant	0.91	0.70, 1.18	0.480	1.05	0.77, 1.43	0.751
TSH mIU/L	1.02	1.00, 1.04	0.124	1.01	0.98, 1.04	0.689
Log(NT-proBNP)	0.95	0.85, 1.06	0.392	1.20	1.04, 1.38	0.012
hs-CRP mg/litre	1.01	1.00, 1.01	0.159	1.00	0.99, 1.01	0.899
Alanine transaminase IU/L	1.00	0.99, 1.00	0.394	1.00	1.00, 1.00	0.521
Creatine kinase p/50	0.87	0.74, 1.03	0.106	0.79	0.64, 0.96	0.019
Creatinine µmol/L	1.00	1.00, 1.00	0.994	1.00	0.99, 1.00	0.159
Low density lipoprotein mmol/L	0.96	0.85, 1.09	0.529	0.95	0.82, 1.10	0.485

*Correlates of change in dyspnoea (*see Table 9-*8)*: Older age was associated with a 2% reduced risk of reporting a decrease in dyspnoea (RR 0.98, 95% CI 0.96-1.00, p value=0.01).

Table 9-8 Correlates of change in dyspnoea severity

	Decrease in dyspnoea			Increase in dyspnoea		
	RR	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
Dyspnoea 2 vs. 1	2.23	1.22, 4.07	0.009	0.25	0.18, 0.37	<0.001
Dyspnoea 3 vs. 1	11.49	5.97, 22.07	<0.001	0.04	0.02, 0.06	<0.001
Age	0.98	0.96, 1.00	0.013	1.01	0.99, 1.03	0.336
Female	0.92	0.70, 1.21	0.571	1.08	0.74, 1.56	0.698
LVEF %	1.02	0.15, 7.07	0.987	0.27	0.02, 3.38	0.310
NYHA III/IV	0.52	0.38, 0.73	<0.001	1.86	1.29, 2.67	0.001
Overweight	0.82	0.64, 1.06	0.126	1.04	0.74, 1.45	0.840
Obese	0.95	0.70, 1.28	0.723	1.02	0.67, 1.56	0.932
Systolic BP p/10 mmHg	0.95	0.88, 1.01	0.124	0.90	0.82, 0.99	0.034
Heart rate p/10 beats/min	0.92	0.83, 1.02	0.111	0.96	0.83, 1.10	0.564
Years w/heart failure	0.99	0.96, 1.01	0.243	1.00	0.97, 1.04	0.764
Myocardial Infarction	0.77	0.62, 0.97	0.028	0.90	0.66, 1.23	0.512
History of Diabetes	0.97	0.74, 1.26	0.823	1.23	0.87, 1.76	0.246
Stroke	1.13	0.82, 1.55	0.450	1.39	0.93, 2.07	0.113
Hypertension*	1.17	0.92, 1.48	0.196	1.23	0.90, 1.69	0.192
Baseline atrial fibrillation/flutter	0.84	0.62, 1.14	0.254	1.00	0.66, 1.50	0.984
History of angina*	0.63	0.50, 0.80	<0.0001	1.04	0.75, 1.45	0.799
Intermittent Claudication	0.83	0.60, 1.15	0.270	2.18	1.50, 3.16	<0.0001
CABG/PCI	1.42	1.11, 1.81	0.006	0.96	0.68, 1.34	0.802
Pacemaker	1.08	0.78, 1.50	0.622	1.11	0.72, 1.71	0.634
ICD	1.37	0.79, 2.40	0.264	1.06	0.48, 2.33	0.884
MRAs*	0.79	0.63, 0.99	0.044	1.19	0.88, 1.61	0.257
Loop/thiazide	0.83	0.59, 1.16	0.279	1.21	0.75, 1.98	0.437
Beta-blocker	0.85	0.66, 1.09	0.196	0.74	0.53, 1.04	0.083
Nitrate	0.80	0.62, 1.03	0.083	1.07	0.77, 1.49	0.689
Insulin	0.96	0.61, 1.51	0.849	0.97	0.52, 1.78	0.909
Antiarrhythmic	0.92	0.65, 1.31	0.652	0.88	0.55, 1.41	0.587
ACE inhibitor or ARB	1.15	0.74, 1.76	0.535	1.76	0.92, 3.37	0.088
Digoxin	1.22	0.96, 1.55	0.105	1.22	0.88, 1.70	0.223
Anticoagulant	1.01	0.79, 1.30	0.910	0.94	0.66, 1.32	0.732
TSH mIU/L	0.95	0.90, 1.01	0.088	1.00	0.97, 1.03	0.989
Log(NT-proBNP)	1.07	0.96, 1.19	0.200	1.32	1.12, 1.54	0.001
hs-CRP mg/litre	1.00	0.99, 1.01	0.987	1.00	0.99, 1.01	0.898
Alanine transaminase IU/L	1.00	0.99, 1.00	0.378	1.00	1.00, 1.00	0.527
Creatine kinase p/50	0.87	0.74, 1.02	0.092	0.85	0.69, 1.04	0.122
Creatinine µmol/L	1.00	1.00, 1.01	0.359	1.00	0.99, 1.01	0.854
Low density lipoprotein mmol/L	0.96	0.85, 1.08	0.469	0.97	0.83, 1.15	0.755

9.2.2 Change in symptom severity and outcomes

9.2.2.1 Unadjusted outcomes

Those reporting an increase in fatigue were significantly more likely to die from any cause than those reporting no change or decrease in fatigue severity (CV death – HR 1.50 95% CI [1.24, 1.82]; all-cause death-HR 1.45 95% CI [1.22, 1.72]). Increase in fatigue severity from baseline to six months was also associated with hospitalisation due to worsening heart failure (HR 1.42 95% CI [1.17, 1.72]) and the composite of cardiovascular death or heart failure hospitalisation (HR 1.42 95% CI [1.21, 1.65]). (Table 9-9 and Table 9-10 and Figure 9-1)

Similarly to fatigue, increase in dyspnoea was associated with fatal outcomes (CV death-HR 1.52 95% CI [1.24, 1.87]; all death-HR 1.40 95% CI [1.16, 1.69]), heart failure hospitalisation (HR 1.64 95% CI [1.35, 2.01]) and the composite outcome of CV death or heart failure hospitalisation HR 1.55 95% CI [1.31, 1.83]). (Table 9-10 and Figure 9-2)

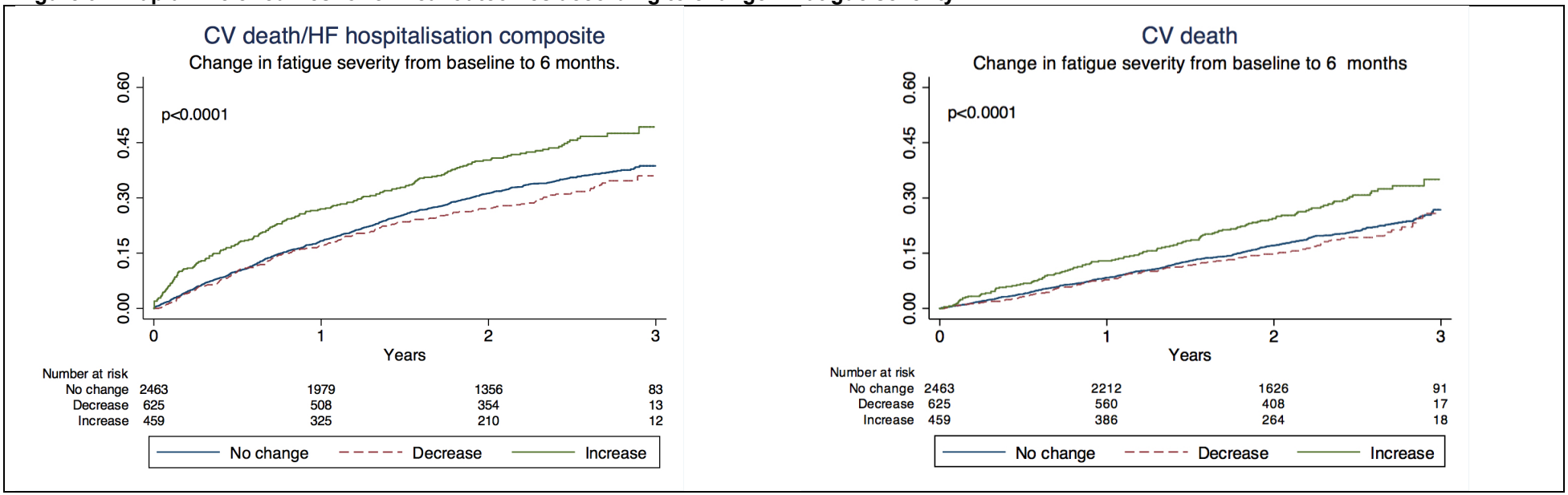
Table 9-9 Numbers of events by change in symptoms at 6 months

	Fatigue				Dyspnoea			
	Unchanged (n=2463)	**Decrease (n=625)**	**Increase (n=459)**	**P**	**Unchanged (n=2507)**	**Decrease (n=667)**	**Increase (n=374)**	**P**
Cardiovascular death/Heart failure hospitalisation	300/541 (34.2%)	64/126 (30.4%)	70/128 (43.1%)	<0.001	310/542 (34.0%)	69/137 (30.9%)	55/116 (45.7%)	<0.001
Cardiovascular death	502 (20.4%)	115 (18.4%)	130 (28.3%)	<0.001	521 (20.8%)	117 (17.5%)	109 (29.2%)	<0.001
Heart failure hospitalisation	541 (22.0%)	126 (20.2%)	128 (27.9%)	0.007	542 (21.6%)	137 (20.5%)	116 (31.0%)	<0.001
All-cause death	639 (25.9%)	153 (24.5%)	160 (34.9%)	<0.001	664 (26.5%)	160 (24.0%)	128 (34.3%)	0.001

Table 9-10 Unadjusted HR for change in symptom severity and outcomes

	CV Death/HF hospitalisation HR (95%CI)	**P**	**Cardiovascular death HR (95%CI)**	**P**	**HF hospitalisation HR (95%CI)**	**P**	**All-cause death HR (95%CI)**	**P**
Change in fatigue								
Decrease	0.88 (0.75, 1.03)	0.114	0.91 (0.74, 1.11)	0.339	0.91 (0.75, 1.10)	0.331	0.94 (0.79, 1.13)	0.522
Increase	1.42 (1.21, 1.65)	<0.001	1.50 (1.24, 1.82)	<0.001	1.42 (1.17, 1.72)	<0.001	1.45 (1.22, 1.72)	<0.001
Change in dyspnoea								
Decrease	0.90 (0.77, 1.05)	0.173	0.85 (0.69, 1.03)	0.103	0.94 (0.78, 1.13)	0.503	0.91 (0.76, 1.08)	0.274
Increase	1.55 (1.31, 1.83)	<0.001	1.52 (1.24, 1.87)	<0.001	1.64 (1.35, 2.01)	<0.001	1.40 (1.16, 1.69)	<0.001

Figure 9-1 Kaplan Meier curves for clinical outcomes according to change in fatigue severity



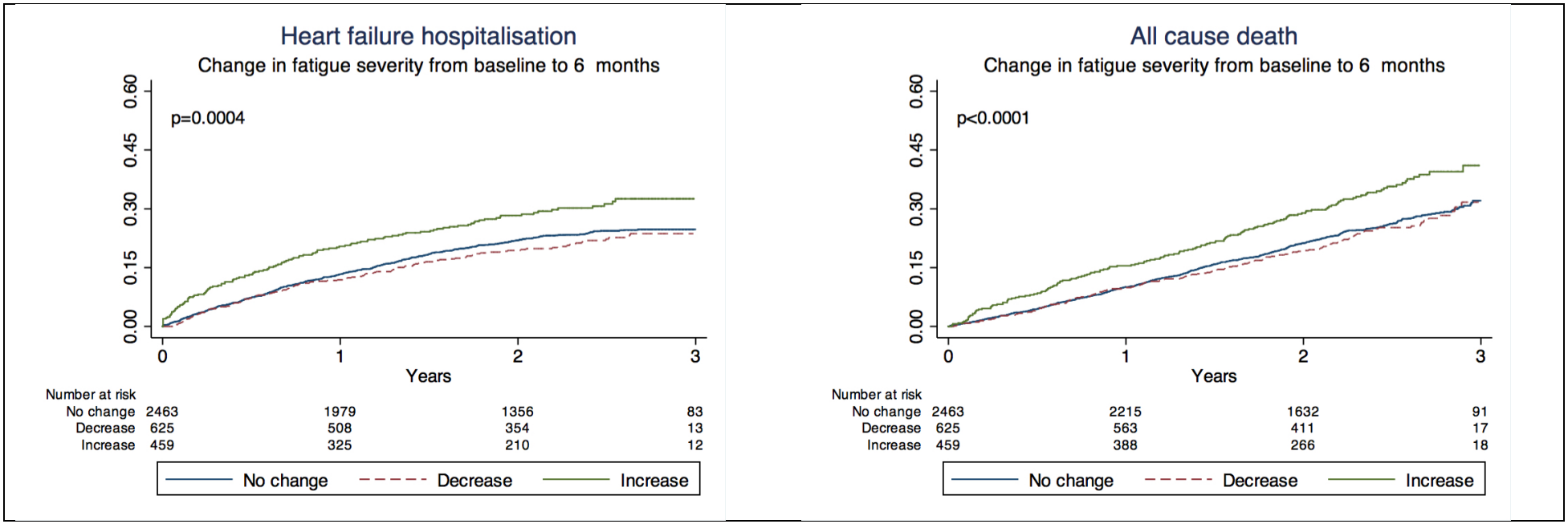
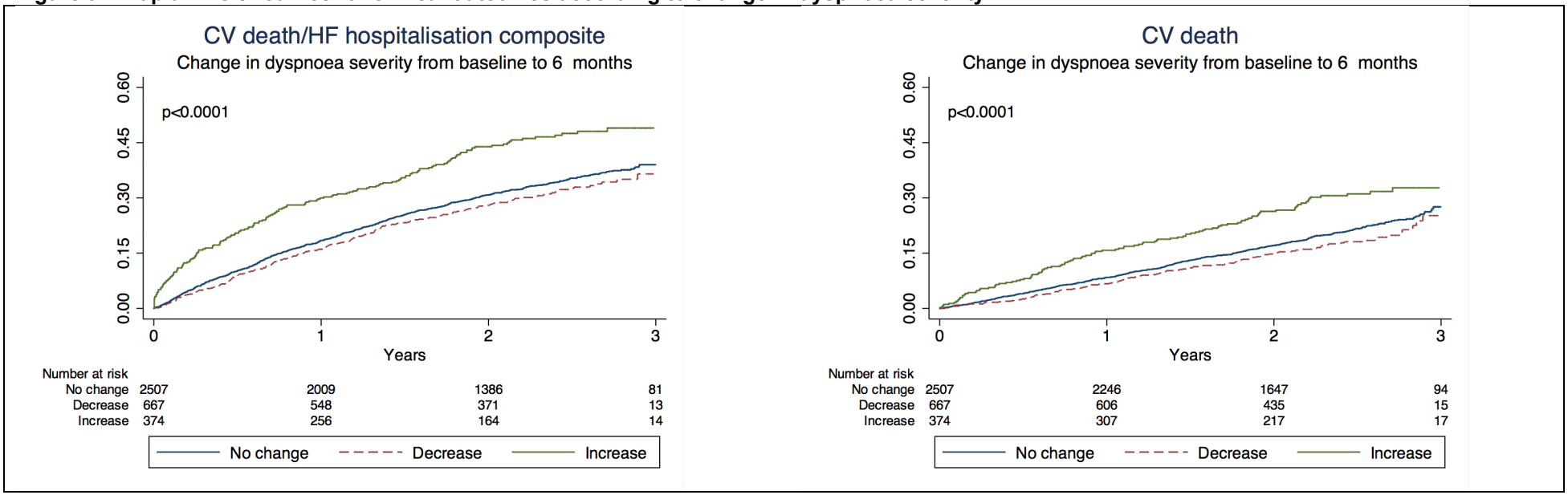
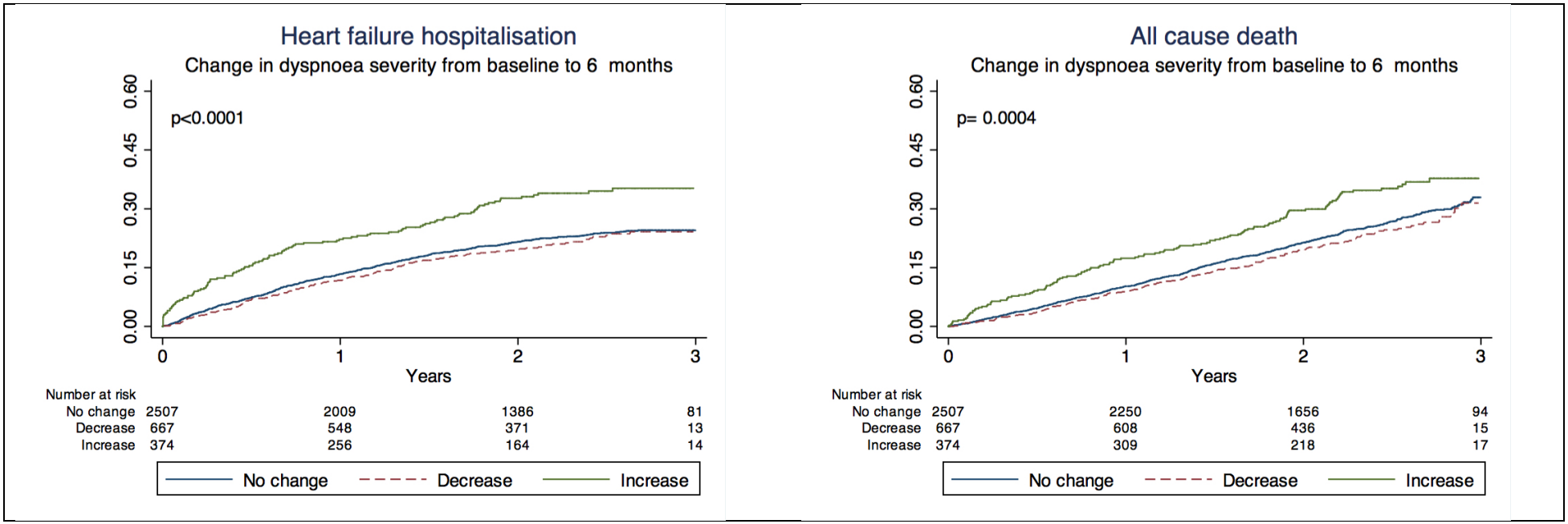

Heart failure hospitalisation
Change in fatigue severity from baseline to 6 months
p=0.0004
0.00
0.15
0.30
0.45
0.60
0
1
2
3
Years
Number at risk
No change 2463 1979 1356 83
Decrease 625 508 354 13
Increase 459 325 210 12
No change
Decrease
Increase
All cause death
Change in fatigue severity from baseline to 6 months
p<0.0001
0.00
0.15
0.30
0.45
0.60
0
1
2
3
Years
Number at risk
No change 2463 2215 1632 91
Decrease 625 563 411 17
Increase 459 388 266 18
No change
Decrease
Increase

Figure 9-2 Kaplan Meier curves for clinical outcomes according to change in dyspnoea severity




Heart failure hospitalisation
Change in dyspnoea severity from baseline to 6 months
p<0.0001
0.00
0.15
0.30
0.45
0.60
0
1
2
3
Years
Number at risk
No change 2507 2009 1386 81
Decrease 667 548 371 13
Increase 374 256 164 14
No change
Decrease
Increase
All cause death
Change in dyspnoea severity from baseline to 6 months
p= 0.0004
0.00
0.15
0.30
0.45
0.60
0
1
2
3
Years
Number at risk
No change 2507 2250 1656 94
Decrease 667 608 436 15
Increase 374 309 218 17
No change
Decrease
Increase

9.2.2.2 Adjusted outcomes

A total of 2525 (71.2%) patients were included in the complete-case analyses.

Adjustment for other variables (including NT-proBNP) seemed to strengthen the relationship between change in symptom severity and death (Table 9-11). Compared with those exhibiting no change in symptoms, those with an increase in either symptom had a higher hazard ratio for all outcomes (and the adjusted hazard ratio for these outcomes was lower in patients reporting a decrease in either fatigue or dyspnoea). Patients with an increase in dyspnoea had a significantly higher risk of the composite outcome of cardiovascular death or heart failure hospitalisation (HR 1.83 [95%CI 1.47, 1.97]) and the components of this composite (CV death HR 1.49 [95%CI 1.12, 1.97]; HF hospitalisation HR 2.39 [95%CI 1.84, 3.09]). The corresponding findings for increase in fatigue were: CV death or heart failure hospitalisation - HR 1.56 (1.27, 1.93); CV death- HR 1.48 (1.13, 1.92); and HF hospitalisation- HR 1.78 (1.38, 2.28).

Similarly, when compared with those reporting no change in symptom severity, patients with a decrease in symptom severity had lower risks for all outcomes, particularly for dyspnoea. Patients with a decrease in dyspnoea had approximately a 27% decrease in the risk of the composite outcome of CV death of HF hospitalisation (HR 0.73 95% CI [0.60, 0.88]) and similar rates for the components of the composite outcome (CV death HR 0.69 95% CI [0.53, 0.88; HF hospitalisation HR 0.72, 95% CI [0.57, 0.9]), with similar findings for fatigue. (Table 9-11)

Table 9-11 Adjusted HR for change in symptom severity and outcomes

	CV Death/HF hospitalisation HR (95%CI)	P	Cardiovascular death HR (95%CI)	P	HF hospitalisation HR (95%CI)	P	All-cause death HR (95%CI)	P
Change in fatigue								
Decrease	0.74 (0.61, 0.90)	0.002	0.73 (0.56, 0.94)	0.016	0.75 (0.59, 0.95)	0.019	0.74 (0.59, 0.93)	0.009
Increase	1.56 (1.27, 1.93)	<0.001	1.48 (1.13, 1.92)	0.004	1.78 (1.38, 2.28)	<0.001	1.45 (1.15, 1.82)	0.002
Change in dyspnoea								
Decrease	0.73 (0.60, 0.88)	0.001	0.69 (0.53, 0.88)	0.003	0.72 (0.57,0.91)	0.005	0.75 (0.60, 0.93)	0.008
Increase	1.83 (1.47, 2.29)	<0.001	1.49 (1.12, 1.97)	0.006	2.39 (1.84, 3.09)	<0.001	1.33 (1.03, 1.72)	0.029

Adjusted for: age, sex, NYHA class, LVEF, body mass index, systolic blood pressure, heart rate, smoking, myocardial infarction, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter, stroke, intermittent claudication, pacemaker and cardioverter-defibrillator implantations, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, and log NT-proBNP and baseline symptom severity.

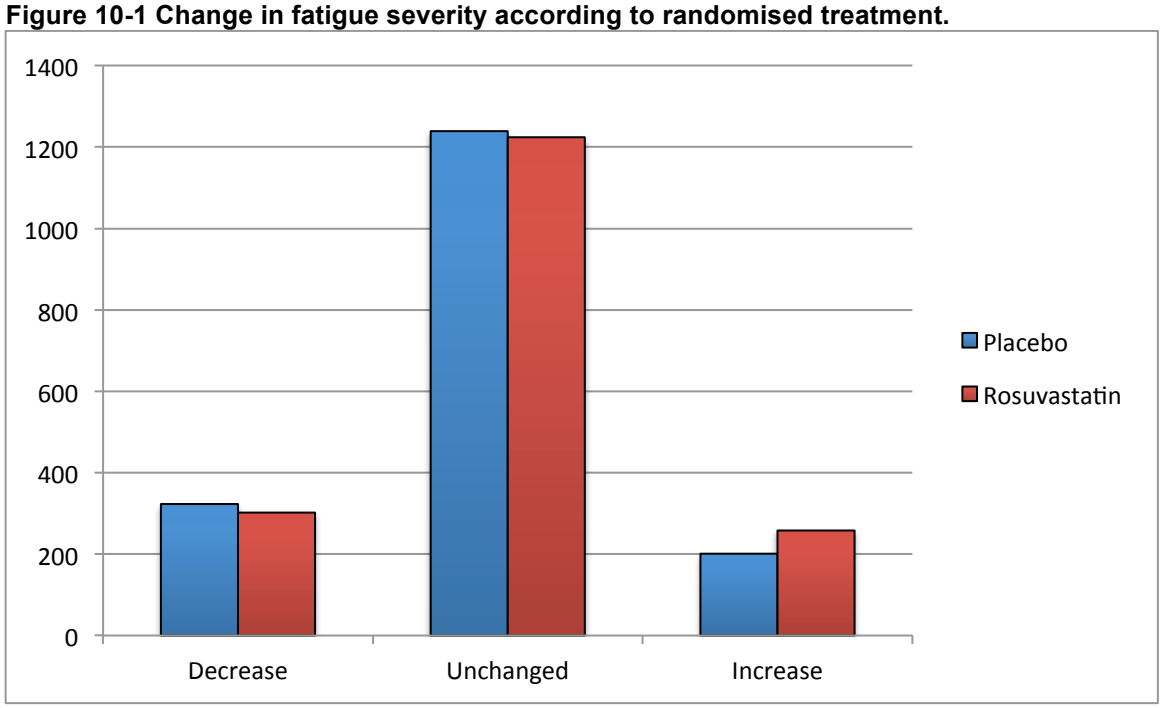
10 Impact of rosuvastatin on change in symptom severity

In this chapter I will examine whether treatment with 10 mg rosuvastatin had an impact on change in symptom severity from baseline to 6-month visit.

10.1 Results

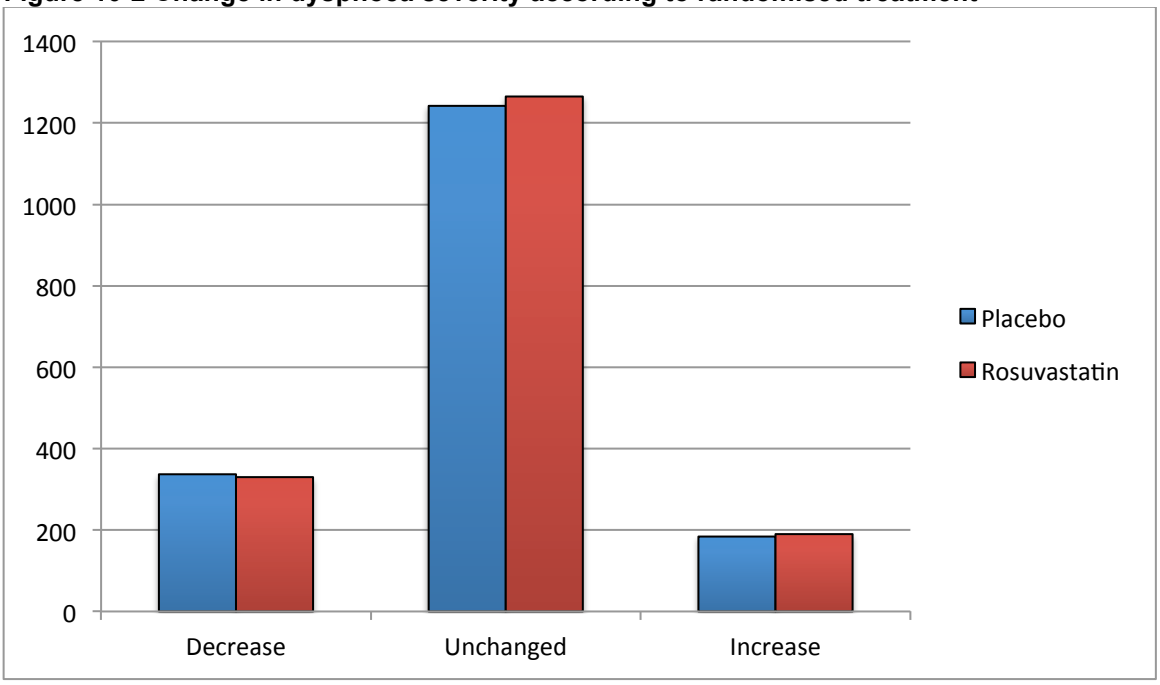
Compared to placebo, a small excess of patients (n=57 +3.1%) on rosuvastatin treatment reported an increase in fatigue over six months, and 21 (-1.4%) fewer reported improvement, most reported no change 1224 (68.6%) rosuvastatin and 1196 (70.3%) placebo-treated patients (p value= 0. 021). (Figure 10-1)

Figure 10-1 Change in fatigue severity according to randomised treatment.



For dyspnoea a similar trend is seen. When compared to placebo, a small excess of patients (n=14 +0.4%) on statin treatment reported an increase of symptom severity over six months, while fewer patients (n=7 -0.6%) reported an improvement of dyspnoea. Same as with fatigue, most patients reported no change: 1265 (70.9%) rosuvastatin and 1242 (70.5%) placebo-treated patients (p value= 0.885). (Figure 10-2)

Figure 10-2 Change in dyspnoea severity according to randomised treatment



Including randomised treatment in the multivariable model did not change the results obtained in the previous analysis. An increase in symptom severity at 6 months continued to be associated with fatal outcomes and hospitalisation due to worsening heart failure, and a decrease in symptom severity continued to be protective of any outcome (Table 10-1). Treatment with rosuvastatin was not a significant predictor of any of the outcomes analysed at the significance level that we are considering.

Table 10-1 Adjusted HR for change in symptom severity and outcomes: -including randomised treatment

	CV Death/HF hospitalisation HR (95%CI)	P	Cardiovascular death HR (95%CI)	P	HF hospitalisation HR (95%CI)	P	All-cause death HR (95%CI)	P
Change in fatigue								
Decrease	0.73 (0.60, 0.89)	0.002	0.73 (0.56, 0.95)	0.017	0.74 (0.58, 0.94)	0.014	0.74 (0.59, 0.93)	0.009
Increase	1.58 (1.29, 1.95)	<0.001	1.47 (1.13, 1.91)	0.004	1.82 (1.42, 2.34)	<0.001	1.44 (1.14, 1.82)	0.002
Change in dyspnoea								
Decrease	0.73 (0.60, 0.88)	0.001	0.69 (0.53, 0.88)	0.003	0.72 (0.57, 0.91)	0.005	0.75 (0.60, 0.93)	0.008
Increase	1.84 (1.48, 2.30)	<0.001	1.48 (1.12, 1.97)	0.007	2.41 (1.86, 3.12)	<0.001	1.33 (1.03, 1.72)	0.030

Adjusted for: age, sex, NYHA class, LVEF, body mass index, systolic blood pressure, heart rate, smoking, myocardial infarction, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter, stroke, intermittent claudication, pacemaker and cardioverter-defibrillator implantations, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, and log NT-proBNP, baseline symptom severity and randomised treatment

10.2 Summary of results

I found that a limited number of variables (lower symptom severity at baseline, higher NT-proBNP, intermittent claudication and NYHA class III/IV) were independently associated with a higher risk of worsening symptoms after 6 months, while history of angina was inversely associated with an increase in symptoms. Statin treatment was not associated with change in symptoms over time, however a trend is evident where a small proportion statin-treated patients are more likely to report worsening of fatigue. The results I obtained from this cohort mirror the results from my previously published paper looking at the impact of statin treatment on fatigue in patients with heart failure which was done at the same time point (randomisation visit). (269) In said publication the entire spectrum of LVEF (n=5010) was analysed.

Although most patients reported no change in symptoms over time, worsening symptoms were associated with an increased risk of adverse outcomes (both fatal and non-fatal), while a decrease in symptoms over time was associated with a lower risk of adverse outcomes. Treatment with rosuvastatin was not a significant predictor of any of the outcomes analysed.

11 Analyses on PARADIGM-HF

In this section I will present results from analyses performed on 8399 patients enrolled in the PARADIGM-HF trial.

11.1 Symptoms on effort

Of the 8399 patients randomised in PARADIGH-HF, 8382 had an observation for fatigue on effort at randomisation visit, out of which, 4343 (51.8%) reported having fatigue on effort, while 8383 had record for dyspnoea at randomisation, with 7207 (86%) reporting dyspnoea on effort and only 309 (3.7%) dyspnoea at rest. Due to small numbers, dyspnoea on rest was not analysed.

Overall, 4068 (48.5%) of the patients reported some level of fatigue and dyspnoea, while only 901 (11%) reported not having either fatigue or dyspnoea on effort. Table 11-1

Table 11-1 Cross-tabulation between symptoms on effort at randomisation: PRADIGM-HF

	Dyspnoea		
Fatigue	**No Dyspnoea**	**Dyspnoea on effort**	**Total**
No fatigue	901 (10.8%)	3138 (37.4%)	4093 (48.2%)
Fatigue on effort	275 (3.3%)	4068 (48.5%)	4343 (51.8%)
Total	1176 (14.0%)	7206 (86.0%)	8382(100%)[3]

[3] Percentages in brackets represent cell percentages (i.e. 8382 is the denominator).

Table 11-2

Table 11-3 show the distribution of fatigue and dyspnoea within each NHYA class.

Table 11-2 Tabulation between fatigue and NYHA class at baseline

Fatigue status	NYHA class at baseline				
	I	II	III	IV	Total
No fatigue	348 (8.6%)	3242 (80.3%)	445 (11.0%)	4 (0.1%)	4039
Fatigue on effort	41 (0.9%)	2673 (61.2%)	1573 (36.2%)	56 (1.3%)	4343
Total	389 (4.6%)	5915 (70.6%)	2018 (24.1%)	60 (0.7%)	8382

Table 11-3 Tabulation between dyspnoea and NYHA class at baseline

Dyspnoea status	NYHA class at baseline				
	I	II	III	IV	Total
No dyspnoea	271 (23.0%)	835 (71.0%)	67 (5.7%)	3 (0.3%)	1176
Dyspnoea on effort	118 (1.6%)	5081 (70.5%)	1951 (27.1%)	57 (0.8%)	7207
Total	389 (4.6%)	5915 (70.6%)	2018 (24.1%)	60 (0.7%)	8383

11.2 Correlates of symptoms on effort

Baseline characteristics according to symptom status at randomisation are summarised in Table 11-4.

11.2.1.1 Unadjusted outcomes

In summary, patients who had symptoms on effort (fatigue or dyspnoea) were more likely to be older (on average 1 year older than those without symptoms), Caucasian (fatigue 72%; dyspnoea 68%), female (fatigue 25% vs. 19%; dyspnoea 22% vs. 19%), were less likely to have an implanted cardioverter defibrillator (fatigue 14% vs. 16%; dyspnoea 14% vs. 20%), were more likely to be NYHA class III/IV (fatigue 37% vs. 11%; dyspnoea 28% vs. 6%), had slightly higher systolic blood pressures (both systolic and diastolic) and LVEF. They also had a longer history with heart failure (more than one year since diagnosis), were more likely to have a history of COPD (fatigue 15% vs. 11%; dyspnoea 13% vs. 10%), renal disease (fatigue 20% vs. 15%; dyspnoea 18% vs. 14%), hypertension (fatigue 73%

vs. 68%; dyspnoea 71% vs. 67%), stable angina (fatigue 28% vs. 14%; dyspnoea 23% vs. 14%), myocardial infarction (fatigue 45% vs. 41%; dyspnoea 44% vs. 37%). Patients with symptoms were also more likely to have a history of atrial fibrillation or to have atrial fibrillation on baseline ECG and more commonly had heart failure of ischaemic aetiology (fatigue 63% vs. 57%; dyspnoea 61% vs. 54%). Not surprisingly, higher Kansas City Cardiomyopathy Questionnaire summary scores were associated with no symptoms at randomisation. Patients treated with anticoagulants, diuretics or digoxin were more likely to be symptomatic.

Patients who reported fatigue on effort were heavier (approximately 2 kg heavier or 1 unit in BMI than those without fatigue), had slightly higher heart rate, and were more likely to be current smokers or have a prior hospitalisation due to heart failure (65% vs. 60%). They were also more likely to have a history of unstable angina (13% vs. 10%) or stroke (10% vs. 8%). Patients who reported drinking 1-2 alcoholic drinks per day (vs. less than one drink a day) were also more likely to report fatigue on effort. Higher NT-ProBNP levels were also associated with fatigue on effort, as was use of aspirin, MRAs and digoxin.

Patients who reported having dyspnoea on effort were less likely to have a history of asthma (4% vs. 5%).

Table 11-4 Baseline characteristics according to symptom status

	All patients (n=8399)	No fatigue on effort (n=4039)	Fatigue on effort (n=4343)	p value	No dyspnoea on effort (n=1176)	Dyspnoea on effort (n=7206)	p value
Age	63.79 ± 11.39	63.41 ± 11.41	64.16 ± 11.34	0.003	61.67 ± 11.78	64.15 ± 11.28	<0.001
Race				<0.001			<0.001
Caucasian	5544 (66.0%)	2415 (59.8%)	3119 (71.8%)		625 (53.1%)	4909 (68.1%)	
Black	428 (5.1%)	279 (6.9%)	147 (3.4%)		124 (10.5%)	302 (4.2%)	
Asian	1509 (18.0%)	844 (20.9%)	661 (15.2%)		324 (27.6%)	1182 (16.4%)	
Other	918 (80.9%)	501 (12.4%)	416 (9.6%)		103 (8.8%)	814 (11.3%)	
Region				<0.001			<0.001
North America	602 (7.2%)	284 (7.0%)	316 (7.3%)		148 (12.6%)	452 (6.3%)	
Latin America	1433 (17.1%)	933 (23.1%)	498 (11.5%)		206 (17.5%)	1225 (17.0%)	
Western Europe	2051 (24.45)	1185 (29.3%)	861 (19.8%)		341 (29.0%)	1705 (23.7%)	
Central Europe	2826 (33.7%)	804 (19.9%)	2019 (46.5%)		159 (13.5%)	2664 (37.0%)	
Asia-Pacific	1487 (17.7%)	833 (20.6%)	649 (14.9%)		322 (27.4%)	1161 (16.1%)	
Female	1832 (21.8%)	750 (18.6%)	1082 (24.9%)	<0.001	221 (18.8%)	1611 (22.4%)	0.006
ICD (including CRT)	1243 (14.8%)	651 (16.2%)	590 (13.6%)	<0.001	230 (19.6%)	1011 (14.0%)	<0.001
Weight (kg)	80.65 ± 19.08	79.56 ± 18.59	81.65 ± 19.49	<0.001	79.79 ± 19.41	80.78 ± 19.03	0.099
Body mass index (kg/m^2)	28.17 ± 5.52	27.84 ± 5.33	28.47 ± 5.68	<0.001	27.85 ± 5.57	28.22 ± 5.51	0.036
BMI <25 kg/m^2	2421 (28.9%)	1229 (30.5%)	1188 (27.4%)		366 (31.2%)	2052 (28.5%)	
BMI ≥25 and <30 kg/m^2	13249 (38.7%)	1607 (39.8%)	1635 (37.7%)		453 (38.6%)	2789 (38.7%)	
BMI ≥ 30 kg/m^2	2719 (32.4%)	1198 (29.7%)	1515 (34.9%)	<0.001	354 (30.2%)	2359 (32.8%)	0.099
NYHA class				<0.001			<0.001
I	389 (4.6%)	348 (8.6%)	41 (0.9%)		271 (23.0%)	118 (1.6%)	
II	5919 (70.6%)	3242 (80.3%)	2673 (61.5%)		835 (71.0%)	5081 (70.5%)	
III	2018 (24.1%)	445 (11.0%)	1573 (36.2%)		67 (5.7%)	1951 (27.1%)	
IV	60 (0.72%)	4 (0.1%)	56 (1.3%)		3 (0.3%)	57 (0.8%)	

Heart rate (bmp)	72.35 ± 12.01	71.65 ± 11.78	73.03 ± 12.19	<0.001	71.72 ± 11.90	72.47 ± 12.03	0.048
Systolic blood pressure (mm/Hg)	121.38 ± 15.32	120.73 ± 15.87	122.00 ± 14.76	<0.001	119.69 ± 15.75	121.66 ± 15.23	<0.001
Diastolic blood pressure (mm/Hg)	73.59 ± 10.08	72.96 ± 10.23	74.19 ± 9.90	<0.001	72.69 ± 10.46	73.74 ± 10.01	<0.001
Pulse pressure (mm/Hg)	42.80 ± 12.47	47.77 ± 12.89	47.81 ± 12.07	0.880	47.01 ± 12.99	47.92 ± 12.38	0.020
Current smoker	1208 (14.4%)	536 (13.3%)	669 (15.4%)	0.005	163 (13.9%)	1043 (14.5%)	0.580
LVEF (%)	29.49 ± 6.22	29.13 ± 6.26	29.82 ± 6.16	<0.001	28.32 ± 6.49	29.68 ± 6.15	<0.001
Medical history							
Prior heart failure hospitalisation	5274 (62.8%)	2426 (60.1%)	2838 (65.3%)	<0.001	764 (65.0%)	4501 (62.5%)	0.098
Time since diagnosis of heart failure				0.003			0.003
≤1 year	2523 (30.0%)	1283 (31.8%)	1234 (28.4%)		403 (34.3%)	2115 (29.3%)	
1-5 years	3232 (38.5%)	1502 (37.2%)	1721 (39.6%)		425 (36.1%)	2798 (38.8%)	
≥5 years	2644 (31.5%)	1254 (31.0%)	1388 (32.0%)		348 (29.6%)	2294 (31.8%)	
Asthma	314 (3.7%)	157 (3.9%)	156 (3.6%)	0.476	61 (5.2%)	252 (3.5%)	0.005
COPD	1080 (12.9%)	445 (11.0%)	632 (14.6%)	<0.001	113 (9.6%)	964 (13.4%)	<0.001
Cancer	413 (4.95)	204 (5.1%)	208 (4.8%)	0.580	47 (4.0%)	365 (5.1%)	0.116
Renal disease	1453 (17.3%)	592 (14.7%)	853 (19.6%)	<0.001	167 (14.2%)	1279 (17.7%)	0.003
Hypertension	5940 (70.75)	2746 (68.0%)	3183 (73.3%)	<0.001	783 (66.6%)	5147 (71.4%)	<0.001
Diabetes	2896 (34.5%)	1386 (34.3%)	1516 (34.9%)	0.570	376 (32.0%)	2527 (35.1%)	0.039
Unstable angina	970 (11.6%)	401 (9.9%)	565 (13.0%)	<0.001	120 (10.2%)	846 (11.7%)	0.127
Stable angina	1794 (21.4%)	569 (14.1%)	1219 (28.1%)	<0.001	166 (14.1%)	1622 (22.5%)	<0.001
Myocardial Infarction	3634 (43.35)	1662 (41.1%)	1963 (45.2%)	<0.001	440 (37.4%)	3185 (44.2%)	<0.001
PCI	1801 (21.4%)	892 (22.1%)	903 (20.8%)	0.150	280 (23.8%)	1515 (21.0%)	0.031
CABG	1303 (15.5%)	617 (15.3%)	682 (15.7%)	0.589	171 (14.5%)	1128 (15.7%)	0.3291
History of AF	3091 (36.8%)	1297 (32.1%)	1787 (41.1%)	<0.001	346 (29.4%)	2738 (38.0%)	<0.001
AF on baseline ECG	2036 (24.2%)	803 (19.9%)	1229 (28.3%)	<0.001	201 (17.1%)	1831 (25.4%)	<0.001

Stroke	735 (8.6%)	306 (7.6%)	418 (9.6%)	<0.001	86 (7.3%)	639 (8.9%)	0.079
Ischaemic aetiology	5036 (60.0%)	2298 (56.9%)	2725 (62.7%)	<0.001	639 (54.3%)	4385 (60.8%)	<0.001
TIA	272 (3.2%)	117 (2.9%)	152 (3.5%)	0.118	28 (2.4%)	241 (3.3%)	0.082
Coronary heart disease	4585 (54.6%)	2012 (49.8%)	2563 (59.0%)	<0.001	540 (45.9%)	4036 (56.0%)	<0.001
Clinically significant valvular heart disease	604 (7.2%)	267 (6.6%)	336 (7.7%)	0.046	79 (6.7%)	524 (7.3%)	0.496
Abdominal aortic aneurism	110 (1.3%)	51 (1.3%)	58 (1.3%)	0.769	14 (1.2%)	95 (1.3%)	0.721
Renal artery stenosis	34 (0.4%)	16 (0.4%)	17 (0.4%)	0.973	6 (0.5%)	27 (0.4%)	0.491
Intermittent claudication	392 (4.7%)	167 (4.1%)	224 (5.2%)	0.0265	42 (3.6%)	350 (4.9%)	0.053
Lower limb revascularisation	148 (1.8%)	74 (1.8%)	74 (1.7%)	0.656	21 (1.8%)	127 (1.8%)	0.955
Lower limb stenosis documented by imaging	236 (2.8%)	107 (2.6%)	129 (3.0%)	0.375	31 (2.6%)	205 (2.8%)	0.689
KCCQ clinical summary score	75 ± 19.32	82.09 ± 16.87	70.50 ± 19.71	<0.001	84.33 ± 16.93	74.68 ± 19.34	<0.001
1-2 drinks (alcohol) per day	983 (11.7%)	511 (12.7%)	470 (10.8%)	0.009	137 (11.6%)	844 (11.7%)	0.952
Medication							
ACE inhibitors	6532 (77.8%)	3080 (76.3%)	3436 (79.1%)	0.002	898 (76.4%)	5619 (78.0%)	0.220
ARBs	1892 (22.5%)	969 (24.0%)	922 (21.2%)	0.003	276 (23.5%)	1615 (22.4%)	0.420
MRAs	4671 (55.6%)	2145 (53.15)	2518 (58.0%)	<0.001	643 (54.7%)	4021 (55.8%)	0.475
Beta-blocker	7811 (93.0%)	3753 (92.9%)	4043 (93.1%)	0.7560	1091 (92.8%)	6706 (93.1%)	0.730
Digoxin	2539 (30.2%)	1124 (27.85)	1414 (32.6%)	<0.001	3169 (26.9%)	2222 (30.8%)	0.006
Anticoagulant	2685 (32.0%)	1158 (28.7%)	1523 (35.1%)	<0.001	300 (25.5%)	2381 (33.0%)	0.0001
Aspirin	4349 (51.8%)	2172 (53.8%)	2166 (49.9%)	<0.001	626 (53.2%)	3713 (51.5%)	0.276
Adenosine diphospate antagonist	1260 (15.0%)	608 (15.1%)	649 (14.9%)	0.888	182 (15.5%)	1075 (14.9%)	0.618
Lipid lowering	4729 (56.3%)	2307 (57.1%)	2413 (55.6%)	0.151	640 (54.4%)	4081 (56.6%)	0.158
Diuretics	6738 (80.2%)	3145 (77.9%)	3582 (82.5%)	<0.001	835 (71.0%)	5893 (81.8%)	<0.001
ACE inhibitors or ARB	8379 (99.8%)	4028 (99.7%)	4334 (99.8%)	0.542	1168 (99.3%)	7195 (99.8%)	0.001
Laboratories							

NT-proBNP -pmol/litre (median)	1615 [888, 3231]	1557.5 [879.0, 3024.0]	1669.0 [903.0, 3431.0]	0.007	1568.0 [888.0, 3202.0]	1620.0 [888.0, 3234.0]	0.806
Haemoglobin A1C %	6.5 ± 1.4	6.5 ± 1.4	6.6 ± 1.4	0.042	6.5 ± 1.4	6.6 ± 1.4	0.079
Estimated GFR (mL/min/1.73m^2)	67.7 ± 20.11	68.04 ± 20.15	67.40 ± 20.04	0.149	68.61 ± 19.98	67.56 ± 20.11	0.095
Creatinine (umol/L)	99.31 ± 26.32	99.97 ± 25.88	98.64 ± 26.71	0.021	100.12 ± 25.26	99.15 ± 26.49	0.241
Haemoglobin g/L	139.4 ± 16.0	139.5 ± 16.0	139.3 ± 16.0	0.623	139.0 ± 16.3	139.4 ± 16.0	0.392

LVEF – left ventricular ejection fraction, NYHA – New York Heart Association functional class, BMI – body mass index BP – blood pressure, CABG/PCI – coronary artery bypass grafting/ percutaneous coronary intervention, ICD – implantable cardioverter defibrillator, LDL – low density lipoprotein, NT-proBNP – N-terminal of the prohormone brain natriuretic peptide, hs-CRP – high-sensitivity C-reactive protein, TSH – thyroid stimulating hormone, ACE – angiotensin converting enzyme, ARB – angiotensin II receptor blocker, MRA – Mineralocorticoid receptor antagonist.

Mean and standard deviation (SD) for continuous variables and percentage for categorical variables are presented.

11.2.2 Multivariate analysis

All available baseline characteristics were included in the model (except for troponin as >75% of the patients were missing a baseline troponin value). A logistic regression adjusted for all variables in Table 11-5 was run for fatigue and then again for dyspnoea. Caucasian race and the region of Western Europe were used as reference.

A total of 7,326 patients were included in the analysis mostly due to missing Kansas City Cardiomyopathy clinical summary scores (776 missing observations) and haemoglobin levels at randomisation (274 missing observations).

Correlates with both fatigue and dyspnoea on effort: People from Central Europe were more likely than those from Western Europe to report symptoms on effort (fatigue OR 2.41 95% CI [2.07, 2.81]; dyspnoea OR 2.19 [1.72, 2.80]). Again, not surprisingly, higher KCCQ summary scores were associated with a lower risk of reporting symptoms (2% lower risk for both fatigue and dyspnoea). Similarly, higher NYHA class was associated with a higher risk of reporting symptoms on effort, with the association being stronger for dyspnoea than for fatigue.

Correlates with fatigue only: Female sex was associated with a 33% higher risk of reporting fatigue on effort (95% CI 1.09-1.63; p value <0.01). People from Latin America were 35% less likely to report fatigue than those from Western Europe (95% CI 0.52-0.81, p value <0.01); the were also less likely to have a history of hypertension (OR 0.82 [0.72, 0.93]) but more likely to have a history of stable angina (OR 1.48 [1.28, 1.71]. People with a normal BMI (<25 kg/m^2) were less likely to report fatigue on effort.

Correlates with dyspnoea only: Only diuretic use was uniquely associated with dyspnoea (OR 1.56, 95% CI [1.29, 1.87] p value<0.01.

Table 11-5 Correlates of symptoms

	Fatigue on effort		Dyspnoea on effort	
	OR (95% CI)	**p value**	**OR (95% CI)**	
Age p/10 years	0.99 (0.93,1.06)	0.802	1.00 (0.94, 1.13)	0.482
Female	1.33 (1.09, 1.63)	0.005	1.10 (0.81, 1.49)	0.542
Race				
Black	0.81 (0.61,1.06)	0.126	0.61 (0.47, 0.90)	0.009
Asian	1.28 (0.69, 2.35)	0.429	1.99 (0.72, 5.48)	0.182
Other	1.88 (1.49, 2.36)	<0.001	1.31 (0.95, 1.80)	0.094
Region				
North America	1.67 (1.34, 2.08)	<0.001	0.61 (0.46, 0.80)	<0.001
Latin America	0.65 (0.52, 0.81)	<0.001	1.39 (1.05, 1.83)	0.020
Central Europe	2.41 (2.07, 2.81)	<0.001	2.19 (1.72, 2.80)	<0.001
Asia-Pacific	1.27 (0.69, 2.35)	0.450	0.65 (0.23, 1.79)	0.323
Pacemaker	1.06 (0.85, 1.32)	0.614	1.10 (0.77, 1.57)	0.584
ICD/CRT	0.84 (0.65, 1.08)	0.168	0.71 (0.48, 1.03)	0.074
Weight (kg)	1.00 (1.00, 1.01)	0.321	1.00 (0.99, 1.01)	0.922
BMI (kg/m^2)	0.98 (0.96, 1.01)	0.142	0.98 (0.95, 1.01)	0.152
KCCQ clinical summary score	0.98 (0.97, 0.98)	<0.001	0.98 (0.98, 0.99)	<0.001
1-2 drinks per day	0.96 (0.82, 1.13)	0.659	1.12 (0.88, 1.43)	0.341
NYHA functional class				
NYHA II	4.45 (3.10, 6.38)	<0.001	12.11 (9.26, 15.85)	<0.001
NYHA III	11.38 (7.77, 16.66)	<0.001	37.68 (25.60, 55.52)	<0.001
NYHA IV	33.46 (9.69, 115.53)	<0.001	22.14 (5.11, 95.92)	<0.001
Heart rate p/10 bpm	1.00 (0.95, 1.04)	0.853	0.98 (0.92, 1.05)	0.662
SBP p/10 mmHg	0.98 (0.95, 1.02)	0.414	1.04 (0.98, 1.09)	0.209
Current smoker	1.18 (1.01, 1.37)	0.040	0.93 (0.74, 1.17)	0.530
LVEF (%)	1.00 (0.99, 1.01)	0.969	1.01 (1.00, 1.02)	0.093
Prior HF hospitalisation	1.01 (0.91, 1.13)	0.813	0.74 (0.63, 0.87)	<0.001
Years since HF diagnosis				
1-5 years	0.97 (0.85, 1.10)	0.618	1.04 (0.86, 1.26)	0.690
>5 years	0.90 (0.78, 1.04)	0.141	1.00 (0.81, 1.23)	0.990
Past medical history				
Asthma	0.85 (0.64, 1.11)	0.225	0.72 (0.50, 1.02)	0.068
COPD	1.02 (0.87, 1.20)	0.775	1.31 (1.01, 1.70)	0.043
Cancer	1.06 (0.83, 1.37)	0.655	1.64 (1.13, 2.40)	0.010
Renal disease	1.20 (1.03, 1.40)	0.021	0.95 (0.75, 1.20)	0.648
Hypertension	0.82 (0.72, 0.93)	0.002	0.90 (0.74, 1.08)	0.241
Diabetes	0.91 (0.79, 1.04)	0.167	1.18 (0.96, 1.45)	0.109
Unstable angina	1.08 (0.91, 1.28)	0.386	0.90 (0.69, 1.16)	0.414
Stable angina	1.48 (1.28, 1.71)	<0.001	1.07 (0.85, 1.34)	0.582
Myocardial infarction	1.04 (0.89, 1.21)	0.650	1.19 (0.94, 1.50)	0.143
Coronary revascularisation	0.99 (0.86, 1.15)	0.933	0.77 (0.61, 0.96)	0.019
History of AF	0.90 (0.76, 1.07)	0.250	0.98 (0.76, 1.26)	0.874
AF on baseline ECG	1.13 (0.93, 1.37)	0.203	1.04 (0.78, 1.40)	0.770
Stroke	1.02 (0.84, 1.23)	0.849	0.94 (0.70, 1.26)	0.686

Ischaemic aetiology of HF	0.85 (0.72, 1.01)	0.072	0.84 (0.65, 1.07)	0.162
TIA	1.24 (0.92, 1.65)	0.154	1.46 (0.92, 2.33)	0.109
Coronary heart disease	1.14 (0.96, 1.34)	0.127	1.25 (0.98, 1.59)	0.072
Valvular heart disease	1.08 (0.88, 1.32)	0.462	1.12 (0.84, 1.51)	0.441
Abdominal aortic aneurysm	0.94 (0.60, 1.45)	0.773	0.87 (0.47, 1.62)	0.660
Renal artery stenosis	0.60 (0.26, 1.37)	0.225	0.72 (0.22, 2.36)	0.591
Intermittent claudication	1.03 (0.80, 1.31)	0.833	1.01 (0.70, 1.48)	0.941
Medication				
ARB/ACE	1.50 (0.52, 4.33)	0.451	4.11 (1.31, 12.88)	0.015
MRAs	1.13 (1.01, 1.26)	0.029	1.00 (0.85, 1.18)	0.994
Beta-blocker	0.99 (0.79, 1.22)	0.898	0.96 (0.69, 1.33)	0.805
Digoxin	1.14 (1.01, 1.30)	0.039	1.10 (0.91, 1.33)	0.327
Diuretics	0.94 (0.82, 1.08)	0.357	1.56 (1.29, 1.87)	<0.001
Anticoagulant	1.10 (0.95, 1.28)	0.208	1.07 (0.85, 1.33)	0.570
Aspirin	0.92 (0.82, 1.05)	0.217	0.97 (0.81, 1.17)	0.776
Adenosine diphospate antagonist	1.03 (0.88, 1.20)	0.748	1.10 (0.86, 1.39)	0.449
Lipid lowering	0.94 (0.84, 1.07)	0.356	1.19 (0.99, 1.43)	0.064
Laboratories				
eGFR (mL/min/1.73m^2)	1.00 (0.99, 1.01)	0.707	1.00 (0.99, 1.01)	0.496
Creatinine µmol/L	1.00 (1.00, 1.01)	0.838	1.00 (0.99, 1.01)	0.576
Log(NT-proBnp)	0.97 (0.92, 1.03)	0.313	0.91 (0.84, 1.00)	0.044
Haemoglobin A1C	1.03 (0.99, 1.08)	0.172	1.00 (0.93, 1.07)	0.918
Haemoglobin	1.00 (1.00, 1.00)	0.954	1.00 (1.00, 1.01)	0.245

11.3 Symptoms as predictors of outcome: PARADIGM-HF

I tested the prognostic value of each symptom in relation to the composite outcome of cardiovascular death or hospitalisation due to worsening heart failure (heart failure) using Cox proportional-hazard regression models (described in Methods chapter). Cardiovascular death or hospitalisation due to worsening heart failure was the primary composite endpoint for PARADIGM-HF. I also analysed the components of the composite (cardiovascular death and heart failure hospitalisation individually) and all-cause death. I used two different models: one similar to the one used in the CORONA analyses (with all available variables in PARADIGM) and another model which is currently being developed for the composite endpoint of cardiovascular death or heart failure hospitalisation (J. Simpson- BHF Cardiovascular Research Centre, University of Glasgow).

The model similar to the one used in the CORONA cohort was adjusted for the following variables: sex, age, NYHA class, LVEF, systolic blood pressure, heart rate, smoking status, baseline BMI, coronary intervention (CABG/PCI), history of myocardial infarction, history of aortic aneurism, history of hypertension, stroke, diabetes, intermittent claudication, pacemaker or cardioverter defibrillator implantation, atrial fibrillation at baseline ECG, serum creatinine and a logarithmic transformation of NT-proBNP; thyroid stimulating hormone, hs-CRP, CK, ALT Apo-A1 and Apo-B were not available in PRADIGM-HF, hence were not included in the model.

The model under development for PARADIGM-HF was adjusted for the following covariates: age, sex, race, region, systolic blood pressure, heart rate, NYHA class, LVEF, prior HF hospitalisation, time since diagnosis of HF, history of myocardial infarction, diabetes, coronary intervention, haemoglobin levels, serum creatinine, albumin levels, haemoglobin A1C levels, potassium levels, beta-blocker use, randomised treatment, the interaction between prior heart failure hospitalisation and region, and NT-proBNP. Continuous variables were dichotomised to allow for non-linear relationships with outcomes.

Kaplan-Meier cumulative event curves are presented by symptom category and compared with log-rank tests.

11.3.1.1 Unadjusted outcomes

Of the 8399 patients analysed, 2031 (24.2%) had a heart failure hospitalisation or cardiovascular death with a median survival time of 345 days (IQR 168-599). (see Table 11-6) For the 6368 patients who did not have a composite outcome of cardiovascular death or heart failure hospitalisation median survival time was 853 days (IQR 614-1096).

Patients who reported symptoms on effort were more likely to die from any cause (CV death: fatigue HR 1.18 95% CI[1.06, 1.32]; dyspnoea HR 1.35 [1.13, 1.61]. All cause death: fatigue HR 1.15 [1.05, 1.28]; dyspnoea HR 1.25 [1.07, 1.46]). Symptoms on effort were also associated with to a higher risk of the primary composite outcome (fatigue HR 1.18 [1.18, 1.29]; dyspnoea 1.19 [1.05, 1.37]). (Table 11-6 Table 11-7 and Figure 11-1 and Figure 11-2)

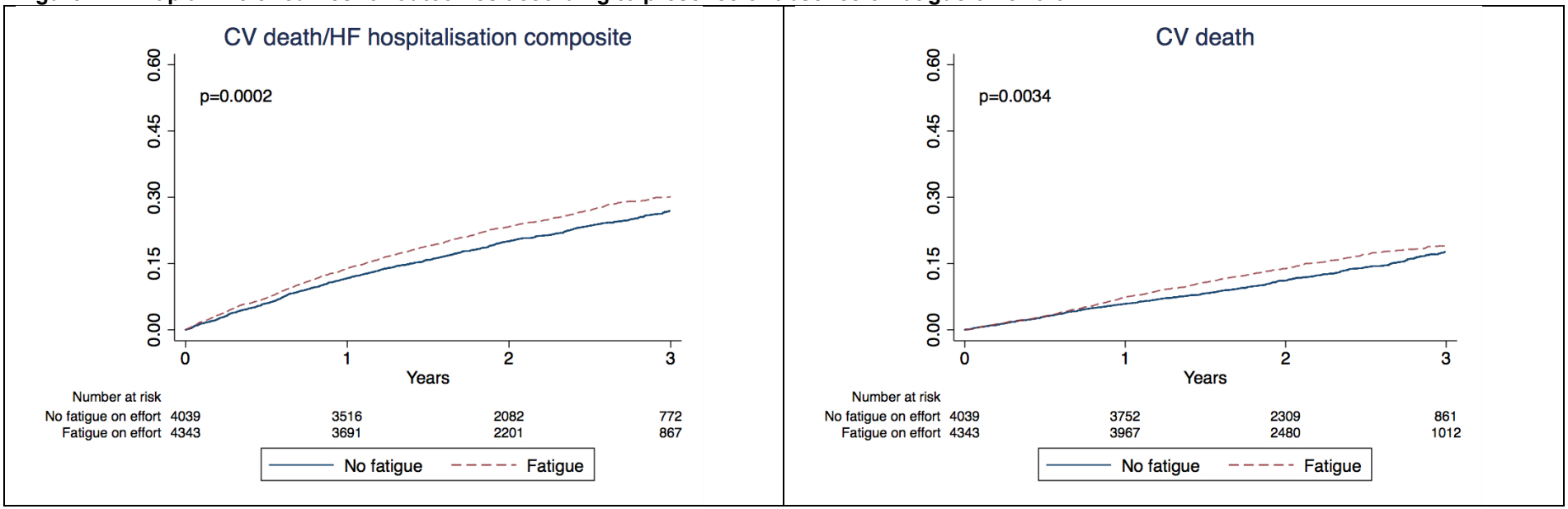
Table 11-6 Clinical outcomes according to presence of symptoms

	Fatigue on effort (n=4343)		Dyspnoea on effort (n=7207)	
n (%)	**Number of events**	**p value**	**Number of events**	**p value**
CV death/HF composite	1125 (25.9)	<0.001	1782 (24.7)	0.007
Heart failure hospitalisation	651 (15.0)	0.043	1043 (14.5)	0.138
CV death	698 (16.1)	0.002	1114 (15.5)	0.001
All cause death	855 (19.7)	0.002	1365 (18.9)	0.004

Table 11-7 Hazard ratio for symptoms and clinical outcomes: Unadjusted analysis

	Fatigue on effort		Dyspnoea on effort	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
CV death/HF composite	1.18 (1.08, 1.29)	<0.001	1.19 (1.05, 1.37)	0.008
Heart failure hospitalisation	1.13 (1.02, 1.28)	0.025	1.15 (0.97, 1.37)	0.106
CV death	1.18 (1.06, 1.32)	0.003	1.35 (1.13, 1.61)	0.001
All cause death	1.15 (1.05, 1.28)	0.004	1.25 (1.07, 1.46)	0.005

Figure 11-1 Kaplan Meier curves for outcomes according to presence or absence of fatigue on effort



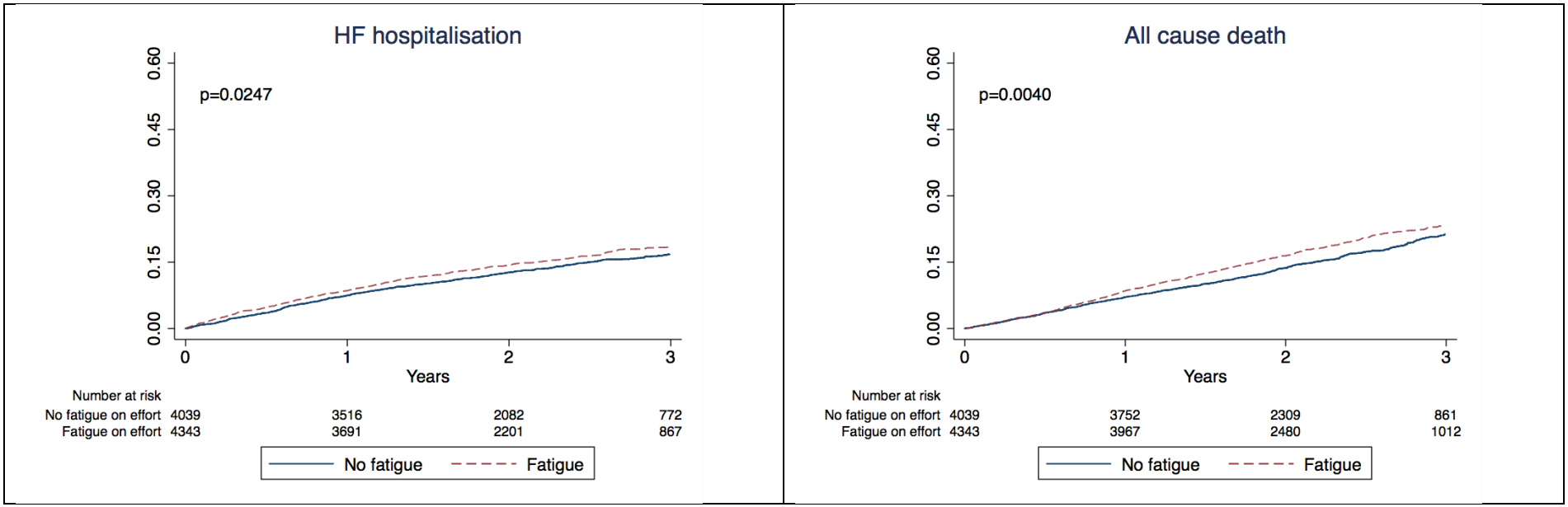
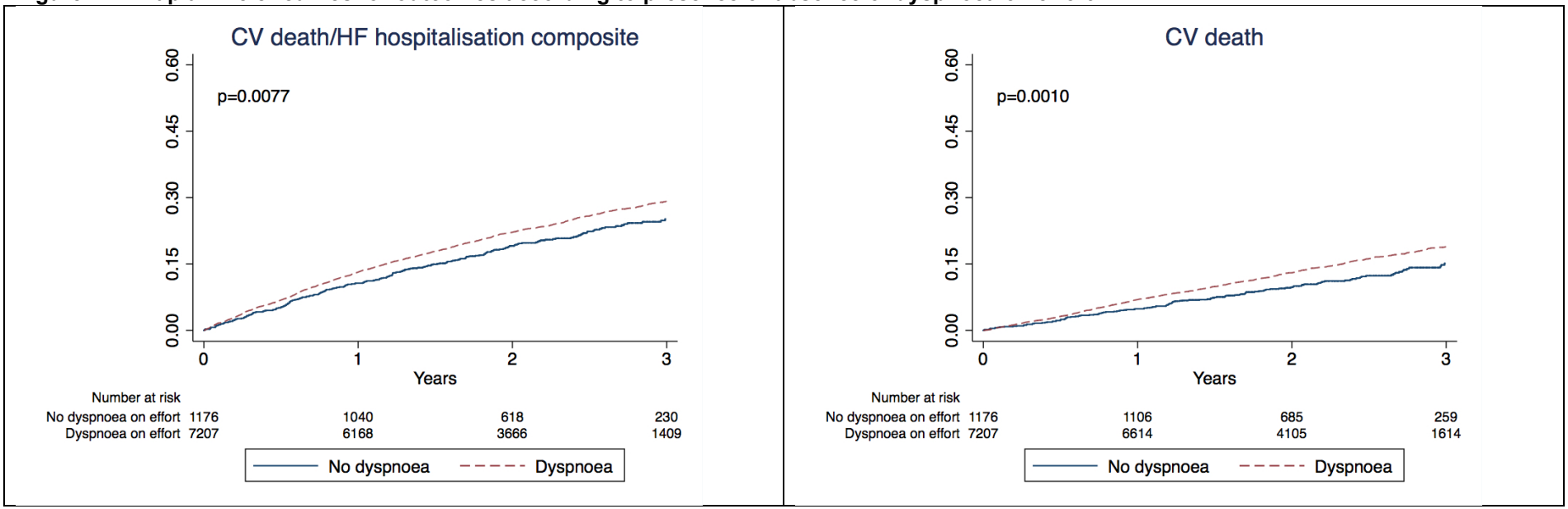
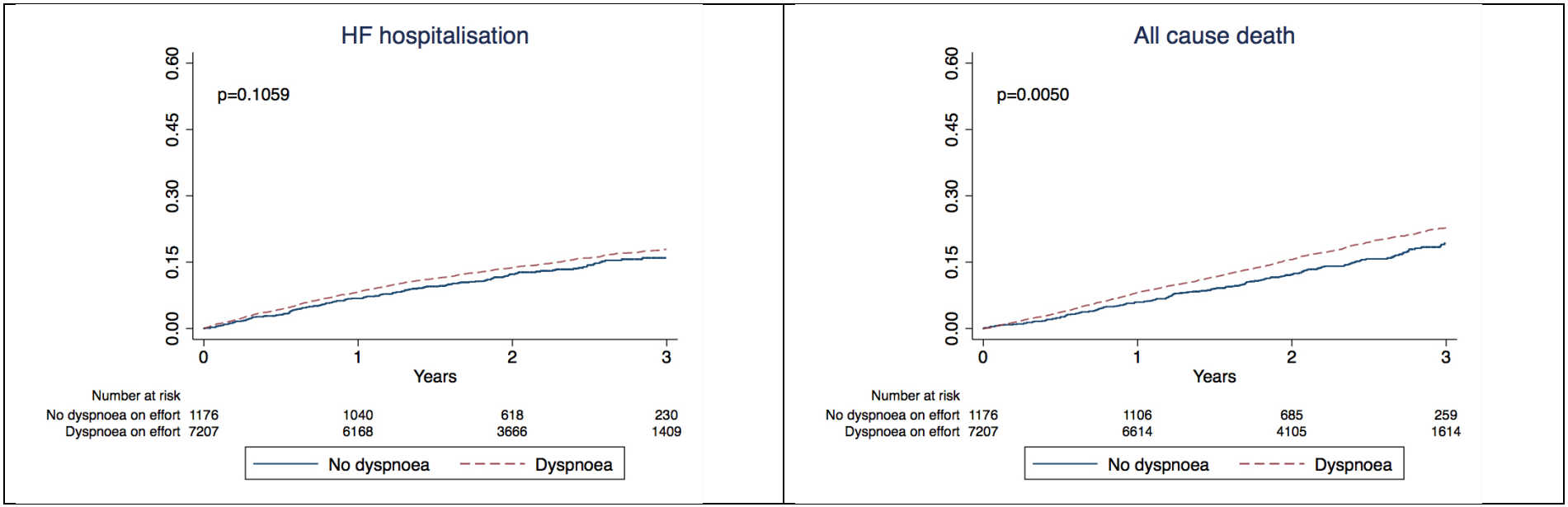

HF hospitalisation
p=0.0247
0.00
0.15
0.30
0.45
0.60
0
1
2
3
Years
Number at risk
No fatigue on effort 4039 3516 2082 772
Fatigue on effort 4343 3691 2201 867
No fatigue
Fatigue
All cause death
p=0.0040
0.00
0.15
0.30
0.45
0.60
0
1
2
3
Years
Number at risk
No fatigue on effort 4039 3752 2309 861
Fatigue on effort 4343 3967 2480 1012
No fatigue
Fatigue

Figure 11-2 Kaplan Meier curves for outcomes according to presence or absence of dyspnoea on effort




HF hospitalisation
p=0.1059
0.00
0.15
0.30
0.45
0.60
0
1
2
3
Years
Number at risk
No dyspnoea on effort 1176 1040 618 230
Dyspnoea on effort 7207 6168 3666 1409
No dyspnoea
Dyspnoea
All cause death
p=0.0050
0.00
0.15
0.30
0.45
0.60
0
1
2
3
Years
Number at risk
No dyspnoea on effort 1176 1106 685 259
Dyspnoea on effort 7207 6614 4105 1614
No dyspnoea
Dyspnoea

11.3.2 Multivariate analysis

Adjustment for other variables mentioned in section 11.3 of this chapter (for both multivariate models) weakened the relationship between the presence of symptoms and all outcomes. A total of 8008 (95%) patients were included in the analyses, 274 patients were omitted mainly due to missing haemoglobin value. (Table 11-8 Table 11-9)

Only dyspnoea on effort remained predictive of cardiovascular death (HR 1.28 95% CI 1.06-1.50) in the model currently under development for PARADIGM-HF.

Table 11-8 Hazard ratio for symptoms and clinical outcomes: Multivariable analysis using model similar to CORONA

	Fatigue		Dyspnoea	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Cardiovascular death or heart failure hospitalisation	1.04 (0.95, 1.15)	0.393	1.13 (0.97, 1.30)	0.109
Cardiovascular death	1.03 (0.91, 1.16)	0.689	1.24 (1.03,1.51)	0.026
Heart failure hospitalisation	1.02 (0.90, 1.15)	0.737	1.12 (0.93, 1.35)	0.246
All-cause death	1.03 (0.92, 1.15)	0.609	1.16 (0.98, 1.37)	0.083

Adjusted for: age, sex, NYHA class, LVEF, body mass index (BMI), systolic blood pressure, heart rate, smoking, MI, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter (AF), stroke, intermittent claudication, pacemaker and ICD implantations, creatinine, and log NT-proBNP.

Table 11-9 Hazard ratio for symptoms and clinical outcomes: Multivariable analysis PRADIGM-HF model

	Fatigue		Dyspnoea	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Cardiovascular death or heart failure hospitalisation	1.05 (0.95, 1.16)	0.313	1.20 (1.04, 1.38)	0.012
Cardiovascular death	1.06 (0.93, 1.20)	0.377	1.28 (1.06, 1.54)	0.009
Heart failure hospitalisation	1.03 (0.91, 1.17)	0.662	1.24 (1.03, 1.50)	0.020
All-cause death	1.05 (0.94, 1.17)	0.423	1.20 (1.02, 1.42)	0.028

Adjusted for: age, sex, race, region, NYHA class, LVEF, systolic blood pressure, heart rate, MI, clinically significant valvular heart disease, prior heart failure hospitalisation, time since diagnosis of heart failure, coronary artery intervention, haemoglobin A1C, haemoglobin, albumin, potassium, beta-blocker use at randomisation diabetes, the interaction between previous heart failure hospitalisation and region; randomised treatment and NT-proBNP.

11.3.3 Summary of findings

Some of the univariate associations with symptoms on effort such as LVEF, systolic and diastolic blood pressures, although statistically significant, could be considered clinically irrelevant. For example, patients with symptoms on effort had an average of 1.6 mmHg higher systolic blood pressure than those with no symptoms on effort, and had a LVEF of approximately 1% higher. These findings reflect the ability to show that even small differences are statistically significant when studying large numbers of patients. It is also important to note that these associations were attenuated towards the null in multivariable analysis. Same as with the results from CORONA, fatigue and dyspnoea on effort do not differ much in relation to their predictors (NYHA class and KCCQ summary scores), however in the analyses run in PARADIGM-HF, female sex was independently associated with fatigue and not dyspnoea, which coincides with much of the available literature (see section 2.3.2). On the other hand, I did not find haemoglobin levels to be associated with symptoms on effort in this cohort.

Additionally, I found that symptoms at baseline were associated with outcomes in univariate analyses, but that association is lost after adjustment for other well-known prognostic variables like NT-proBNP. This is true for the two models run.

12 Overall summary of findings and discussion

Although dyspnoea is the best recognised symptomatic manifestation of heart failure, fatigue is also a prototypal symptom limiting exercise in this condition. (5, 78, 270) For example, in one community-based survey more than half (59%) of 540 patients with chronic heart failure reported being moderately to extremely troubled by fatigue and few (9%) had not experienced this symptom at all. Of those reporting fatigue, 53% experienced the symptom at least once a day. (271) Similar conclusions have been reported in other studies (272, 273) and my results reflect analogous findings.

12.1 Prevalence and correlates of symptoms

I found the symptom of fatigue to be almost ubiquitous in CORONA (which included only patients with symptoms -i.e. those in NYHA functional class II or greater and with dyspnoea at baseline- and a reduced LVEF) and highly prevalent in PARADIGM-HF. Overall, in CORONA only 5% of patients reported no fatigue and 9% reported fatigue only on severe exertion, while in PARADIGM-HF 52% reported fatigue on effort and 86% reported dyspnoea on effort. For the vast majority in CORONA, fatigue was present on slight (43%) or moderate (43%) exertion.

12.1.1 Origin of symptoms: central vs. peripheral hypothesis

While a number of studies have tried to identify correlates of fatigue and dyspnoea in patients with heart failure, the results have been conflicting. I found both symptoms were associated with a number of variables and these variables were very similar for both symptoms (history of hypertension, angina and myocardial infarction; NYHA functional class; use of mineralocorticoid receptor antagonists). This suggests that the pathophysiological basis of both symptoms may be similar and, as discussed earlier, my findings lend some support to a “peripheral” (muscle) rather than “central” (haemodynamic) explanation for both dyspnoea and fatigue in heart failure. Although no information on haemodynamic measures was available, I would argue that NT-proBNP and LVEF provide a reasonable surrogate for central haemodynamic measures. Given the fact that both the clinical trial cohorts used in this thesis included ambulatory patients it would have been very difficult to obtain “hard”

(i.e. PCWP, LVEDP) measurements as they would require interventions like the insertion of a central venous catheter or a right heart catheterisation.

12.1.2 Correlates of symptoms: two sides of the same coin?

The association between history of coronary heart disease and greater fatigue and dyspnoea is noteworthy. Angina commonly occurs simultaneously with other heart failure symptoms, and previous studies have shown that there is a significant association between chest pain and both greater fatigue and greater dyspnoea. (131, 274) The strength of the associations previously reported is greater for dyspnoea than fatigue (274), however, I found that history of angina was significantly associated with moderate fatigue or dyspnoea (not with severe symptoms).

The deleterious impact of hypertension on quality of life has been documented previously (275-277) but the reasons for this remain unclear. Fatigue has previously been associated with hypertension in patients with HF. (131) It has been hypothesized that this association could be attributable to the hypertension itself, drug treatment and "labelling effect" after diagnosis, but again, the results are conflicting. (278, 279) I found that hypertension was significantly associated with increased fatigue at baseline.

The association between treatment with a MRA and greater fatigue and dyspnoea in CORONA likely reflects confounding by indication, with use of this class of treatment at the start of CORONA recruitment restricted to patients with more advanced heart failure. MRA use is therefore probably a marker of unmeasured severity of heart failure.

12.1.2.1 Coenzyme Q_{10} as a potential treatment

There has been much interest in the potential role of coenzyme Q_{10} as a therapeutic agent in heart failure (155-157), nonetheless I found no association between plasma coenzyme Q_{10} level and symptoms. However, plasma and muscle coenzyme Q_{10} levels are poorly correlated and it would be interesting to analyze muscle coenzyme Q_{10} levels and its relationship to symptoms in heart failure. (280) It is important to call attention to the fact that I had relatively few patients with a coenzyme Q_{10} level and results from this sensitivity analysis should be taken cautiously, as I have discussed in the relevant section.

12.1.2.2 Statins and fatigue

Recently there has been some controversy surrounding statin treatment and changes in fatigue severity, with some authors stating that statins have a deleterious impact on energy and exertional fatigue (153, 281), while some other groups advocate for the safety and tolerability of statin treatment, specifically in patients with heart failure (152, 153, 269, 281). I did not find a statistically significant association between statin treatment and either change in symptom severity or outcomes. I found little evidence supporting the idea that statins could have a deleterious effect on symptom severity in this cohort of patients with heart failure. Albeit I must acknowledge that a slight trend can be seen with a small number of patients treated with rosuvastatin reporting a worsening of fatigue over six months, with questionable clinical significance as the cohort where I studied this association could represent a more vulnerable group to the adverse effects of statins (i.e. older patients with systolic heart failure).

12.1.2.3 CORONA vs. PARADIGM-HF

Although my results from CORONA and PARADIGM-HF differ regarding the correlates of symptoms, specifically for dyspnoea, most predictors of fatigue are common to both cohorts (with the exception of MRAs which were not associated with symptoms in PARADIGM-HF). This could be due to the fact the symptoms in PARADIGM-HF were measured as a dichotomous variable (no symptoms vs. symptoms on effort), potentially leading to a loss of information. Additionally, 86% of the patients in PARADIGM-HF reported having dyspnoea on effort, which makes it difficult to tease out specific predictors of this symptom in this cohort.

Symptoms in PARADIGM-HF appear to be much milder than in CORONA, this could be due to the fact that patients in PARADIGM-HF were on average 9 years younger than those in CORONA (mean age 64 vs. 73). They also had lower mean systolic blood pressures (122 mmHg vs.129 mmHG). Additionally, PARADIGM-HF randomised patients with NYHA class I, while patients in CORONA had to be NYHA class II or higher. Patients in PARADIGM-HF were largely treated with evidence-based medicine as well (93% were on beta-blockers, 80% were on diuretics,78% were on ACE inhibitors, 22% on angiotensin receptor blockers, and 57% were on MRAs).

Also of interest are the things that I found were not significantly associated with either fatigue or dyspnoea. A higher NT-proBNP level might have been expected to correlate with dyspnoea, especially if higher natriuretic peptide levels relate to higher left ventricular filling pressures, which in turn cause dyspnoea. This lack of association lends indirect support to the muscle hypothesis, which states that dyspnoea might have its origins in heart failure as much in abnormal muscle as in congested lungs. It is noteworthy that although in CORONA about one third of the patients were missing values for NT-proBNP, in PARADIGM-HF virtually no observations were missing (only 14 patients did not have an NT-proBNP value; less than 0.2%), making the findings more robust. Likewise, the lack of relationship between ejection fraction and fatigue suggests that symptom does not have a haemodynamic origin related to diminished cardiac output and skeletal muscle blood flow (although the relationships between ejection fraction, cardiac output, systemic vascular resistance and regional distribution of arterial flow are complex). Additionally, it is well known that skeletal muscle metabolism is often abnormal in HF and muscle wasting may develop. (76, 90, 113) Exercise capacity in patients with HF is dependent on both muscle function and bulk (282) and a correlation between serum CK level and lean body mass has been demonstrated by others. (283) Nevertheless I found no association between CK and fatigue or dyspnoea in CORONA (PARADIGM-HF did not measure CK). Additionally, I found that beta-blocker use was not associated with fatigue, although a meta-analysis in 2002 reported that beta-blocker use was associated with a small significant annual increase in risk of reported fatigue (18 per 1000 patients; 95% CI 5-30). (255) Although I am aware that a lack of evidence for association does not necessary equal no association I believe my results to be robust as confidence intervals are generally narrow and point estimates are similar in direction and magnitude in both cohorts analysed. As discussed above, the only surrogates for central haemodynamics available would be NT-proBNP and LVEF, neither of which showed an association with symptom severity.

It is also noteworthy that although both symptoms vary slightly in their correlates, the direction and magnitude of the associations are very similar. A clear trend can be seen for all covariates. This perhaps supports the view that these two symptoms are different expressions of the same underlying disease mechanism or mechanisms. (80, 84) It could be argued that the only real difference lies in NYHA class, where there seems to be a stronger association for

dyspnoea than for fatigue. This association should also be interpreted with care, as it could be due to the fact that in CORONA the range of plausible values for fatigue was wider than for dyspnoea (because some level of dyspnoea was an inclusion criterion). In other words, after grouping, 18% of the patients with fatigue 0/1 were in NYHA III/IV, while only 7.4% of the patients with the lower levels of dyspnoea were classified as NYHA III/IV, making more dyspnoeic patients more likely to be in worse NYHA class. This lends support to the notion that fatigue and dyspnoea share a common pathophysiological background. It is common for the same patient to complain of fatigue or dyspnoea depending on the type of exercise being performed. (138, 284) It is possible that patients have trouble distinguishing between fatigue and dyspnoea, and as my results show, the two symptoms tend to overlap with 75% of patients reporting the same levels of dyspnoea and fatigue.

My results from CORONA are supported by my findings from PARADIGM-HF, the largest, most contemporary heart failure clinical trial, where patients were largely treated with evidence based medicine and where virtually no data was missing. So why is my main analysis on CORONA and not PARADIGM-HF? The data from PARADIGM-HF became available to me a little less than one year ago, with it being ready to analyse only until late in my studies, where I could not focus on this trial population. Additionally, symptoms in PARADIGM-HF were measured as a dichotomous variable (as mentioned earlier), which leads to a loss of valuable information regarding severity of symptoms and how it relates to outcome. Having said this, I believe that neither cohort is better for the purpose of this thesis, but that results both provide important insights into the two pivotal symptoms of heart failure. If I were *required* to choose one, I would probably go for CORONA mostly because symptoms were measured in an ordinal scale. As I have mentioned before the fact that symptoms were dichotomised in PARADIGM-HF deducts from their importance and possibly lead to investigators and patients under-reporting *subtle* changes. As I have shown in this thesis, symptoms can change in short periods of time and the change in symptoms is associated to outcome -something that I will analyse in the future using PARADIGM-HF. However, just asking patients to report whether they have or have not got symptoms on effort may have made it difficult for them to describe the ordinal character of symptoms; for these reasons I would be prefer CORONA over PARADIGM-HF.

12.2 Symptoms as predictors of outcome

Except for dyspnoea, which remained a significant predictor of the composite outcome of HF hospitalisation or cardiovascular death, as well as for it's individual components, symptoms at randomisation were not predictive of outcome, although as have mentioned before, a trend is evident both from the univariate analyses and from the direction and magnitude of the point estimates (hazard ratios) and it could be argued that symptoms of baseline show a tendency to be associated with adverse clinical outcomes. Results from both cohorts (CORONA and PARADIGM-HF) showed the same trend.

The only other large trial that I know of which analysed fatigue independently to NYHA class in an ambulatory setting (not hospitalised patients) was the Carvedilol Or Metoprolol European Trial (COMET) which used a 5 point scale, although this was labelled differently (1 asymptomatic; 2 walking up stairs at normal pace; 3 walking at normal pace on a flat surface; 4 walking slowly on a flat surface or during washing or dressing; and 5 at rest). Few patients (<8%) were given the lowest or highest score on this scale although there was a more even distribution across the middle three scores in COMET compared with CORONA, presumably reflecting the different scale-labelling, different patient characteristics or both. For example, patients in CORONA were an average of 10 years older than those in COMET and more likely to have a history of myocardial infarction, hypertension or diabetes, and to be treated with beta-blockers at baseline; they were less likely to be treated with ACE inhibitors or diuretics.

12.3 Change in symptoms: correlates and their importance as predictors of outcome

First I must draw attention to the fact most patients who did not have a 6-month visit died before this visit, hence the analysis on change in symptoms should be interpreted with caution, as it is an analysis of the surviving cohort. Having said this, I found in the CORONA cohort of older patients with ischaemic heart failure also largely treated with evidence based medicine (93% were treated with ARB/ACE inhibitors, 74% with beta-blockers, and 88% were on loop/thiazide diuretics) symptoms were mostly unchanged over six months: 66-69% of the patients reported no change in symptoms severity for both fatigue and dyspnoea; it is also possible that symptoms varied within these two time points

but might have been the same when measured at the times analysed. Around 20-22% of the patients reported an improvement of symptoms over time and worsening was reported in 9-13% of the patients. Given that symptoms can change rapidly, I wanted to analyse if patients who had longer periods of time between visits were more likely to report a change in symptoms, however there was no association with time between visits and how symptom severity changed after six months.

Not surprisingly, the most important correlates of change in symptom severity were baseline symptoms, where a regression to the mean is evident, as patients with worse symptoms at baseline could not worsen after six months. This is partly why higher symptom severity at baseline was associated with a decrease in symptoms at six months and vice versa. As were higher Kansas City clinical questionnaire summary scores strongly associated with a decreased risk of reporting symptoms on effort; higher scores represent better health status.

Fatigue and dyspnoea are quite subjective, and are commonly associated with other quality of life measures, this could be why intermittent claudication was significantly associated with an increase in symptoms, or it could be a surrogate for other cardiovascular risk factors and reflects “sicker” patients. A similar phenomenon might be occurring with NYHA class and its association to change in symptom severity, where patients with a worse functional class were more likely to report an increase in symptoms, this could be a reflection of worse overall health or could be associated with overall quality of life, or both.

A worsening of either symptom over six months was associated with fatal outcomes and heart failure hospitalisation, even after adjusting for other well-known prognostic factors like NT-proBNP. Additionally, decreasing symptom severity was shown to be protective of both fatal and non-fatal outcomes. This association between change in symptoms and clinical outcomes has been previously documented in a few studies (18, 85, 99, 100, 143, 258) and the results from this thesis, together with the results from my previously published work (18, 85, 285) provide support to this very important link between symptom change and clinical outcomes, though most previous studies have looked at hospitalised and not ambulatory patients. A small study by Moser *et al* (203) showed that variability in daily symptoms and not their severity was associated with adverse outcomes. My results show that the direction of such variation is

important, with improving symptoms being associated with a lower risk of adverse outcomes, while the opposite is also true, with worsening symptoms associated with higher risk of clinical adverse outcomes. While having measurements from only two time points the results imply a direction of the effect, it is possible that symptoms could have fluctuated in different directions, thus the importance of studying symptoms at different times, as I have shown in section 5.2 they can vary substantially in short periods of time.

12.4 Limitations

This study has several limitations. It was not a pre-specified analysis of the CORONA trial. The patients enrolled were older subjects with systolic heart failure of ischemic aetiology. 1181 patients (23.6%) were excluded from the analyses because patients with a LVEF >35% (and ≤40%) had to be in NYHA class III or IV and I wished to examine the predictive value of fatigue and dyspnoea in addition to NYHA functional class. However additional analyses including these patients gave similar results. While my findings are consistent with those of COMET and therefore probably can be generalized to most patients with heart failure and reduced ejection fraction, I do not know about the prevalence or prognostic importance of fatigue in patients with heart failure and preserved ejection fraction. Fatigue was not measured using a validated score although I do not know of any instrument has been fully validated in heart failure and is suitable for use in a large multinational trial. Because dyspnoea was an inclusion criterion in CORONA, the dyspnoea scale had only 4 possible points as opposed to 5 for fatigue. Subjects were asked about symptoms over “the past few days” and investigators recorded these.

The scale used in CORONA is not dissimilar to the Dyspnoea-Fatigue index (“Yale scale”), which is a validated instrument in heart failure although that instrument uses a 0-4 scale to assess three domains – “magnitude of task”, “magnitude of pace” and “functional limitation”. However, simple Likert-like sales such as the one I used are commonly employed to assess symptoms in clinical trials in heart failure and do seem to identify changes with treatment. Several studies comparing xamoterol with placebo, digoxin or both used a 5 point Likert scale to assess “tiredness” (and “breathlessness”) and demonstrated significant differences between active therapy and placebo. (286, 287)

The Diabetes Symptom Checklist (DSC) records a number of symptoms, including fatigue, on a 5-point scale ranging from 1 (not at all) to 5 (extremely). This scale was able to demonstrate a significant difference between two beta-blockers (carvedilol and metoprolol) in The Glycemic Effect in Diabetes Mellitus: Carvedilol–Metoprolol Comparison in Hypertensives (GEMINI) study of approximately 1200 patients randomised to metoprolol or carvedilol in a 3 to 2 ratio. (288)

On the other hand, it is widely accepted for dyspnoea to be measured with a visual analogue scale (289), or with a modification of the Borg scale for perceived exertion. (290) Both of these scales are similar to the scale used in CORONA to measure dyspnoea, and there is no evidence that either the visual analogue scale or the modified Borg scale are better at measuring dyspnoea. (289)

So, as far as I can tell, simple scales such as the ones used in CORONA do detect the effect of therapies on symptoms and are also predictive of morbidity/mortality.

A skeletal myopathy may occur in heart failure and this, in turn, may arise as a result of disturbed anabolic-catabolic imbalance. (76) Activation of metabolic or ergo-receptors in muscle may also lead to sympathetic nervous system activation which is known to be detrimental in heart failure. Severity of fatigue is also related to depressive symptoms (73, 162, 271) and depression is also an adverse prognostic finding in heart failure. Whether there is a mechanistic link between fatigue, muscle dysfunction and depression (e.g. autonomic dysfunction) is unknown. Depression, which is predictive of adverse events in patients with cardiovascular disease, was not measured in CORONA. (291) Fatigue in heart failure is also associated with anaemia, another adverse prognostic finding. (96) CORONA did not measure haemoglobin levels, iron indices or sodium levels and these may be relevant to both dyspnoea and fatigue.

As I mentioned earlier, in CORONA about 30% of the patients were missing NT-proBNP values and only 25% had an observation for coenzyme-Q^{10}, and although my analyses on imputed data do not change my results, these results should be taken cautiously as multiple imputation has some strong assumptions that might

not hold, particularly for the analyses on the imputed coenzyme-Q^{10} where data are probably not missing at random.

The multivariate model for CORONA was not adjusted for race or region (country), and there is historical evidence to support the notion that culture (hence race and/or country of origin) affects how symptoms are reported and experienced. (171, 172, 292, 293) These differences have been attributed to a variety of possible factors, including variation in translations of the quality of life questionnaires, clinicians' differences in recommendation of one treatment or other, socioeconomic status, educational level, amongst others. More recently, other authors have found no association between the experience of symptoms and culture. (294, 295) However, I found an association between region/race and presence or absence of symptoms among patients in the PARADIGM-HF trial, where Caucasians and people from Western Europe were more likely to report symptoms on effort. These results could have been the result of confounding by unmeasured variables, such as socioeconomic status or educational levels, but this cannot be determined from the present data. These considerations do, however, warrant adjusting for race in CORONA.

Another important limitation is the fact that in CORONA, subjects who were already on a statin, or considered by their own doctor to need (or have a contraindication to) a statin were not randomised. This means that patients who had a history of statin induced myopathy or serious hypersensitivity reactions to statins were excluded. This would limit the validity of the multivariate analysis including statin treatment looking at the impact of symptoms and outcome and the impact of creatine kinase as a correlate of symptoms.

For the analyses on change in symptom severity, I analysed only two time points as have discussed in the preceding section leading to potentially misleading results, as any variation within the two time points will not have been detected. Additionally, as mentioned before, analyses were run basically on survivors, as most of the patients who did not have a 6-month visit had died before this visit.

Lower haemoglobin levels and anaemia have both been independently related to dyspnoea and fatigue, and currently it would be almost unthinkable to run a clinical trial in heart failure where haemoglobin levels are not measured. In CORONA, which randomised patients between the years 2003 and 2005,

haemoglobin levels were in fact not measured, leading to a potentially important oversight of relevant predictor of symptoms. Although haemoglobin levels were not associated with symptoms on effort in the PARADIGM-HF cohort (neither on univariate or multivariate analysis), it is important to note that haemoglobin levels were largely within a normal range in this cohort (in g/L range: 101-194, IQR: 129-195, mean 139, median 140), which may explain why no association was found.

As with any results from clinical trials, the generalizability of my results is questionable as it is well known that patients who participate in clinical trials tend to have different prognosis than the "real-world" heart failure population.

12.5 Conclusions

Fatigue and dyspnoea in heart failure appear to be two sides of the same coin, having very similar (it could be argued identical) correlates and predicting clinical outcomes in the same manner and with associations of similar magnitude. My results provide evidence to support the notion that symptoms in heart failure have a peripheral or muscular, if not origin, strong component.

This thesis shows that although baseline symptoms were not independently associated with outcome, a trend is evident and more studies are justified and needed to clarify this potential association. Importantly, worsening symptoms are an adverse prognostic development and, improvement of symptoms was associated with lower risk of adverse clinical outcomes. These findings suggest that closer attention should be paid to symptoms in clinical practice; more should be done to standardise their measurement, efforts to understand there origins intensified and better treatment strategies developed.

Advising patients to keep a daily diary on their symptoms and keeping track of how they change might prove beneficial by making them aware of fluctuations which may pass unnoticed otherwise, and prompting them to seek medical attention if they notice their symptoms are fluctuating frequently. Patients should be made aware of how symptom variability could be associated with adverse clinical outcomes and should be advised notify medical personnel if they notice changes.

These results provide convincing evidence that early intervention not only to improve but also to prevent deterioration of functional status in patients with heart failure could prove beneficial, although this is a hypothesis that needs to be tested prospectively.

12.6 Future work

The next step for me is to try and validate the results I got from CORONA regarding change in symptom severity in PARADIGM-HF, where change in overall symptoms was recorded by the Kansas City cardiomyopathy questionnaire in every visit. I will then repeat the analyses in MERIT-HF and investigate if the findings from this thesis are valid in patients with heart failure with preserved ejection fraction by analysing data from I-PRESERVE. I am also interested in exploring if the results presented here differ between patients with and without AF.

If changing symptoms are shown conclusively to be prognostic factors, this could warrant a longitudinal study similar to the one performed by Moser *et al* (203) to evaluate the impact of changing symptom severity on pre-specified clinical outcomes, or a cluster clinical trial where patients could be randomised to record symptoms daily vs. not recording them and evaluating the impact of symptom awareness on outcome.

Appendix 1: Search strategies fatigue

Search strategies employed in the search of the literature regarding fatigue

MEDLINE (OVID)

exp cardiac output, low/ or exp cardiomyopathy, dilated/ or exp heart failiure/ or exp ventricular dysfunction/
(heart adj2 failure*).tw.
(congestive adj2 heart).tw
(cardiac adj2 failure*).tw.
(heart adj2 decompensation*).tw.
(myocardial adj2 failure*).tw.
paroxysmal dyspnea*.tw.
cardiac asthma.tw.
cardiac edema*.tw.
(congest* heart adj2 failure).tw.
(left side* heart adj2 failure).tw.
(right side* heart adj2 failure).tw.
(congest* adj1 cardiomyopath*).tw.
low cardiac output.tw.
(left ventric* adj1 dysfunction).tw.
(right ventric* adj1 dysfunction).tw.
or/1-16
exp asthenia/ or exp fatigue/
asthenia.tw.
fatigue.tw.
exhaustion.tw.
(muscle adj2 fatigue).tw.
tiredness.tw.
lassitude.tw.
or/18-24
17 and 25
limit 26 to (English language and humans)

EMBASE (0VID)

exp cardiac output, low/ or exp cardiomyopathy, dilated/ or exp heart failiure/ or exp ventricular dysfunction/
(heart adj2 failure*).tw.
(congestive adj2 heart).tw
(cardiac adj2 failure*).tw.
(heart adj2 decompensation*).tw.
(myocardial adj2 failure*).tw.
paroxysmal dyspnea*.tw.
cardiac asthma.tw.
cardiac edema*.tw.

(congest* heart adj2 failure).tw.
(left side* heart adj2 failure).tw.
(right side* heart adj2 failure).tw.
(congest* adj1 cardiomyopath*).tw.
low cardiac output.tw.
(left ventric* adj1 dysfunction).tw.
(right ventric* adj1 dysfunction).tw.
or/1-16
exp asthenia/ or exp fatigue/
asthenia.tw.
fatigue.tw.
exhaustion.tw.
(muscle adj2 fatigue).tw.
tiredness.tw.
lassitude.tw.
or/18-24
17 and 25
limit 26 to (english language and humans)
limit 27 to embase
limit 28 to adult
limit 29 to meta analysis
29 not 30
limit 31 to “reviews (maximizes sensitivity)
31 not 32

Appendix 2: Search strategies dyspnoea

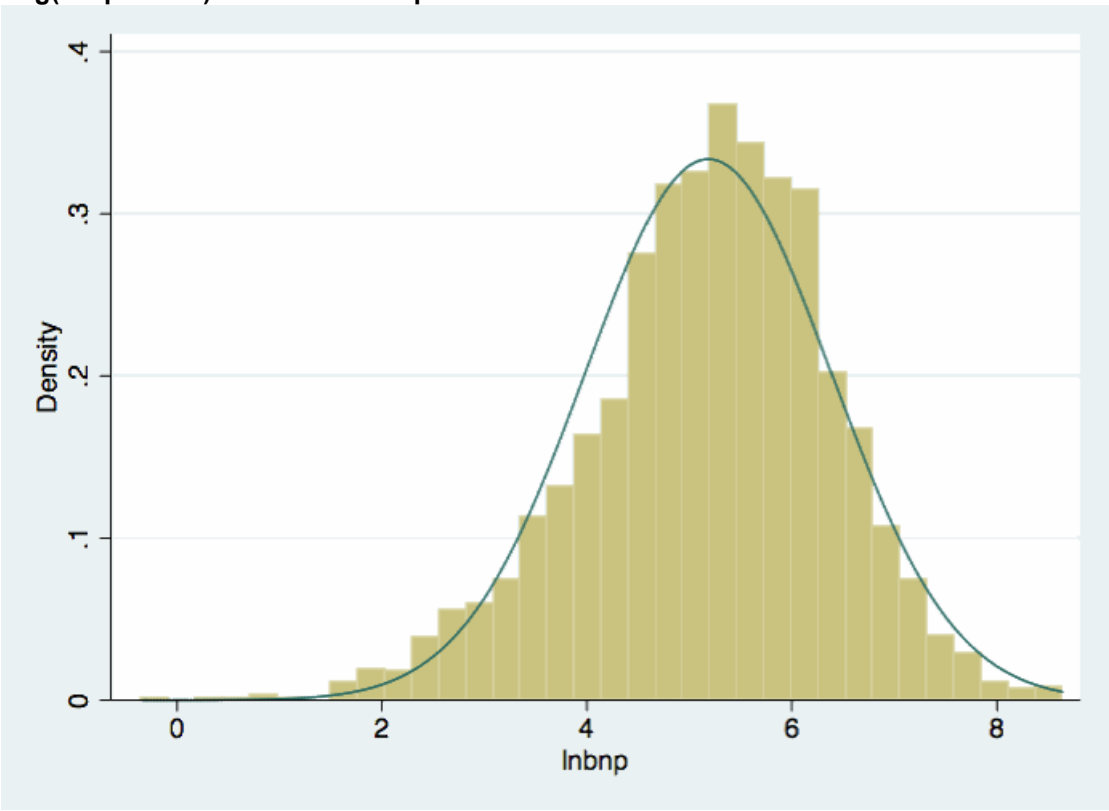
Search strategies employed in the search of the literature regarding dyspnoea

MEDLINE (OVID)

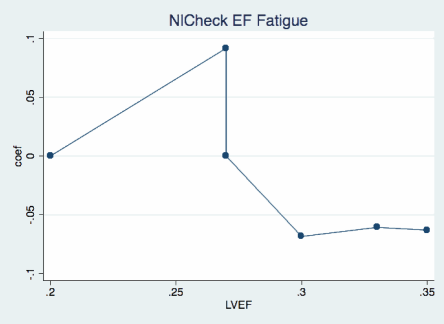
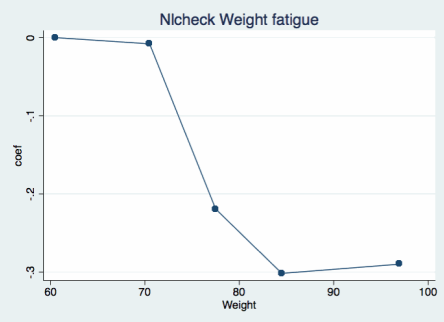
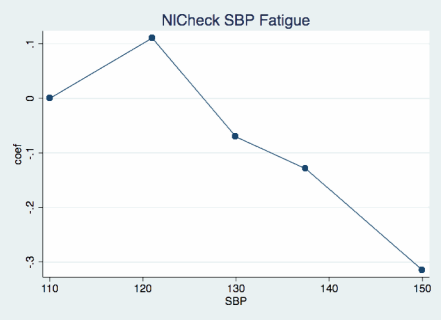
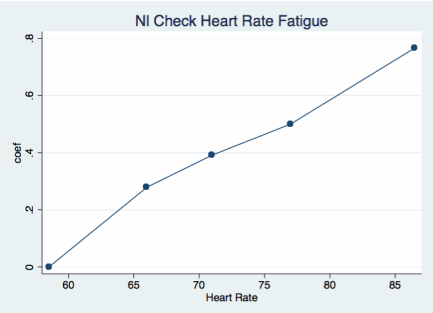
exp cardiac output, low/ or exp cardiomyopathy, dilated/ or exp heart failiure/ or exp ventricular dysfunction/
(heart adj2 failure*).tw.
(congestive adj2 heart).tw
(cardiac adj2 failure*).tw.
(heart adj2 decompensation*).tw.
(myocardial adj2 failure*).tw.
paroxysmal dyspnea*.tw.
cardiac asthma.tw.
cardiac edema*.tw.
(congest* heart adj2 failure).tw.
(left side* heart adj2 failure).tw.
(right side* heart adj2 failure).tw.
(congest* adj1 cardiomyopath*).tw.
low cardiac output.tw.
(left ventric* adj1 dysfunction).tw.
(right ventric* adj1 dysfunction).tw.
or/1-16
exp Dyspnea, Paroxysmal/ or exp Dyspnea/
dyspn?ea.tw.
breathlessness*.tw.
(shortn* adj2 breath).tw.
(breath* adj2 shortne*).tw.
or/18-22
17 and 23
limit 24 to (English language and humans)

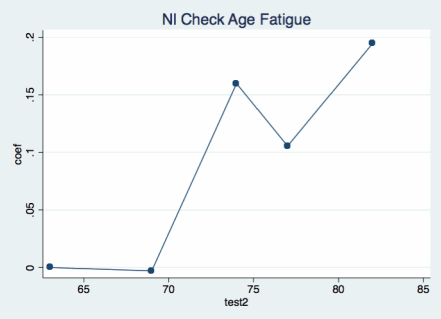
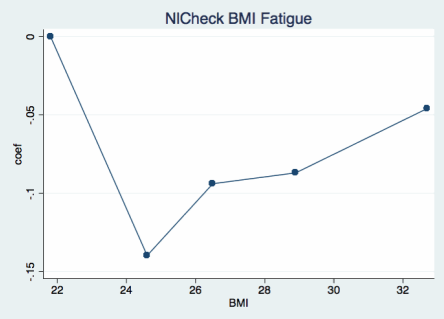
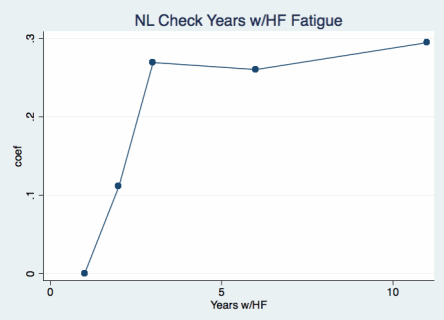
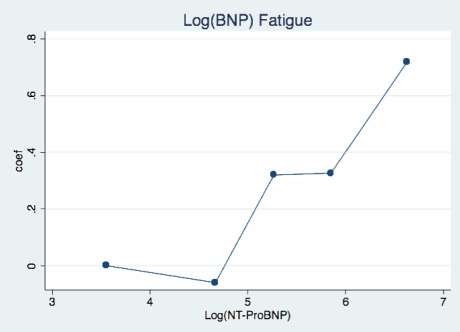
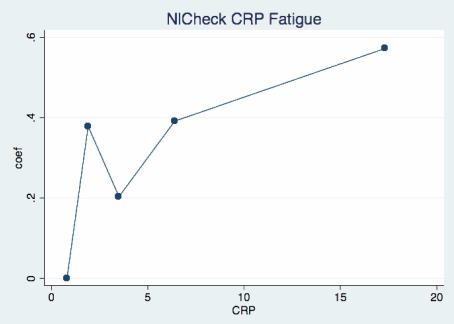
Appendix 3: Linearity assessment

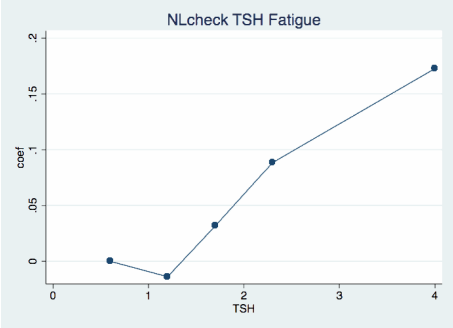
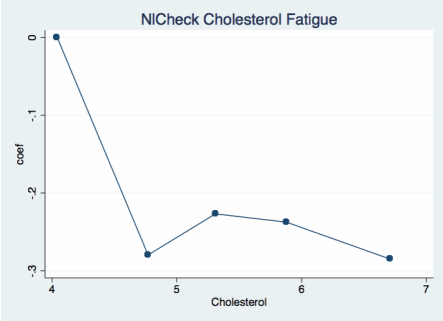
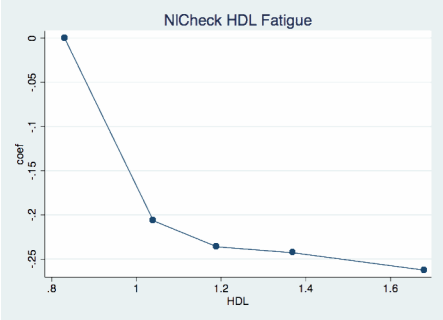
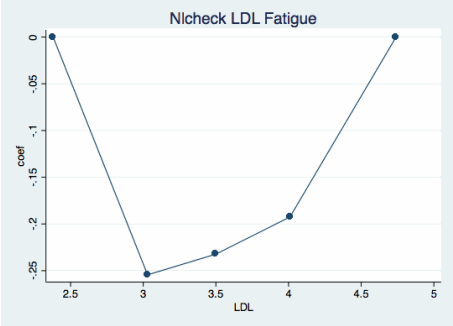
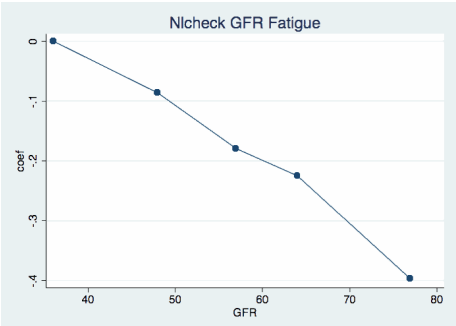
Log(NT-proBNP) distribution on patients with LVEF ≤35%: CORONA

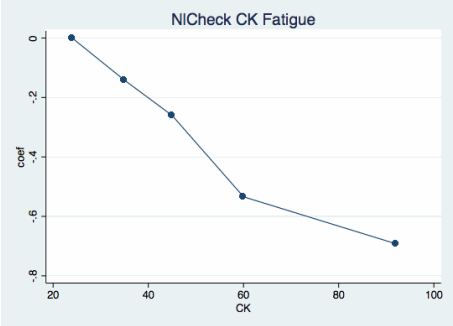
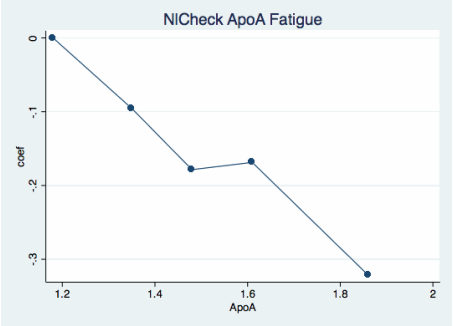
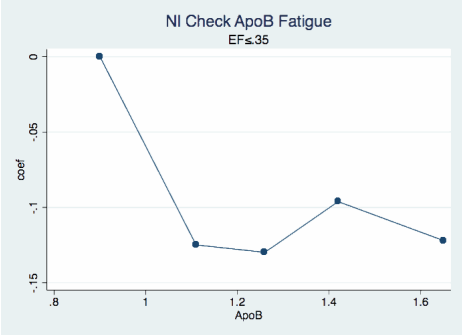
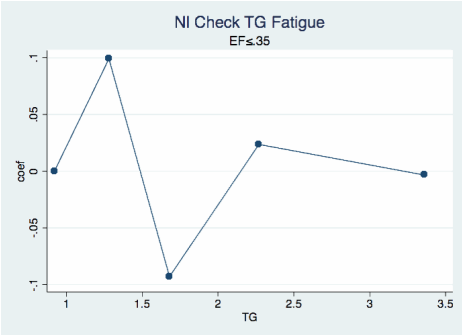
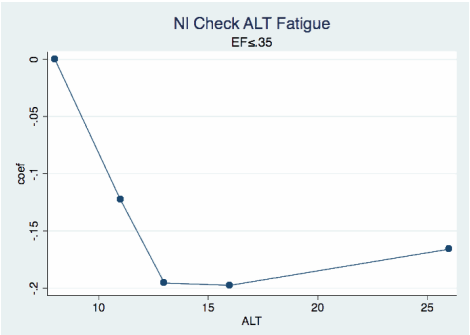


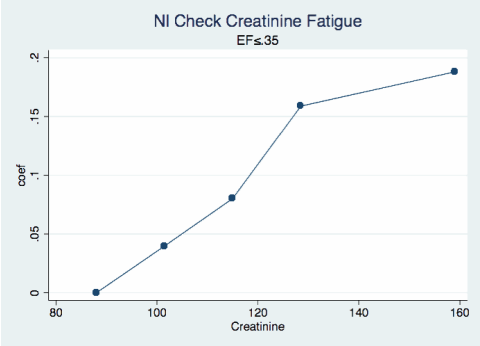
Linearity assessment fatigue on patients with LVEF≤35%: CORONA

	Fatigue	NI Check
LVEF		0.2049
Weight		0.5016
SBP		0.1125
Heart Rate		0.3525

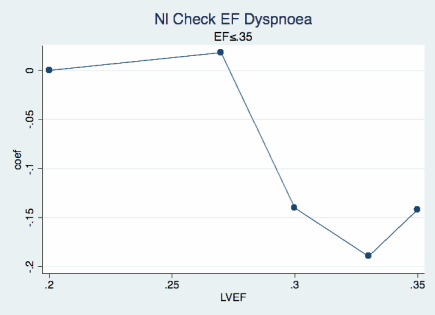
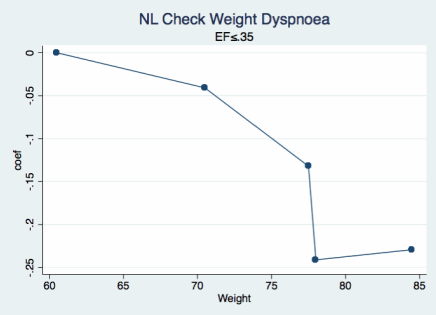
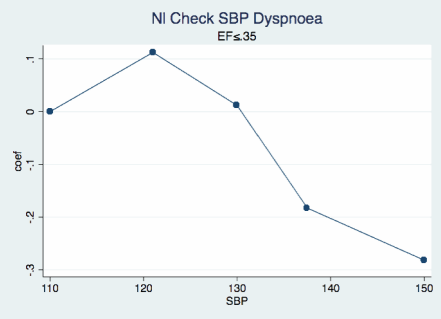
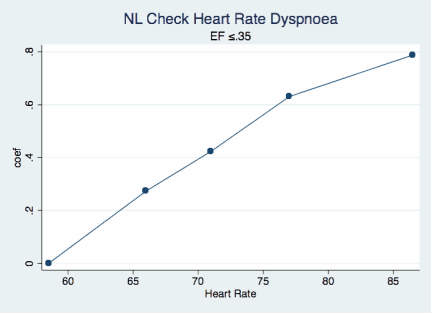
Age		0.3838
BMI		0.8101
Years w/HF		0.1767
Log(BNP)		0.0013
CRP		0.0217

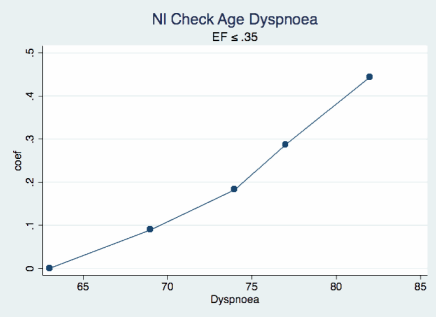
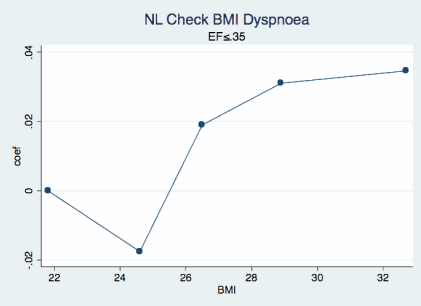
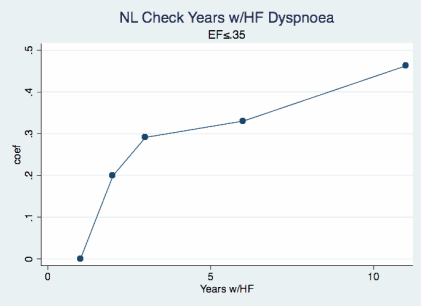
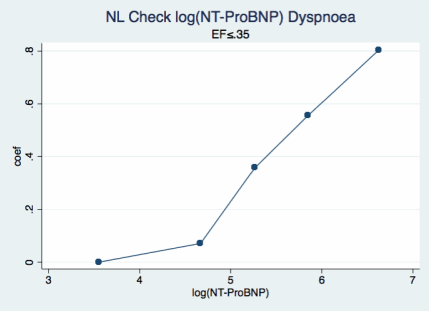
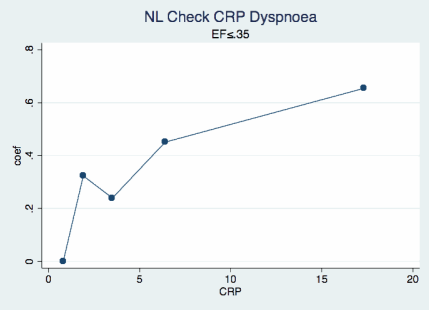
TSH		0.7054
Cholesterol		0.0618
HDL		0.7133
LDL		0.1254
GFR		0.5789

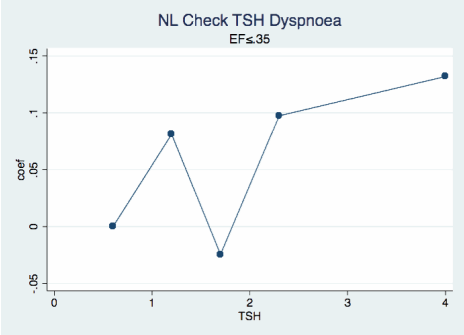
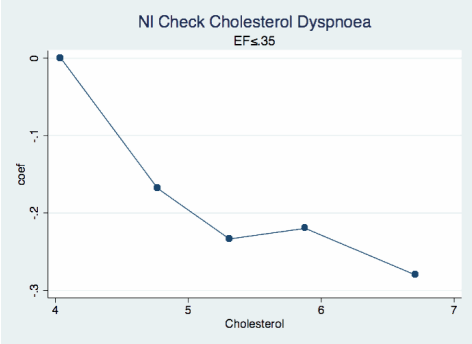
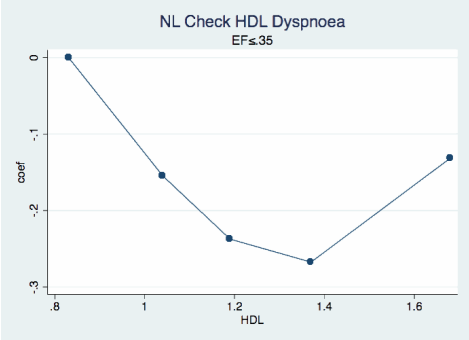
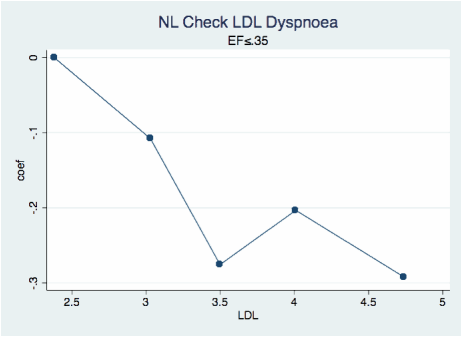
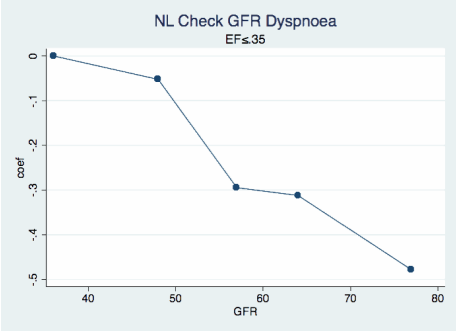
CK		0.000
ApoA		0.0548
ApoB		0.2423
TG		0.7865
ALT		0.0094

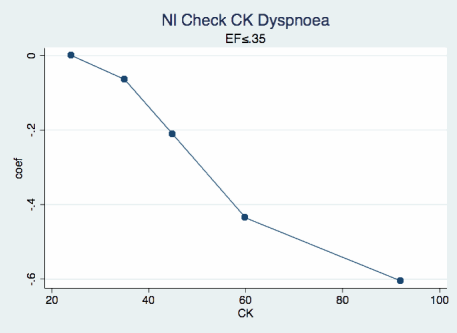
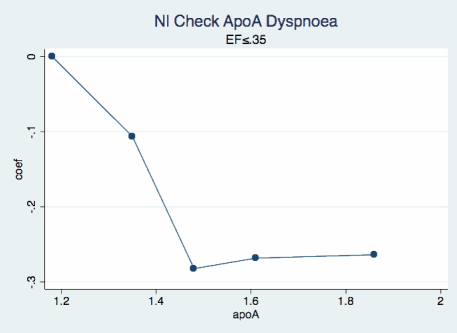
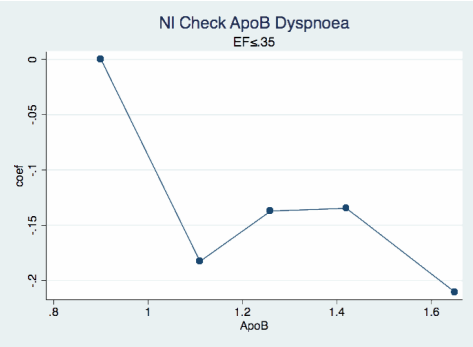
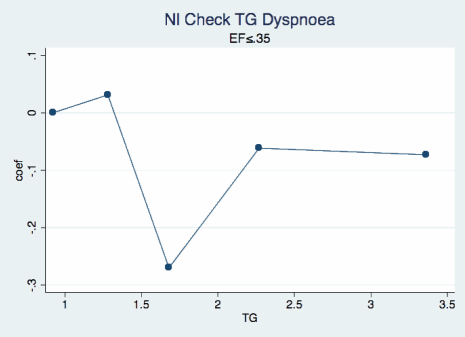
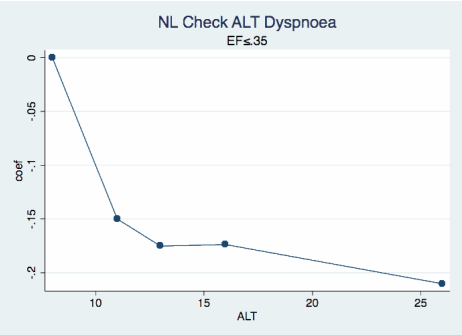
Creat	 NI Check Creatinine Fatigue EF≤.35 coef 0 .05 .1 .15 .2 80 100 120 140 160 Creatinine	0.5261

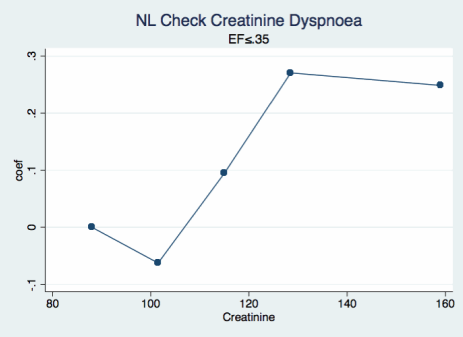
Linearity assessment dyspnoea on patients with LVEF≤35%: CORONA

	Dyspnoea	Nl Check
LVEF		0.4374
Weight		0.6706
SBP		0.2552
Heart Rate		0.3307

Age		0.1735
BMI		0.7686
Years w/HF		0.0014
Log(BNP)		0.1044
CRP		0.0004

TSH		0.6277
Cholesterol		0.0066
HDL		0.0126
LDL		0.0282
GFR		0.1194

CK		0.0005
ApoA		0.1634
ApoB		0.1785
TG		0.0923
ALT		0.0038

Creat	 NL Check Creatinine Dyspnoea EF≤.35 coef -.1 0 .1 .2 .3 80 100 120 140 160 Creatinine	0.2618

Appendix 4: Imputed data

This appendix shows results from analyses run on imputed data. Running the models on imputed data made no difference to my overall results.

Summary of imputed data

	Complete	Incomplete	Imputed	Total
Log(NT-proBNP)	3664	1347	1347	5011
Baseline BMI	4997	14	14	5011
Obese	5011	0	0	5011
Overweight	5011	0	0	5011
Baseline weight	5008	3	3	5011
Baseline systolic blood pressure	5010	1	1	5011
Baseline diastolic blood pressure	5010	1	1	5011
hs-CRP	5009	2	2	5011
TSH	4987	24	24	5011
TG	4985	26	26	5011
Cholesterol	4985	26	26	5011
HDL	4985	26	26	5011
LDL	4985	26	26	5011
apoB	4958	53	53	5011
apoA	4958	53	53	5011
ApoB_ApoA	4958	53	53	5011
Co –enzyme Q_{10}	1191	3820	3820	5011

Correlates of dyspnoea severity: imputed data

	Fatigue		Dyspnoea	
Variable	OR (95% CI)	P value	OR (95% CI)	P value
Age p/10 years	1.03 (0.92, 1.14)	0.612	1.20 (1.07, 1.36)	0.002
Female	1.46 (1.22, 1.75)	<0.001	1.17 (0.96, 1.43)	0.124
LVEF	1.86 (0.53, 6.55)	0.334	1.25 (0.31, 5.10)	0.753
NYHA III/IV*				
**fatigue/dyspnoea 2 vs. 1*	5.15 (4.08, 6.51)	<0.001	13.43 (8.83, 20.41)	<0.001
**fatigue/dyspnoea 3 vs.1*	13.82 (11.61, 16.44)	<0.001	30.00 (24.74, 36.39)	<0.001
Baseline BMI kg/m^2			1.02 (1.00, 1.04)	0.022
**fatigue 2 vs. 1*	1.03 (1.00, 1.05)	0.025		
**fatigue 3 vs.1*	1.00 (0.98, 1.02)	0.895		
Systolic BP p/10 mmHg	0.96 (0.91, 1.00)	0.043	0.99 (0.94, 1.03)	0.550
Heart rate p/10 beats/min	1.07 (1.00, 1.14)	0.048	1.16 (1.07, 1.24)	<0.001
Years w/heart failure	1.00 (0.99, 1.02)	0.740	1.00 (0.98, 1.02)	0.975
Myocardial Infarction			1.39 (1.18, 1.64)	<0.001
**fatigue 2 vs. 1*	1.68 (1.38, 2.06)	<0.001		
**fatigue 3 vs.1*	1.24 (1.05, 1.47)	0.012		
History of Diabetes	1.03 (0.86, 1.22)	0.772	1.11 (0.91, 1.35)	0.300
Stroke	1.35 (1.09, 1.67)	0.005	1.02 (0.81, 1.29)	0.853
Hypertension*	1.37 (1.18, 1.58)	<0.001	1.17 (0.99, 1.37)	0.069
History of angina*	1.31 (1.12, 1.53)	0.001		
* *dyspnoea 2 vs. 1*			1.54 (1.21, 1.98)	0.001
* *dyspnoea 3 vs. 1*			0.95 (0.77, 1.28)	0.606
Baseline atrial fibrillation/flutter			1.02 (0.82, 1.28)	0.839
**fatigue 2 vs. 1*	1.26 (0.91, 1.76)	0.167		
**fatigue 3 vs.1*	0.99 (0.79, 1.24)	0.942		
Intermittent Claudication	1.07 (0.87, 1.32)	0.495	1.08 (0.86, 1.36)	0.494
CABG/PCI	0.89 (0.76, 1.05)	0.166	0.92 (0.77, 1.10)	0.351
Pacemaker	0.89 (0.72, 1.10)	0.289	1.19 (0.93, 1.53)	0.163
ICD	0.67 (0.45, 0.97)	0.036	0.79 (0.52, 1.20)	0.275
MRAs*	1.29 (1.11, 1.49)	0.001		
* *dyspnoea 2 vs. 1*			0.90 (0.69, 1.17)	0.421
* *dyspnoea 3 vs. 1*			1.40 (1.16, 1.68)	<0.001
Loop/thiazide	0.97 (0.79, 1.20)	0.808		
* *dyspnoea 2 vs. 1*			1.38 (1.02, 1.87)	0.040
* *dyspnoea 3 vs. 1*			0.91 (0.67, 1.22)	0.510
Beta-blocker	1.07 (0.91, 1.25)	0.427	1.06 (0.89, 1.27)	0.505
Nitrate	1.11 (0.95, 1.30)	0.183	1.25 (1.05, 1.49)	0.014
Insulin	1.05 (0.78, 1.40)	0.754	0.94 (0.68, 1.30)	0.720
Antiarrhythmic	1.15 (0.93, 1.43)	0.199	0.91 (0.72, 1.16)	0.450
ACE inhibitor or ARB	0.97 (0.74, 1.25)	0.791	0.99 (0.73, 1.33)	0.941
Digoxin			1.22 (1.02, 1.46)	0.026
**fatigue 2 vs. 1*	1.29 (1.01, 1.64)	0.041		
**fatigue 3 vs.1*	1.22 (1.02, 1.45)	0.028		
Anticoagulant	0.90 (0.77,1.06)	0.218	0.89 (0.74, 1.06)	0.189
TSH mIU/L	1.00 (0.99, 1.02)	0.721		
* *dyspnoea 2 vs. 1*			1.02 (0.93, 1.12)	0.615
* *dyspnoea 3 vs. 1*			1.00 (0.98, 1.02)	0.893

Log(NT-proBNP)	1.07 (0.99, 1.15)	0.086	1.01 (0.93, 1.10)	0.739
hs-CRP mg/litre	1.00 (1.00, 1.01)	0.070	1.00 (1.00, 1.01)	0.276
Alanine transaminase IU/L	1.00 (1.00, 1.00)	0.547	1.00 (1.00, 1.00)	0.636
Creatine kinase p/50 IU/L	0.93 (0.85, 1.02)	0.146	0.95 (0.86, 1.06)	0.359
Creatinine μmol/L	1.00 (1.00, 1.00)	0.149	1.00 (0.99, 1.00)	0.076
Low density lipoprotein mmol/L	1.00 (0.93, 1.08)	0.945	0.96 (0.88, 1.04)	0.318

*Did not fulfil proportional odds (PO) assumption

LVEF – left ventricular ejection fraction, NYHA – New York Heart Association functional class, BP –blood pressure, CABG/PCI – coronary artery bypass grafting/ percutaneous coronary intervention, ICD – implantable cardioverter defibrillator, MRA – Mineralocorticoid receptor antagonists, ACE – angiotensin converting enzyme, ARB – angiotensin II receptor blocker, TSH – thyroid stimulating hormone, NT-proBNP – N-terminal of the prohormone brain natriuretic peptide, CRP – high-sensitivity C-reactive protein.

Adjusted hazard ratio for symptom severity and clinical outcomes: imputed data

	Fatigue				Dyspnoea			
	2 vs. 1		3 vs. 1		2 vs. 1		3 vs. 1	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular death or heart failure hospitalisation	1.02 (0.85, 1.21)	0.865	1.16 (0.97, 1.40)	0.111	1.12 (0.89, 1.40)	0.308	1.22 (0.96, 1.56)	0.103
Cardiovascular death	0.98 (0.78, 1.22)	0.827	1.13 (0.89, 1.44)	0.309	1.02 (0.77, 1.35)	0.884	1.13 (0.83, 1.53)	0.442
Heart failure hospitalisation	1.03 (0.83, 1.28)	0.762	1.20 (0.95, 1.52)	0.118	1.38 (1.02, 1.87)	0.039	1.60 (1.15, 2.21)	0.005
All-cause death	1.02 (0.84, 1.24)	0.815	1.15 (0.93, 1.42)	0.208	1.09 (0.85, 1.40)	0.492	1.14 (0.86, 1.50)	0.359

Adjusted for: age, sex, NYHA class, LVEF, body mass index (BMI), systolic blood pressure, heart rate, smoking, MI, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter (AF), stroke, intermittent claudication, pacemaker and ICD implantations, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, and log NT-proBNP.

Adjusted hazard ratio for symptom severity and clinical outcomes *including randomised treatment*: imputed data

	Fatigue				Dyspnoea			
	2 vs. 1		3 vs. 1		2 vs. 1		3 vs. 1	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular death or heart failure hospitalisation	1.02 (0.85, 1.21)	0.864	1.16 (0.96, 1.40)	0.113	1.13 (0.90, 1.41)	0.296	1.22 (0.96, 1.56)	0.106
Cardiovascular death	0.98 (0.78, 1.22)	0.827	1.13 (0.89, 1.44)	0.310	1.02 (0.77, 1.35)	0.883	1.13 (0.83, 1.53)	0.443
Heart failure hospitalisation	1.03 (0.83, 1.28)	0.767	1.20 (0.95, 1.51)	0.125	1.38 (1.02, 1.87)	0.037	1.59 (1.15, 2.21)	0.005
All-cause death	1.02 (0.84, 1.25)	0.812	1.15 (0.93, 1.42)	0.206	1.09 (0.85, 1.40)	0.488	1.14 (0.84, 1.50)	0.359

Adjusted for: age, sex, NYHA class, LVEF, body mass index (BMI), systolic blood pressure, heart rate, smoking, MI, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter (AF), stroke, intermittent claudication, pacemaker and ICD implantations, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, log NT-proBNP and randomised treatment.

Adjusted HR for *change* in symptom severity and outcomes: imputed data

	CV Death/HF hospitalisation HR (95%CI)	P	Cardiovascular death HR (95%CI)	P	HF hospitalisation HR (95%CI)	P	All-cause death HR (95%CI)	P
Change in fatigue								
Decrease	0.62 (0.54, 0.73)	<0.001	0.57 (0.46, 0.70)	<0.001	0.70 (0.59, 0.85)	<0.001	0.61 (0.51, 0.73)	<0.001
Increase	1.45 (1.24, 1.70)	<0.001	1.17 (0.95, 1.43)	0.137	1.83 (1.52, 2.20)	<0.001	1.13 (0.94, 1.35)	0.187
Change in dyspnoea								
Decrease	0.64 (0.55, 0.74)	<0.001	0.53 (0.44, 0.65)	<0.001	0.72 (0.60, 0.85)	<0.001	0.59 (0.50, 0.71)	<0.001
Increase	1.60 (1.35, 1.89)	<0.001	1.13 (0.91, 1.41)	0.269	2.29 (1.89, 2.77)	<0.001	1.04 (0.85, 1.27)	0.710

Adjusted for: age, sex, NYHA class, LVEF, body mass index, systolic blood pressure, heart rate, smoking, myocardial infarction, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter, stroke, intermittent claudication, pacemaker and cardioverter-defibrillator implantation, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, and log NT-proBNP and baseline symptom severity.

Adjusted HR for *change* in symptom severity and *outcomes including randomised treatment*: imputed data

	CV Death/HF hospitalisation **HR (95%CI)**	**P**	**Cardiovascular death** **HR (95%CI)**	**P**	**HF hospitalisation** **HR (95%CI)**	**P**	**All-cause death** **HR (95%CI)**	**P**
Change in fatigue								
Decrease	0.63 (0.54, 0.73)	<0.001	0.57 (0.46, 0.70)	<0.001	0.70 (0.58, 0.84)	<0.001	0.61 (0.51, 0.73)	<0.001
Increase	1.44 (1.23, 1.69)	<0.001	1.17 (0.95, 1.43)	0.135	1.85 (1.54, 2.22)	<0.001	1.13 (0.95, 1.36)	0.176
Change in dyspnoea								
Decrease	0.64 (0.55, 0.74)	<0.001	0.53 (0.44, 0.65)	<0.001	0.72 (0.60,0.85)	<0.001	0.59 (0.50, 0.71)	<0.001
Increase	1.60 (1.35, 1.89)	<0.001	1.13 (0.91, 1.41)	0.269	2.30 (1.89, 2.79)	<0.001	1.04 (0.85, 1.27)	0.706

Adjusted for: age, sex, NYHA class, LVEF, body mass index, systolic blood pressure, heart rate, smoking, myocardial infarction, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter, stroke, intermittent claudication, pacemaker and cardioverter-defibrillator implantation, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, and log NT-proBNP, baseline symptom severity and randomised treatment.

Appendix 4: Entire spectrum of LVEF

This appendix shows results from sensitivity analyses run on the entire cohort (entire spectrum of LVEF) available from CORONA.

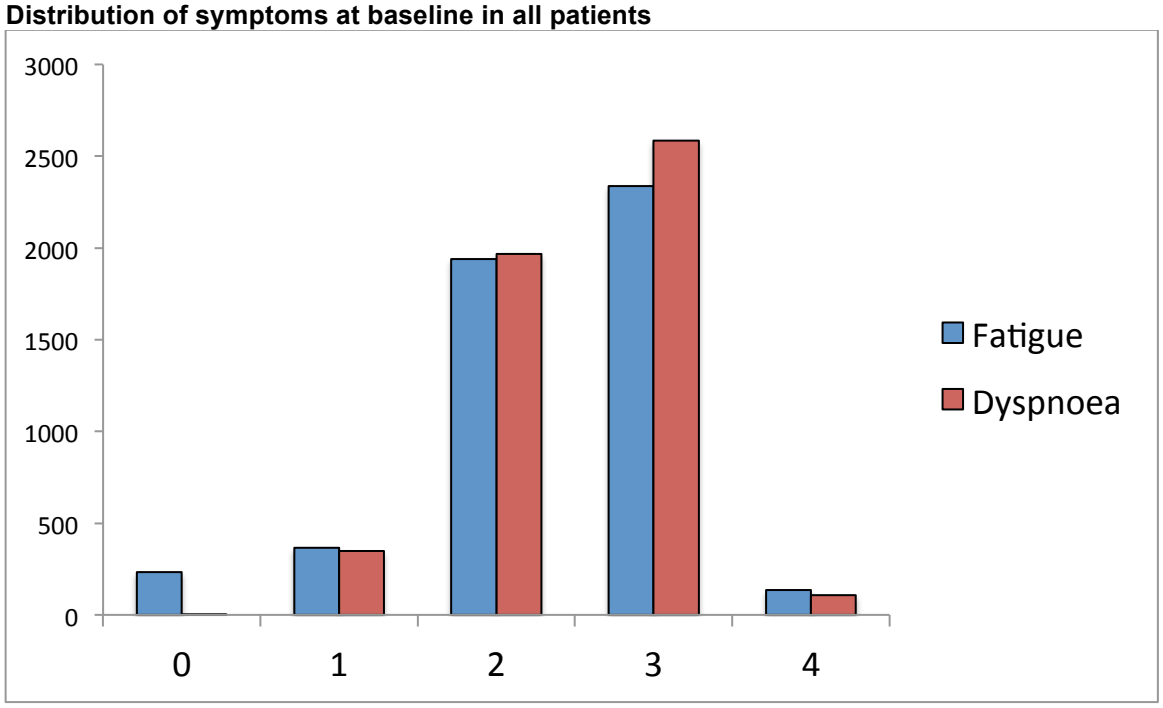
Tabulation between dyspnoea and NYHA class at baseline

Dyspnoea status	NYHA class at baseline			
	II	III	IV	Total
0	1 (0.02%)	0 (0.0%)	0 (0.0%)	1 (0.02%)
1	317 (6.3%)	32 (06%)	0 (0.0%)	349 (7.0%)
2	1346 (28.9%)	620 (12.4%)	2 (0.04%)	1968 (39.3%)
3	182 (3.6%)	2380 (47.5%)	23 (0.5%)	2585 (51.6%)
4	11 (0.2%)	49 (1.0%)	48 (1.0%)	108 (2.2%)
Total	1857 (37.1%)	3081 (61.5%)	73 (1.46%)	5011 (100%)

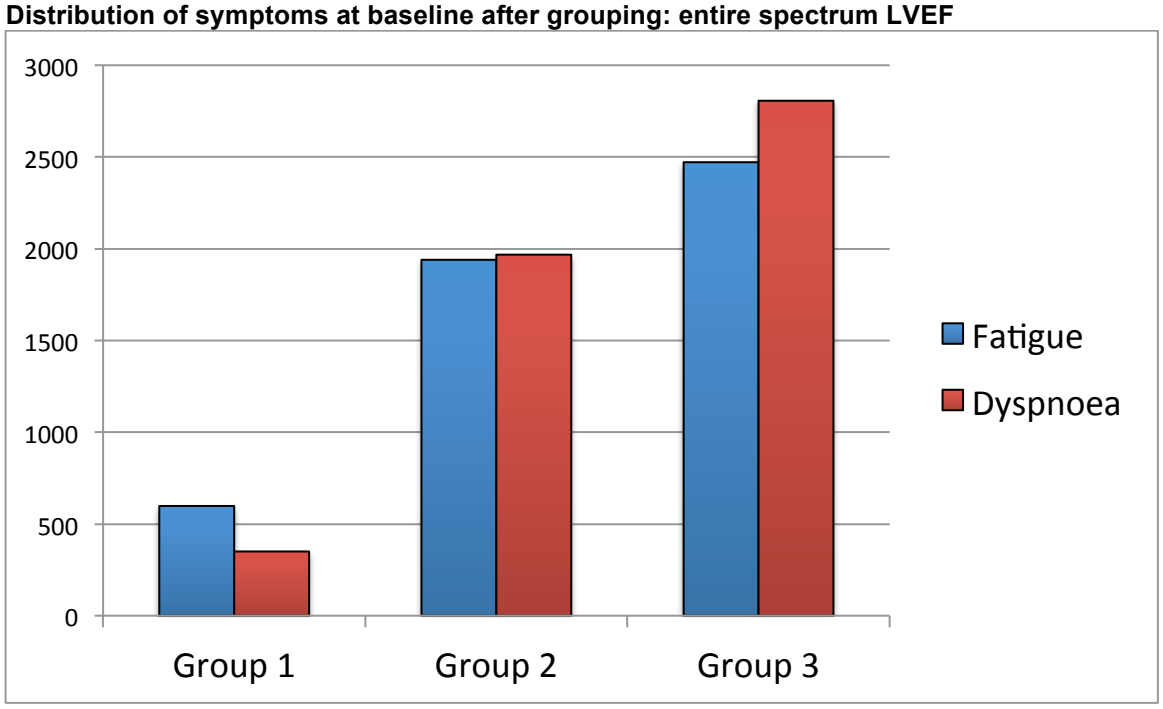
Tabulation between fatigue and NYHA class at baseline

Fatigue status	NYHA class at baseline			
	II	III	IV	Total
0	155 (3.1%)	75 (1.5%)	3 (0.1%)	233 (4.7%)
1	302 (6.0%)	61 (1.2%)	2 (0.04%)	365 (7.3%)
2	1160 (23.2%)	775 (15.5%)	5 (0.1%)	1940 (38.7%)
3	209 (4.2%)	2097 (41.9%)	31 (0.6%)	2337 (46.7%)
4	30 (0.6%)	73 (1.5%)	32 (0.6%)	135 (2.7%)
Total	1856 (37.1%)	3081 (61.5%)	73 (1.5%)	5010 (100%)

Distribution of symptoms at baseline in all patients



Distribution of symptoms at baseline after grouping: entire spectrum LVEF



The table below shows a cross tabulation between the merged groups of fatigue and dyspnoea at baseline for the entire cohort. Although there is some evidence of collinearity, 400 (8%) patients had more severe fatigue than dyspnoea while 916 (18%) had more severe dyspnoea than fatigue at baseline. 3695 (74%) had the same symptom severity at baseline.

Cross-tabulation between symptoms at baseline: entire spectrum of LVEF

	Dyspnoea			
Fatigue	1	2	3/4	Total
0/1	239 (4.8%)	267 (5.3%)	92 (1.8%)	598 (11.9%)
2	81 (1.6%)	1427 (5.5%)	432 (8.6%)	1940 (38.7%)
3/4	30 (0.6%)	273 (5.5%)	2169 (43.3%)	2472 (49.3%)
Total	350 (7.0%)	1967 (39.3%)	2693 (53.8%)	5010 (100%)

Baseline characteristics according to symptom severity entire spectrum of LVEF

	All patients (n=5011)	Fatigue 0/1 (n=598)	Fatigue 2 (n=1940)	Fatigue 3/4 (n=2472)	p value	Dyspnoea 1 (n=350)	Dyspnoea 2 (n=1968)	Dyspnoea 3/4 (n=2693)	p value
Age	72.7 ± 7.1	72.65 ± 6.90	72.69 ± 7.04	72.72 ± 7.16	0.8364	72.27 ± 7.08	72.51 ± 7.03	72.89 ± 7.12	0.0350
Female	1180 (23.6%)	95 (15.9%)	377 (19.4%)	708 (28.6%)	0.0001	55 (15.7%)	387 (19.7%)	738 (27.4%)	0.0001
Race									
Caucasian	4939 (98.6%)	589 (98.5%)	1915 (98.7%)	2435 (98.5%)		346 (98.9%)	1940 (98.6%)	2653 (98.5%)	
Black	13 (0.3%)	3 (0.5%)	5 (0.3%)	4 (0.2%)		1 (0.3%)	7 (0.4%)	5 (0.2%)	
Asian	38 (0.8%)	3 (0.5%)	11 (0.6%)	24 (1.0%)		3 (0.9%)	10 (0.5%)	25 (0.9%)	
Other	21 (0.4%)	3 (0.5%)	9 (0.5%)	9 (0.4%)	0.8007	0 (0.0%)	11 (0.6%)	10 (0.4%)	0.6540
NYHA III/IV	3154 (62.9%)	141 (23.6%)	780 (40.2%)	2233 (90.3%)	0.0001	32 (9.1%)	622 (31.6%)	2500 (92.8%)	0.0001
LVEF (%)	30.8 ± 0.6	29.10 ± 6.28	30.20 ± 6.19	31.79 ± 6.61	< 0.0001	28.66 ± 6.06	29.96 ± 6.12	31.80 ± 6.63	< 0.0001
Systolic BP mm/Hg	129.3 ± 16.5	129.55 ± 17.33	130.19 ± 16.56	128.50 ± 16.12	0.0092	129.52 ± 16.74	130.04 ± 16.64	128.68 ± 16.27	0.0201
Heart Rate bpm	71.7 ± 11.2	69.51 ± 10.56	71.13 ± 11.45	72.59 ± 11.05	< 0.0001	68.80 ± 11.04	70.63 ± 11.03	72.78 ± 11.20	< 0.0001
BMI kg/m2	27.2 ±4.5	26.71 ± 4.05	27.16 ± 4.48	27.35 ± 4.68	0.0022	26.46 ± 3.98	27.05 ± 4.46	27.41 ± 4.64	< 0.0001
BMI <25 kg/m^2	1,637 (32.8%)								
BMI ≥25 and <30 kg/m^2	2,181 (46.7%)	217 (36.4%) 265 (44.5%)	626 (32.4%) 846 (43.8%)	794 (32.2%) 1070 (43.3%)		135 (38.7%) 149 (42.7%)	659 (33.7%) 851 (43.5%)	843 (31.3%) 1181 (43.9%)	
BMI >=30 kg/m^2	1,179 (23.6%)	114 (19.1%)	459 (23.8%)	605 (24.5%)	0.0192	65 (18.6%)	448 (22.9%)	666 (24.8%)	0.0010
Years with heart failure	4.2 ± 4.6	3.83 ± 4.69	4.08 ± 4.61	4.30 ± 4.62	0.0145	3.63 ± 4.50	4.07 ± 4.60	4.30 ± 4.65	0.0058
Current Smoker	430 (8.6%)	72 (12.0%)	167 (8.6%)	191 (7.7%)	0.0021	36 (10.3%)	171 (8.7%)	223 (8.3%)	0.2556
	Past Medical History								
MI	3004 (60.0%)	307 (51.3%)	1159 (59.7%)	1537 (62.2%)	0.0001	172 (49.1%)	1173 (59.6%)	1659 (61.6%)	0.0001
Angina	3638 (72.6%)	369 (61.7%)	1367 (70.5%)	1901 (76.9%)	0.0001	200 (57.1%)	1394 (70.8%)	2044 (75.9%)	0.0001
CABG/PCI	1298 (25(%)	170 (28.4%)	553 (28.5%)	575 (23.3%)	0.0002	88 (25.1%)	584 (29.7%)	626 (23.2%)	0.0004
Hypertension	3175 (63.4%)	308 (51.5%)	1160 (59.8%)	1706 (69.0%)	0.0001	180 (51.4%)	1171 (59.5%)	1824 (67.7%)	0.0001
Diabetes	1477 (29.5)	142 (23.7%)	541 (27.9%)	793 (32.1%)	0.0001	76 (21.7%)	520 (26.4%)	881 (32.7%)	0.0001

Baseline atrial fibrillation/ flutter	1194 (23.8%)	94 (15.7%)	436 (22.5%)	664 (26.9%)	0.0001	65 (18.6%)	402 (20.4%)	727 (27.0%)	0.0001
Stroke	624 (12.5%)	49 (8.2%)	215 (11.1%)	360 (14.6%)	0.0001	34 (9.7%)	217 (11.0%)	373 (13.9%)	0.0012
Intermittent Claudication	638 (12.7%)	73 (12.2%)	220 (11.3%)	344 (13.9%)	0.0436	35 (10.0%)	225 (11.4%)	377 (14.0%)	0.0027
Pacemaker	561 (11.2%)	63 (10.5%)	209 (10.8%)	289 (11.7%)	0.2926	26 (7.4%)	206 (10.5%)	329 (12.2%)	0.0034
ICD	136 (2.7%)	25 (4.2%)	55 (2.8%)	56 (2.3%)	0.0120	10 (2.9%)	63 (3.2%)	63 (2.3%)	0.1398
	Laboratory measurements								
Cholesterol **mmol/L**	5.35 ± 1.08	5.44 ± 1.03	5.37 ± 1.05	5.31 ± 1.12	0.0044	5.45 ± 1.05	5.40 ± 1.05	5.30 ± 1.11	0.0002
ApoB:ApoA-1 ratio	0.87 ± 0.25	0.86 ± 0.24	0.86 ± 0.24	0.88 ± 0.26	0.0111	0.86 ± 0.24	0.87 ± 0.24	0.88 ± 0.26	0.2533
ApoB g/L	1.27 ± 0.30	1.28 ± 0.28	1.27 ± 0.30	1.27 ± 0.31	0.3391	1.28 ± 0.29	1.28 ± 0.29	1.26 ± 0.31	0.0350
ApoA g**/L**	1.50 ± 0.28	1.52 ± 0.27	1.52 ± 0.28	1.48 ± 0.28	< 0.0001	1.53 ± 0.27	1.51 ± 0.28	1.48 ± 0.28	0.0001
TSH mIU/L	2.19 ± 4.02	2.04 ± 2.59	2.13 ± 4.21	2.28 ± 4.16	0.1095	1.85 ± 1.38	2.18 ± 4.37	2.25 ± 3.99	0.1265
ALT IU/L	17.33 ± 37.79	18.07 ± 26.32	17.33 ± 36.01	17.03 ± 40.87	0.5553	19.87 ± 31.22	17.28 ± 35.20	17.04 ± 40.32	0.3138
LDL mmol/L	3.55 ± 0.94	3.60 ± 0.90	3.56 ± 0.92	3.53 ± 0.96	0.0790	3.63 ± 0.93	3.59 ± 0.92	3.51 ± 0.95	0.0007
NT-proBNP--pmol/litre (median)	173.3 [73.0, 368.2]	65 (10.9%)	230 (11.9%)	329 (13.3%)	0.0003	143.1 [74.9, 310.6]	166.4 [70.9, 348.1]	183.5 [73.7, 394.7]	0.0069
hs-CRP mg/litre (median)	3.5 [1.6, 7.4]	140.4 [71.4, 280.7]	170.0 [70.9, 359.7]	186.6 [76.1, 396.1]	< 0.0001	2.4 [1.2, 5.5]	3.2 [1.5, 6.7]	3.9 [1.7, 8.3]	< 0.000
Co-enzyme Q_{10} mmol/L	0.7 [0.6, 1.0]	2.9 [1.3, 6.4]	3.3 [1.5, 6.8]	3.8 [1.6, 8.2]	0.0006	0.7 [0.6, 1.0]	0.8 [0.6, 1.0]	0.7 [0.5, 1.0]	0.0149
CK	45.0 [32.0, 65.0]	50.0 [36.0, 70.0]	50.0 [36.0, 70.0]	42.0 [31.0, 61.0]	<0.0001	49.5 [34.0, 73.0]	48.0 [34.0, 67.0]	42.0 [31.0, 61.0]	<0.0001
Creatinine	115.32 ± 28.08	115.11 ±	115.57 ± 27.70	115.15 ±	0.8392	115.73 ± 27.65	115.32 ± 27.32	115.27 ± 28.69	0.8167

µmol/L		26.08		28.83					
eGFR ml/min/1.73m^2	56.30 ± 15.22	57.02 ± 14.94	56.68 ± 15.27	55.83 ± 15.25	0.0312	57.03 ± 15.03	56.89 ± 15.10	55.78 ± 15.32	0.0132
	Medication								
Loop/thiazide diuretics	4416 (88.1%)	57.02 ± 14.94	56.68 ± 15.27	55.83 ± 15.25	0.0001	279 (79.7%)	1676 (85.2%)	2461 (91.4%)	0.0001
ACE inhibitor or ARB	4599 (91.8%)	495 (82.8%)	1664 (85.8%)	2256 (91.3%)	0.0740	324 (92.6%)	1822 (92.6%)	2453 (91.1%)	0.0781
MRAs	1965 (39.2%)	562 (94.0%)	1778 (91.6%)	2258 (91.3%)	0.0001	122 (34.9%)	645 (32.8%)	1198 (44.5%)	0.0001
Digitalis	1648 (32.9%)	187 (31.3%)	666 (34.3%)	1111 (44.9%)	0.0001	85 (24.3%)	594 (30.2%)	969 (36.0%)	0.0001
Anticoagulant	1767 (35.3%)	142 (23.7%)	614 (31.6%)	892 (36.1%)	0.1979	136 (38.9%)	709 (36.0%)	922 (34.2%)	0.0566
Beta-blockers	3766 (75.2%)	214 (35.8%)	708 (36.5%)	845 (34.2%)	0.8379	261 (74.6%)	1493 (75.9%)	2012 (74.7%)	0.6047
Nitrate	1638 (32.7%)	445 (74.4%)	1471 (75.8%)	1849 (74.8%)	0.0001	65 (18.6%)	526 (26.7%)	1047 (38.9%)	0.0001
Insulin	403 (8.0%)	133 (22.2%)	538 (27.7%)	967 (39.1%)	0.0271	20 (5.7%)	147 (7.5%)	236 (8.8%)	0.0216
Antiarrhythmic	624 (12.5%)	38 (6.4%)	147 (7.6%)	218 (8.8%)	0.0570	42 (12.0%)	245 (12.4%)	337 (12.5%)	0.8243

Correlates of symptoms

Unadjusted outcomes

Patients with higher levels of fatigue (i.e. fatigue on slight exertion or at rest) were more likely to be female, and to have lower systolic blood pressure than patients with lower levels of fatigue. They also had higher heart rates and higher LVEFs and were more likely to be in NYHA functional class III or IV. Patients with greater fatigue more frequently had a history of myocardial infarction, angina, hypertension, diabetes, or stroke, lower ApoA-1 levels and higher levels of NT-proBNP and hsCRP. They were less likely to have a history of coronary intervention, smoke or have an ICD implanted. They were more likely to be treated with insulin.

Patients with higher levels of dyspnoea (i.e. dyspnoea at rest or slight exertion) presented a generally similar pattern, although there was no association between level of dyspnoea and history of stroke, ICD or smoking status and they were more likely to have a longer time (in years) with heart failure. They also had lower lipid levels and lower eGFR levels.

Both patients with higher levels fatigue and dyspnoea were more likely to be in atrial fibrillation/flutter at baseline and were more likely to be treated with diuretics and digitalis, nitrates or MRAs.

Adjusted outcomes

3624 (72%) patients were included in the model, mostly due to missing NT-proBNP values.

Running the model on the entire spectrum of LVEF did not substantially change the results obtained from running the analyses on patients with LVEF≤35%. Overall same correlates persevered, if anything, the associations seemed to grow a bit stronger (i.e. slightly narrower confidence intervals and smaller p values). When compared to my main analysis (i.e. patients with LVEF≤35%), the tendencies in associations persisted and nothing mayor was added by including the entire cohort.

Correlates of symptom severity: entire spectrum LVEF

	Fatigue		Dyspnoea	
Variable	**OR (95% CI)**	**value**	**OR (95% CI)**	**P value**
Age p/10 years	0.94 (0.83, 1.05)	0.244	1.05 (0.93, 1.19)	0.446
Female	1.53 (1.27, 1.84)	<0.001	1.38 (1.12, 1.70)	0.002
LVEF	2.57 (0.76, 8.65)	0.125	1.52 (0.40, 5.88)	0.537
NYHA III/IV*				
**fatigue/dyspnoea 2 vs. 1*	5.42 (4.24, 6.91)	<0.001	17.26 (11.00, 27.08)	<0.001
**fatigue/dyspnoea 3 vs.1*	13.38 (11.02, 16.23)	<0.001	30.38 (24.44, 37.78)	<0.001
Overweight*	1.06 (0.89, 1.25)	0.519	1.20 (1.00, 1.45)	0.053
Obese*			1.21 (0.96, 1.52)	0.109
**fatigue 2 vs. 1*	1.29 (0.96, 1.74)	0.095		
**fatigue 3 vs.1*	0.94 (0.75, 1.17)	0.574		
Systolic BP p/10 mmHg	0.96 (0.91, 1.00)	0.055	0.95 (0.91, 1.00)	0.075
Heart rate p/10 beats/min	1.05 (0.98, 1.12)	0.179	1.10 (1.01, 1.19)	0.020
Years w/heart failure	1.01 (0.99, 1.02)	0.484	1.00 (0.98, 1.02)	0.808
Myocardial Infarction			1.35 (1.14, 1.60)	0.001
**fatigue 2 vs. 1*	1.83 (1.46, 2.30)	<0.001		
**fatigue 3 vs.1*	1.31 (1.11, 1.55)	0.002		
History of Diabetes	1.07 (0.89, 1.28)	0.484	1.29 (1.05, 1.58)	0.016
Stroke	1.32 (1.06, 1.64)	0.015	1.03 (0.81, 1.31)	0.835
Hypertension*	1.49 (1.27, 1.75)	<0.001	1.30 (1.09, 1.55)	0.003
History of angina*				
* *fatigue/dyspnoea 2 vs. 1*	1.45 (1.15, 1.83)	0.002	1.59 (1.20, 2.11)	0.001
* *fatigue/dyspnoea 3 vs. 1*	1.13 (0.94, 1.35)	0.209	1.02 (0.83, 1.26)	0.820
Baseline atrial fibrillation/flutter			1.14 (0.90, 1.44)	0.290
**fatigue 2 vs. 1*	1.59 (1.16, 2.00)	0.004		
**fatigue 3 vs.1*	1.10 (0.88, 1.38)	0.392		
Intermittent Claudication	1.10 (0.89, 1.36)	0.380	1.11 (0.88, 1.41)	0.368
CABG/PCI	0.86 (0.72, 1.01)	0.071	0.87 (0.72, 1.05)	0.142
Pacemaker	0.96 (0.76, 1.21)	0.719	1.15 (0.89, 1.50)	0.288
ICD	0.79 (0.52, 1.19)	0.264	0.83 (0.53, 1.30)	0.415
MRAs*	1.39 (1.19, 1.62)	<0.001	1.25 (1.06, 1.49)	0.010
Loop/thiazide	1.13 (0.90, 1.41)	0.292	1.17 (0.91, 1.49)	0.214
Beta-blocker	1.10 (0.93, 1.31)	0.265	1.11 (0.91, 1.34)	0.296
Nitrate	1.26 (1.07, 1.48)	0.006	1.36 (1.13, 1.64)	0.001

Insulin	0.91 (0.68, 1.22)	0.524	0.80 (0.57, 1.12)	0.199
Antiarrhythmic	1.07 (0.85, 1.34)	0.583	0.86 (0.68, 1.11)	0.252
ACE inhibitor or ARB	1.00 (0.77, 1.30)	0.997	1.13 (0.85, 1.53)	0.384
Digoxin	1.17 (0.99, 1.39)	0.066	1.12 (0.93, 1.36)	0.230
Anticoagulant	0.91 (0.77,1.08)	0.299	0.94 (0.78, 1.13)	0.490
TSH mIU/L	1.00 (0.98, 1.02)	0.892	1.00 (0.98, 1.02)	0.904
Log(NT-proBNP)	1.05 (0.98, 1.13)	0.165	1.00 (0.93, 1.09)	0.910
hs-CRP mg/litre	1.00 (1.00, 1.01)	0.893	1.00 (0.99, 1.00)	0.853
Alanine transaminase IU/L	1.00 (1.00, 1.00)	0.836	1.00 (1.00, 1.00)	0.636
Creatine kinase p/50 IU/L	0.95 (0.86, 1.04)	0.252	0.94 (0.85, 1.04)	0.218
Creatinine μmol/L	1.00 (0.99, 1.00)	0.124	1.00 (0.99, 1.00)	0.026
Low density lipoprotein mmol/L	0.99 (0.91, 1.07)	0.759	0.95 (0.87, 1.03)	0.220

*Did not fulfil proportional odds (PO) assumption

LVEF – left ventricular ejection fraction, NYHA – New York Heart Association functional class, BP –blood pressure, CABG/PCI – coronary artery bypass grafting/ percutaneous coronary intervention, ICD – implantable cardioverter defibrillator, MRA – Mineralocorticoid receptor antagonists, ACE – angiotensin converting enzyme, ARB – angiotensin II receptor blocker, TSH – thyroid stimulating hormone, NT-proBNP – N-terminal of the prohormone brain natriuretic peptide, CRP – – high-sensitivity C-reactive protein.

Correlates of change in fatigue severity: entire spectrum of LVEF

	Decrease in fatigue			Increase in fatigue		
	RR	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
Fatigue 2 vs. 1	2.02	1.24, 3.30	0.005	0.26	0.19, 0.34	<0.001
Fatigue 3 vs. 1	9.07	5.44, 15.11	<0.001	0.03	0.02, 0.04	<0.001
Age	0.98	0.97, 1.00	0.029	1.01	0.99, 1.03	0.184
Female	0.98	0.78, 1.23	0.873	1.05	0.77, 1.43	0.763
LVEF %	0.64	0.13, 2.23	0.575	0.54	0.07, 4.00	0.553
NYHA III/IV	0.52	0.39, 0.68	<0.001	1.71	1.30, 2.26	<0.001
Overweight	0.94	0.75, 1.18	0.607	1.22	0.92, 1.63	0.165
Obese	1.01	0.77, 1.32	0.941	1.28	0.90, 1.82	0.171
Systolic BP p/10 mmHg	0.94	0.88, 1.00	0.040	0.87	0.81, 0.95	0.001
Heart rate p/10 beats/min	0.97	0.88, 1.06	0.472	1.11	0.99, 1.25	0.070
Years w/heart failure	0.98	0.96, 1.00	0.098	1.00	0.97, 1.03	0.970
Myocardial Infarction	0.81	0.66, 0.99	0.039	0.80	0.62, 1.03	0.086
History of Diabetes	1.21	0.96, 1.52	0.098	0.99	0.73, 1.34	0.949
Stroke	1.05	0.80, 1.39	0.704	0.99	0.67, 1.44	0.938
Hypertension*	0.98	0.79, 1.21	0.839	1.09	0.85, 1.43	0.485
Baseline atrial fibrillation/flutter	0.94	0.72, 1.23	0.647	0.80	0.56, 1.14	0.224
History of angina*	0.81	0.66, 1.01	0.061	1.12	0.85, 1.47	0.420
Intermittent Claudication	1.01	0.77, 1.33	0.950	1.69	1.22, 2.36	0.002
CABG/PCI	1.45	1.16, 1.80	0.001	1.04	0.78, 1.38	0.801
Pacemaker	0.89	0.66, 1.21	0.475	0.74	0.50, 1.09	0.129
ICD	1.33	0.78, 2.27	0.300	0.52	0.23, 1.17	0.114
MRAs*	0.84	0.69, 1.02	0.085	1.18	0.92, 1.53	0.199
Loop/thiazide	0.81	0.60, 1.29	0.166	1.27	0.86, 1.89	0.227
Beta-blocker	0.80	0.64, 1.00	0.053	0.66	0.50, 0.87	0.003
Nitrate	0.68	0.55, 0.85	<0.001	1.06	0.81, 1.39	0.653
Insulin	0.88	0.60, 1.29	0.519	0.92	0.56, 1.54	0.763
Antiarrhythmic	0.82	0.60, 1.12	0.211	1.16	0.80, 1.70	0.421
ACE inhibitor or ARB	0.89	0.63, 1.26	0.505	0.84	0.55, 1.29	0.430
Digoxin	1.29	1.04, 1.61	0.021	1.39	1.05, 1.83	0.020
Anticoagulant	0.99	0.79, 1.23	0.904	0.93	0.70, 1.24	0.626
TSH mIU/L	1.01	0.99, 1.04	0.354	1.00	0.98, 1.03	0.744
Log(NT-proBNP)	1.00	0.91, 1.09	0.949	1.15	1.02, 1.31	0.023
hs-CRP	1.00	1.00, 1.01	0.218	1.00	1.00, 1.01	0.198
Alanine transaminase IU/L	1.00	0.99, 1.00	0.568	1.00	1.00, 1.00	0.612
Creatine kinase p/50	0.93	0.82, 1.07	0.317	0.84	0.71, 1.01	0.061
Creatinine μmol/L	1.00	1.00, 1.00	0.559	1.00	0.99, 1.00	0.225
Low density lipoprotein mmol/L	0.93	0.84, 1.03	0.188	0.90	0.79, 1.03	0.127

Correlates of change in dyspnoea severity: entire spectrum LVEF

	Decrease in dyspnoea			Increase in dyspnoea		
	RR	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
Dyspnoea 2 vs. 1	2.43	1.34, 4.43	0.003	0.25	0.17, 0.36	<0.001
Dyspnoea 3 vs. 1	8.64	4.59, 16.30	<0.001	0.03	0.02, 0.05	<0.001
Age	0.99	0.97, 1.00	0.038	1.01	0.99, 1.04	0.163
Female	0.87	0.70, 1.09	0.239	1.22	0.88, 1.70	0.240
LVEF %	0.94	0.21, 4.30	0.941	0.29	0.03, 2.56	0.265
NYHA III/IV	0.68	0.51, 0.91	0.009	1.93	1.40, 2.69	<0.001
Overweight	0.93	0.75, 1.15	0.505	0.99	0.72, 1.35	0.943
Obese	0.95	0.73, 1.22	0.669	1.11	0.76, 1.63	0.577
Systolic BP p/10 mmHg	0.97	0.91, 1.03	0.280	0.93	0.85, 1.01	0.091
Heart rate p/10 beats/min	0.92	0.85, 1.01	0.071	1.01	0.88, 1.14	0.932
Years w/heart failure	0.99	0.97, 1.01	0.151	1.00	0.97, 1.03	0.845
Myocardial Infarction	0.77	0.64, 0.94	0.009	0.90	0.68, 1.19	0.457
History of Diabetes	1.00	0.80, 1.24	0.977	1.20	0.87, 1.68	0.262
Stroke	1.05	0.81, 1.37	0.710	1.32	0.90, 1.92	0.155
Hypertension*	1.10	0.90, 1.34	0.367	1.19	0.89, 1.60	0.241
Baseline atrial fibrillation/flutter	0.88	0.68, 1.14	0.324	1.02	0.70, 1.49	0.910
History of angina*	0.72	0.59, 0.89	0.002	1.10	0.81, 1.50	0.528
Intermittent Claudication	0.83	0.63, 1.09	0.173	1.99	1.40, 2.81	<0.001
CABG/PCI	1.45	1.18, 1.78	0.001	1.04	0.76, 1.42	0.819
Pacemaker	1.20	0.91, 1.59	0.203	1.15	0.77, 1.72	0.502
ICD	1.38	0.83, 2.29	0.218	1.00	0.46, 2.18	0.999
MRAs*	0.76	0.63, 0.92	0.005	1.33	1.00, 1.75	0.047
Loop/thiazide	0.82	0.62, 1.09	0.167	1.29	0.82, 2.03	0.266
Beta-blocker	0.82	0.66, 1.02	0.069	0.72	0.53, 0.98	0.038
Nitrate	0.78	0.64, 0.96	0.019	1.13	0.83, 1.52	0.441
Insulin	0.93	0.64, 1.34	0.684	0.79	0.45, 1.40	0.432
Antiarrhythmic	0.86	0.64, 1.17	0.340	0.85	0.55, 1.31	0.449
ACE inhibitor or ARB	1.14	0.81, 1.61	0.456	1.53	0.89, 2.63	0.120
Digoxin	1.17	0.95, 1.44	0.140	1.15	0.84, 1.55	0.382
Anticoagulant	1.06	0.86, 1.31	0.593	0.91	0.67, 1.24	0.562
TSH	0.94	0.90, 0.99	0.026	1.00	0.97, 1.03	0.829
Log(NT-proBNP)	1.10	1.00, 1.20	0.044	1.26	1.10, 1.45	0.001
hs-CRP	1.00	1.00, 1.01	0.596	1.00	1.00, 1.01	0.275
Alanine transaminase IU/L	1.00	1.00, 1.00	0.450	1.00	1.00, 1.00	0.708
Creatine kinase p/50	0.90	0.79, 1.02	0.099	0.86	0.71, 1.04	0.129
Creatinine μmol/L	1.00	1.00, 1.00	0.500	1.00	0.99, 1.00	0.849
Low density lipoprotein mmol/L	0.94	0.85, 1.04	0.222	0.90	0.77, 1.04	0.147

Symptoms as predictors of outcome: entire spectrum of LVEF

As can be seen in the following tables and figures, including all patients in the analyses made little difference to my results.

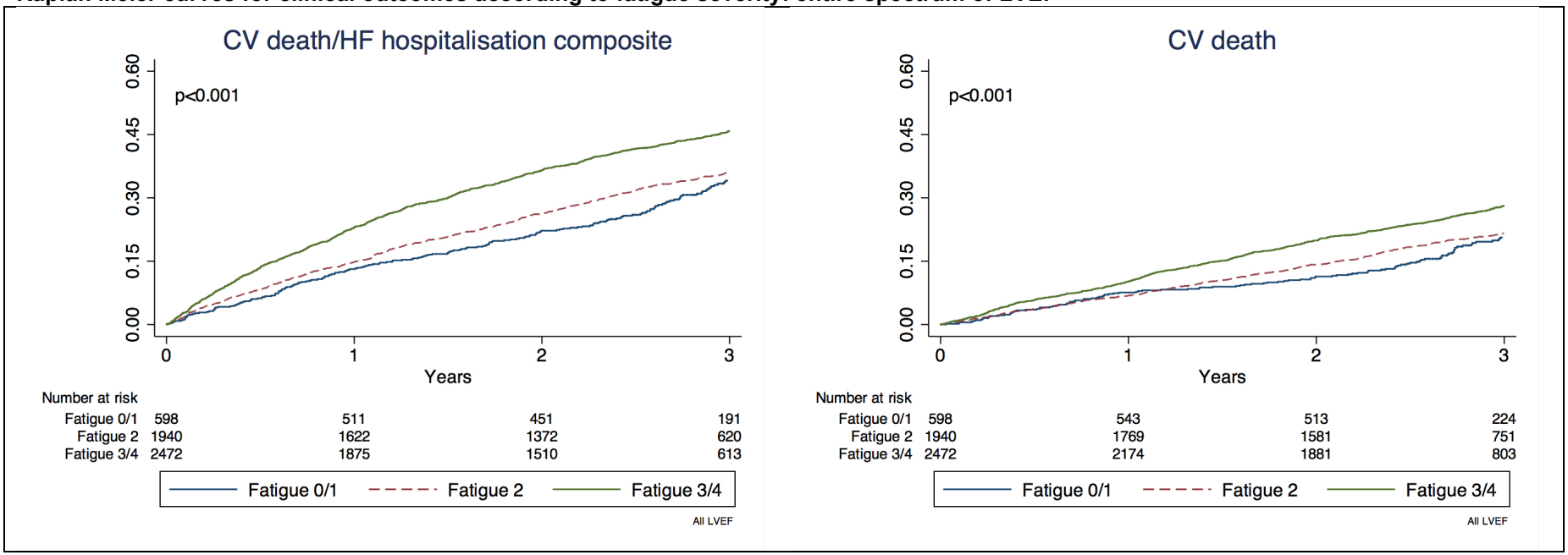
Clinical outcomes according to baseline symptom severity: entire spectrum of LVEF

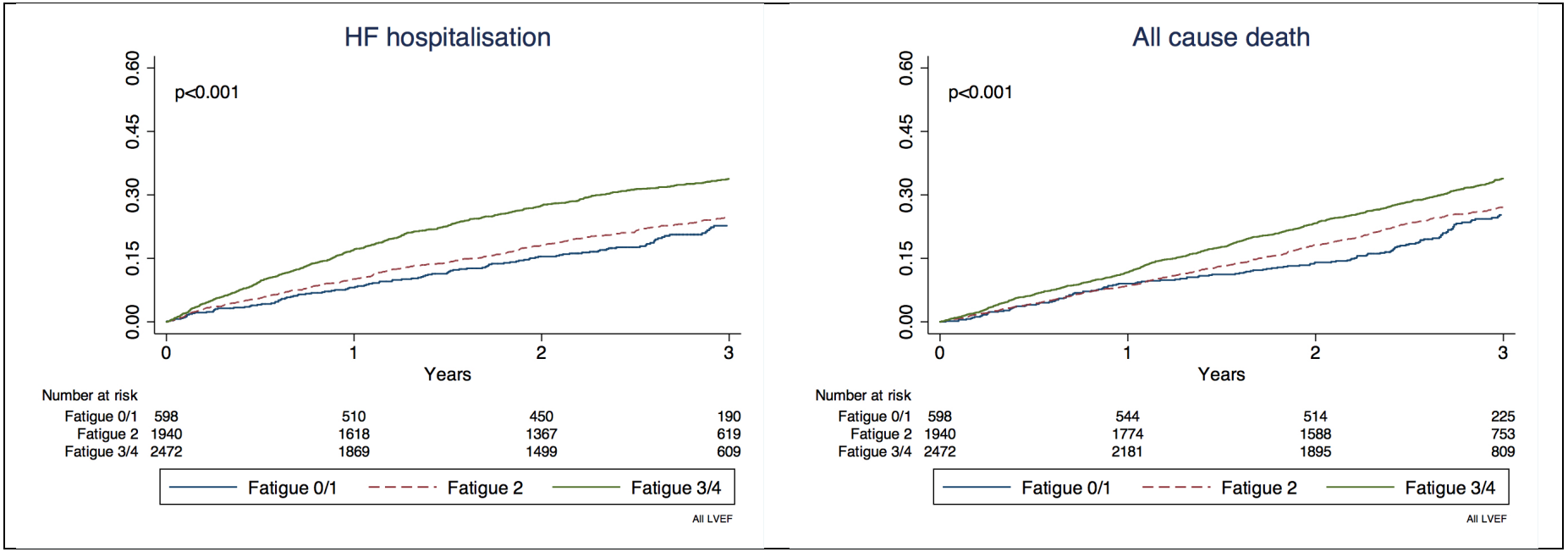
	Fatigue			Dyspnoea		
	0/1	**2**	**3/4**	**1**	**2**	**3/4**
	(n=598)	**(n=1940)**	**(n=2472)**	**(n=350)**	**(n=1968)**	**(n=2693)**
n (%)						
Cardiovascular death or heart failure hospitalisation	68/119 (31.3)	244/426 (35.5)	354/746 (44.5)	48/52 (28.5)	240/431 (34.1)	1378/808 (44.0)
Cardiovascular death	113 (18.9)	398 (20.5)	663 (26.8)	65 (18.6)	390 (19.8)	719 (26.7)
Heart failure hospitalisation	119 (19.9)	426 (22.0)	746 (30.2)	52 (14.9)	431 (21.9)	808 (30.0)
All-cause death	144 (24.1)	521 (26.9)	822 (33.3)	80 (22.9)	518 (26.3)	889 (33.0)

Unadjusted hazard ratio for symptom severity and clinical outcomes: entire spectrum of LVEF

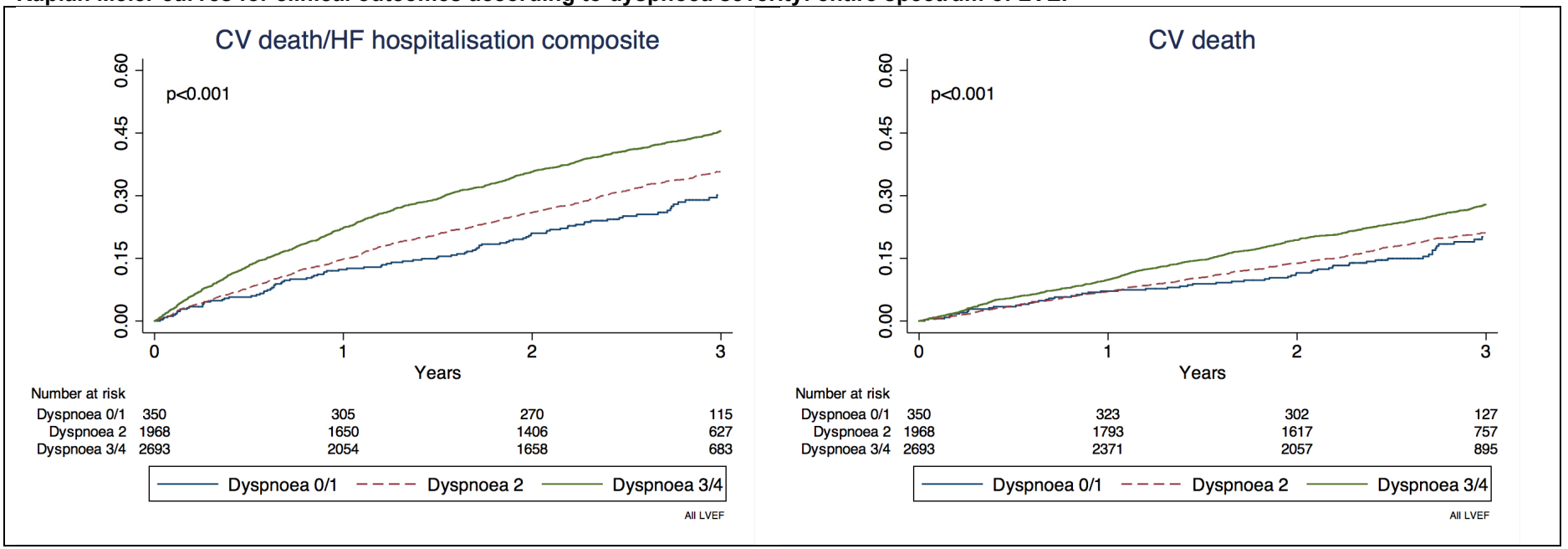
	Fatigue				Dyspnoea			
	2 vs. 1		3 vs. 1		2 vs. 1		3 vs. 1	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular death or heart failure hospitalisation	1.14 (0.97, 1.34)	0.104	1.62 (1.39, 1.90)	<0.001	1.24 (1.01, 1.54)	0.041	1.77 (1.45, 2.17)	<0.001
Cardiovascular death	1.11 (0.90, 1.36)	0.341	1.53 (1.26, 1.87)	<0.001	1.08 (0.83, 1.40)	0.564	1.54 (1.19, 1.99)	0.001
Heart failure hospitalisation	1.14 (0.93, 1.40)	0.200	1.72 (1.42, 2.09)	<0.001	1.54 (1.15, 2.05)	0.003	2.32 (1.75, 3.06)	<0.001
All-cause death	1.14 (0.95, 1.37)	0.171	1.49 (1.25, 1.78)	<0.001	1.16 (0.92, 1.47)	0.204	1.55 (1.23, 1.94)	<0.001

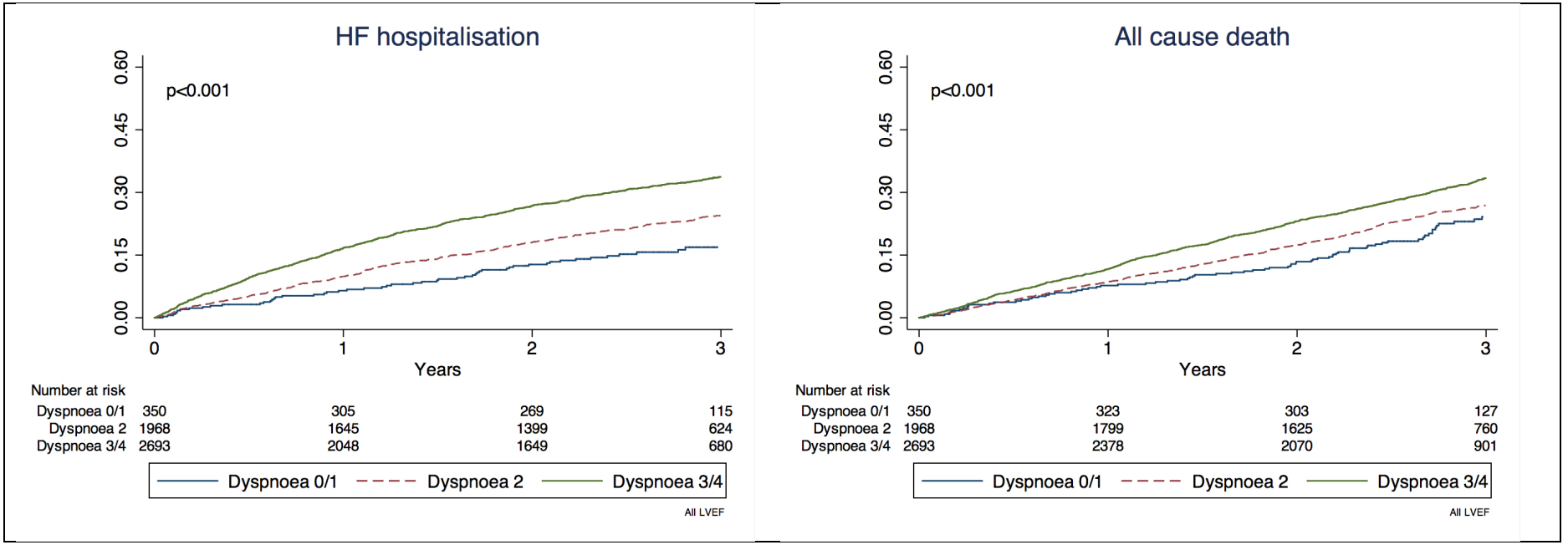
Kaplan Meier curves for clinical outcomes according to fatigue severity: entire spectrum of LVEF




HF hospitalisation
p<0.001
0.00
0.15
0.30
0.45
0.60
0
1
2
3
Years
Number at risk
Fatigue 0/1 598 510 450 190
Fatigue 2 1940 1618 1367 619
Fatigue 3/4 2472 1869 1499 609
Fatigue 0/1
Fatigue 2
Fatigue 3/4
All LVEF
All cause death
p<0.001
0.00
0.15
0.30
0.45
0.60
0
1
2
3
Years
Number at risk
Fatigue 0/1 598 544 514 225
Fatigue 2 1940 1774 1588 753
Fatigue 3/4 2472 2181 1895 809
Fatigue 0/1
Fatigue 2
Fatigue 3/4
All LVEF

Kaplan Meier curves for clinical outcomes according to dyspnoea severity: entire spectrum of LVEF




HF hospitalisation
p<0.001
0.00
0.15
0.30
0.45
0.60
0
1
2
3
Years
Number at risk
Dyspnoea 0/1 350 305 269 115
Dyspnoea 2 1968 1645 1399 624
Dyspnoea 3/4 2693 2048 1649 680
Dyspnoea 0/1
Dyspnoea 2
Dyspnoea 3/4
All LVEF
All cause death
p<0.001
0.00
0.15
0.30
0.45
0.60
0
1
2
3
Years
Number at risk
Dyspnoea 0/1 350 323 303 127
Dyspnoea 2 1968 1799 1625 760
Dyspnoea 3/4 2693 2378 2070 901
Dyspnoea 0/1
Dyspnoea 2
Dyspnoea 3/4
All LVEF

Adjusted outcomes

A total of 3613 (72%) patients were included in the analyses, 1398 were omitted due mostly to missing NT-proBNP values as mentioned previously.

As it is shown below, including the entire spectrum of LVEF did not modify the trends seen in the rest of the models. Although it seems to have weakened the relationship between symptom severity and death (both cardiovascular and all cause death), the confidence intervals in all the models tend to overlap and the hazard ratios all go in the same direction.

Hazard ratio for symptom severity and clinical outcomes: entire spectrum of LVEF

	Fatigue				Dyspnoea			
	2 vs. 1		3 vs. 1		2 vs. 1		3 vs. 1	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular death or heart failure hospitalisation	0.99 (0.81, 1.21)	0.91-	1.11 (0.90, 1.37)	0.334	1.04 (0.81, 1.35)	0.730	1.09 (0.83, 1.44)	0.533
Cardiovascular death	0.98 (0.76, 1.27)	0.893	1.08 (0.82, 1.43)	0.568	1.11 (0.79, 1.55)	0.542	1.24 (0.86, 1.78)	0.249
Heart failure hospitalisation	0.95 (0.74, 1.21)	0.668	1.10 (0.85, 1.42)	0.469	1.17 (0.84, 1.63)	0.346	1.28 (0.91, 1.84)	0.158
All-cause death	1.07 (0.85, 1.34)	0.565	1.11 (0.87, 1.42)	0.396	1.21 (0.90, 1.63)	0.212	1.24 (0.89, 1.71)	0.201

Adjusted for: age, sex, NYHA class, LVEF, body mass index (BMI), systolic blood pressure, heart rate, smoking, MI, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter (AF), stroke, intermittent claudication, pacemaker and ICD implantations, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, and log NT-proBNP

Change in symptom severity: entire spectrum of LVEF

Baseline characteristics according to change in symptom severity: entire spectrum of LVEF

	Fatigue				Dyspnoea			
	Unchanged n=3253	**Decrease** n=855	**Increase** n=545	**P value**	**Unchanged** n=3306	**Decrease** n=914	**Increase** n=434	**P value**
Age	72.60 ± 7.08	72.24 ± 6.96	73.41 ± 7.11	0.1219	72.53 ± 7.08	72.47 ± 7.04	73.72 ± 6.93	0.0105
Female	779 (23.9%)	206 (24.1%)	118 (21.7%)	0.3417	806 (24.4%)	200 (21.9%)	97 (22.4%)	0.1331
Race				0.7434				0.4876
Caucasian	3212 (98.7%)	836 (97.8%)	540 (99.1%)		3263 (98.7%)	897 (98.1%)	428 (98.6%)	
Black	7 (0.2%)	3 (0.4%)	1 (0.2%)		6 (0.2%)	3 (0.3%)	3 (0.7%)	
Asian	21 (0.6%)	11 (1.3%)	3 (0.6%)		22 (0.7%)	10 (1.1%)	3 (0.7%)	
Other	13 (0.4%)	5 (0.6%)	1 (0.2%)		15 (0.5%)	4 (0.4%)	0 (0.0%)	
NYHA III/IV	2037 (62.6%)	586 (68.5%)	271 (49.7%)	0.0003	2032 (61.5%)	665 (72.8%)	197 (45.4%)	0.0224
LVEF (%)	31.08 ± 6.40	31.19 ± 6.51	29.83 ± 6.43	0.0007	31.06 ± 6.35	31.23 ± 6.66	29.54 ± 6.38	0.0006
Systolic BP mm/Hg	130.16 ± 16.16	128.43 ± 16.38	128.13 ± 17.37	0.0007	130.18 ± 16.03	128.35 ± 16.60	127.87 ± 18.13	0.0003
Heart Rate bpm	71.35 ± 11.13	71.35 ± 11.06	72.11 ± 11.51	0.2192	71.43 ± 11.04	71.29 ± 11.29	71.83 ± 11.82	0.6877
BMI kg/m2	27.31 ± 4.50	27.27 ± 4.69	27.13 ± 4.50	0.4132	27.35 ± 4.50	27.19 ± 4.56	26.97 ± 4.75	0.0726
BMI <25kg/m^2	1020 (31.4%)	283 (33.3%)	189 (34.8%)		1027 (31.1%)	302 (33.2%)	163 (37.8%)	
BMI ≥25kg/m^2 and <30	1449 (44.6%)	358 (42.1%)	232 (42.7%)		1468 (44.5%)	398 (43.7%)	173 (40.1%)	
BMI ≥30kg/m^2	777 (23.9%)	209 (24.6%)	122 (22.5%)		804 (24.4%)	210 (23.1%)	95 (22.0%)	
Years with heart failure	4.17 ± 4.59	4.08 ± 4.60	3.97 ± 4.49	0.3301	4.13 ± 4.54	4.08 ± 4.68	4.24 ± 4.69	0.7937
Current	290 (8.9%)	63 (7.4%)	43 (7.9%)	0.2089	292 (8.8%)	74 (8.1%)	30 (6.9%)	0.1544

Smoker								
MI	1996 (61.4%)	479 (56.0%)	306 (56.1%)	0.002	2020 (61.1%)	508 (55.6%)	254 (58.5%)	0.0236
Angina	2402 (73.8%)	601 (70.3%)	384 (70.5%)	0.0257	2452 (74.2%)	630 (68.9%)	306 (70.5%)	0.0051
CABG/PCI	815 (25.1%)	246 (28.8%)	158 (29.0%)	0.0114	834 (25.2%)	256 (28.0%)	129 (29.7%)	0.0154
Hypertension	2084 (64.1%)	550 (64.3%)	316 (58.0%)	0.0243	2103 (63.6%)	590 (64.6%)	258 (59.4%)	0.2629
Diabetes	930 (28.6%)	258 (30.2%)	155 (28.4%)	0.7569	942 (28.5%)	266 (29.1%)	136 (31.3%)	0.2448
Baseline atrial fibrillation/ flutter	750 (23.1%)	215 (25.1%)	128 (23.5%)	0.4801	764 (23.1%)	225 (24.6%)	104 (24.0%)	0.4409
Stroke	397 (12.2%)	111 (13.0%)	56 (10.3%)	0.4071	385 (11.6%)	122 (13.3%)	57 (13.1%)	0.1662
Intermittent Claudication	391 (12.0%)	111 (13.0%)	80 (14.7%)	0.0755	401 (12.1%)	109 (11.9%)	72 (16.6%)	0.0399
Pacemaker	373 (11.5%)	96 (11.2%)	58 (10.6%)	0.579	348 (10.5%)	124 (13.6%)	55 (12.7%)	0.0219
ICD	84 (2.6%)	29 (3.4%)	13 (2.4%)	0.7607	83 (2.5%)	30 (3.3%)	13 (3.0%)	0.2815
Cholesterol mmol/L	5.39 ± 1.09	5.31 ± 1.01	5.33 ± 1.08	0.0721	5.40 ± 1.08	5.30 ± 1.04	5.30 ± 1.08	0.0055
ApoB:ApoA-1 ratio	0.88 ± 0.25	0.87 ± 0.25	0.86 ± 0.25	0.1728	0.88 ± 0.25	0.87 ± 0.25	0.86 ± 0.25	0.226
ApoB g/L	1.28 ± 0.30	1.26 ± 0.28	1.26 ± 0.30	0.0264	1.28 ± 0.30	1.25 ± 0.29	1.25 ± 0.30	0.0051
ApoA g/L	1.51 ± 0.27	1.50 ± 0.28	1.50 ± 0.29	0.698	1.51 ± 0.27	1.49 ± 0.28	1.50 ± 0.30	0.2693
TSH mIU/L	2.17 ± 3.71	2.24 ± 6.07	2.08 ± 1.91	0.8207	2.23 ± 4.69	1.99 ± 2.12	2.08 ± 1.72	0.1822
ALT IU/L	17.29 ± 40.10	16.34 ± 14.05	17.89 ± 26.26	0.9771	17.42 ± 39.53	16.66 ± 20.63	17.23 ± 27.22	0.7211
LDL mmol/L	3.59 ± 0.95	3.53 ± 0.89	3.52 ± 0.93	0.0281	3.60 ± 0.94	3.51 ± 0.92	3.49 ± 0.93	0.0017
NT-proBNP-- pmol/litre (median)	157.2 [65.9, 334.2]	178.8 [73.1, 354.0]	174.6 [84.2, 399.8]	0.0067	150.4 [63.1, 320.1]	188.0 [77.0, 374.2]	239.5 [110.2, 427.9]	0.0001
hs-CRP mg/litre	3.3 [1.5, 6.8]	3.6 [1.5, 7.8]	3.7 [1.6, 7.8]	0.0093	3.3 [1.5, 7.0]	3.4 [1.5, 7.8]	3.6 [1.5, 7.4]	0.2289

(median)								
Co-enzyme Q_{10} mmol/L	0.8 [0.6, 1.0]	0.7 [0.5, 0.9]	0.7 [0.6, 1.0]	0.1884	0.8 [0.6, 1.0]	0.7 [0.5, 0.9]	0.7 [0.6, 1.0]	0.2314
CK IU/L	46.0 [33.0, 65.0]	44.0 [32.0, 63.0]	43.0 [32.0, 62.0]	0.094	46.0 [33.0, 66.0]	44.0 [31.0, 61.0]	45.0 [32.0, 63.0]	0.0208
Creatinine µmol/L	114.59 ± 27.63	114.64 ± 27.67	116.58 ± 28.54	0.1847	114.20 ± 27.71	114.92 ± 27.34	119.56 ± 28.64	0.0007
eGFR ml/min/1.73m^2	56.43 ± 15.28	56.94 ± 14.86	55.86 ± 15.31	0.737	56.71 ± 15.21	56.77 ± 14.89	53.88 ± 15.60	0.0038
Loop/thiazide diuretics	2850 (87.6%)	740 (86.5%)	489 (89.7%)	0.404	2888 (87.4%)	799 (87.4%)	393 (90.6%)	0.1184
ACE inhibitor or ARB	3000 (92.2%)	786 (91.9%)	501 (91.9%)	0.7522	3035 (91.8%)	845 (92.5%)	408 (94.0%)	0.109
MRAs	1263 (38.8%)	329 (38.5%)	218 (40.0%)	0.7147	1286 (38.9%)	337 (36.9%)	188 (43.3%)	0.3655
Digitalis	1002 (30.8%)	306 (35.8%)	194 (35.6%)	0.0027	1048 (31.7%)	313 (34.2%)	141 (32.5%)	0.3376
Anticoagulant	1140 (35.0%)	298 (34.9%)	201 (36.9%)	0.5088	1145 (34.6%)	328 (35.9%)	166 (38.2%)	0.1259
Beta-blocker	2498 (76.8%)	637 (74.5%)	384 (70.5%)	0.0011	2527 (76.4%)	680 (74.4%)	313 (72.1%)	0.0282
Nitrate	1113 (34.2%)	227 (26.5%)	163 (29.9%)	0.0006	1110 (33.6%)	266 (29.1%)	127 (29.3%)	0.0075
Insulin	256 (7.9%)	66 (7.7%)	44 (8.1%)	0.9367	259 (7.8%)	71 (7.8%)	36 (8.3%)	0.8108
Antiarrhythmic	403 (12.4%)	95 (11.1%)	69 (12.7%)	0.7948	410 (12.4%)	103 (11.3%)	54 (12.4%)	0.6741

Cross tabulation between change in fatigue and change in dyspnoea: entire spectrum of LVEF

	Dyspnoea			
Fatigue	**Unchanged**	**Decrease**	**Increase**	**Total**
Unchanged	2803 (60.2%)	304 (6.5%)	146 (3.1%)	3253 (69.9%)
Decrease	261 (5.6%)	559 (12.0%)	35 (0.8%)	855 (18.4%)
Increase	242 (5.2%)	51 (1.1%)	252 (5.4%)	545 (11.7%)
Total	3306 (71.1%)	914 (19.6%)	433 (9.3%)	4653

Cross tabulation between fatigue level at baseline and 6-month visit

	Fatigue at 6-month visit					
Fatigue at Baseline	**0**	**1**	**2**	**3**	**4**	**Total**
0	132 (2.8%)	26 (0.6%)	39 (0.8%)	16 (0.3%)	5 (0.1%)	218 (5.5%)
1	29 (0.8%)	203 (4.4%)	92 (2.0%)	21 (0.5%)	5 (0.1%)	350 (7.5%)
2	41 (0.9%)	168 (3.6%)	1,337 (28.7%)	268 (5.8%)	16 (0.3%)	1,830 (39.3%)
3	27 (0.6%)	45 (1.0%)	479 (10.3%)	1528 (32.8%)	57 (1.2%)	2136 (45.9%)
4	6 (0.1%)	11 (0.2%)	17 (0.4%)	32 (0.7%)	53 (1.1%)	119 (2.6%)
Total	235 (5.1%)	453 (9.7%)	1,964 (42.2%)	1,865 (40.1%)	136 (2.9%)	4653

Cross tabulation between dyspnoea level at baseline and 6-month visit: entire spectrum LVEF

	Dyspnoea at 6-month visit					
Dyspnoea at Baseline	**0**	**1**	**2**	**3**	**4**	**Total**
0	1 (0.02%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.02%)
1	18 (0.4%)	215 (4.6%)	84 (1.8%)	14 (0.3%)	3 (0.1%)	334 (7.2%)
2	17 (0.4%)	196 (4.2%)	1,368 (29.4%)	265 (5.7%)	7 (0.2%)	1,853 (39.8%)
3	18 (0.4%)	45 (1.0%)	557 (12.0%)	1690 (36.3%)	61 (1.3%)	2371 (45.9%)
4	1 (0.02%)	8 (0.2%)	9 (0.2%)	45 (1.0%)	32 (0.7%)	95 (2.0%)
Total	55 (1.2%)	464 (10.0%)	2018 (43.4%)	2014 (43.3%)	103 (2.2%)	4654

Change in symptom severity and outcomes

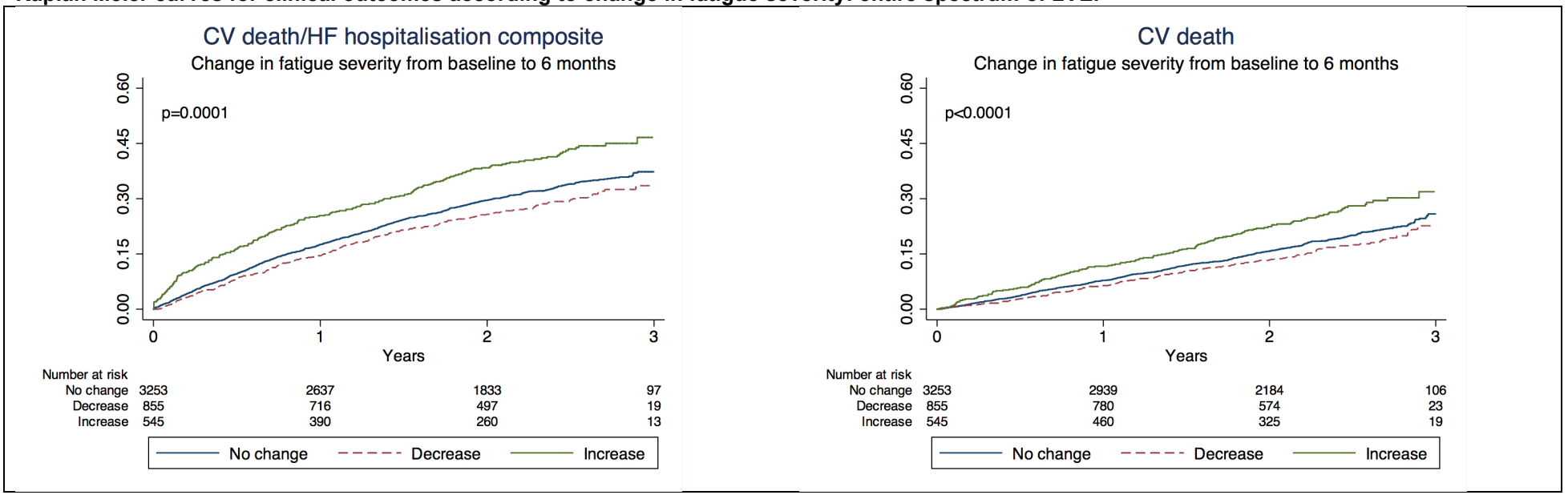
Numbers of events by change in symptoms at 6 months: entire spectrum of LVEF

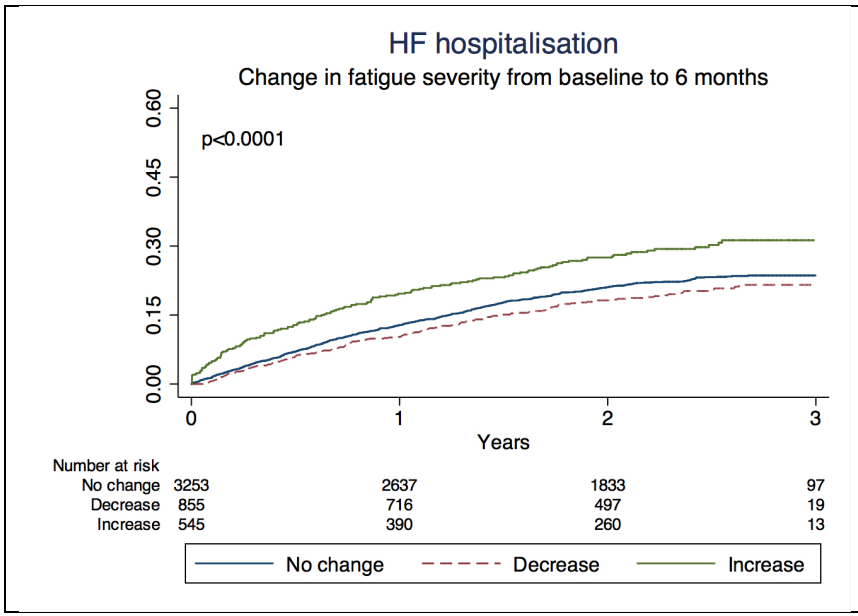
	Fatigue				Dyspnoea			
	Unchanged (n=3253)	**Decrease (n=855)**	**Increase (n=545)**	**P**	**Unchanged (n=3306)**	**Decrease (n=914)**	**Increase (n=434)**	**P**
Cardiovascular death/Heart failure hospitalisation	374/684 (32.5%)	85/159 (28.5%)	75/148 (40.9%)	<0.001	386/685 (32.4%)	90/170 (28.5%)	58/136 (44.7%)	<0.001
Cardiovascular death	624 (19.2%)	141 (16.5%)	140 (25.7%)	<0.001	642 (19.4%)	147 (16.1%)	116 (26.7%)	<0.001
Heart failure hospitalisation	684 (21.0%)	159 (18.6%)	148 (27.2%)	0.001	685 (20.7%)	170 (18.6%)	136 (31.3%)	<0.001
All-cause death	802 (24.7%)	192 (22.5%)	179 (32.4%)	<0.001	827 (25.0%)	206 (22.5%)	140 (32.3%)	0.001

Unadjusted HR for change in symptom severity and outcomes: entire spectrum of LVEF

	CV Death/HF hospitalisation HR (95%CI)	P	Cardiovascular death HR (95%CI)	P	HF hospitalisation HR (95%CI)	P	All-cause death HR (95%CI)	P
Change in fatigue								
Decrease	0.86 (0.75, 0.99)	0.034	0.86 (0.71, 1.03)	0.094	0.87 (0.73, 1.03)	0.105	0.90 (0.77, 1.05)	0.174
Increase	1.40 (1.21, 1.62)	<0.001	1.43 (1.20, 1.72)	<0.001	1.43 (1.19, 1.71)	<0.001	1.38 (1.51, 1.65)	<0.001
Change in dyspnoea								
Decrease	0.86 (0.75, 0.99)	0.032	0.83 (0.69, 0.99)	0.037	0.88 (0.74, 1.04)	0.131	0.91 (0.77, 1.06)	0.217
Increase	1.58 (1.36, 1.84)	<0.001	1.47 (1.21, 1.80)	<0.001	1.73 (1.44, 2.08)	<0.001	1.42 (1.21, 1.68)	<0.001

Kaplan Meier curves for clinical outcomes according to change in fatigue severity: entire spectrum of LVEF




HF hospitalisation
Change in fatigue severity from baseline to 6 months
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0.00
0.15
0.30
0.45
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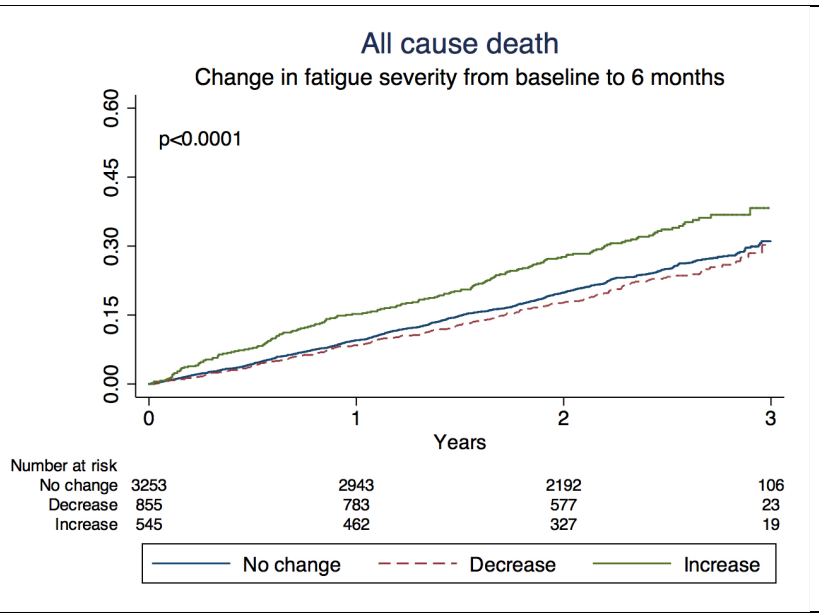
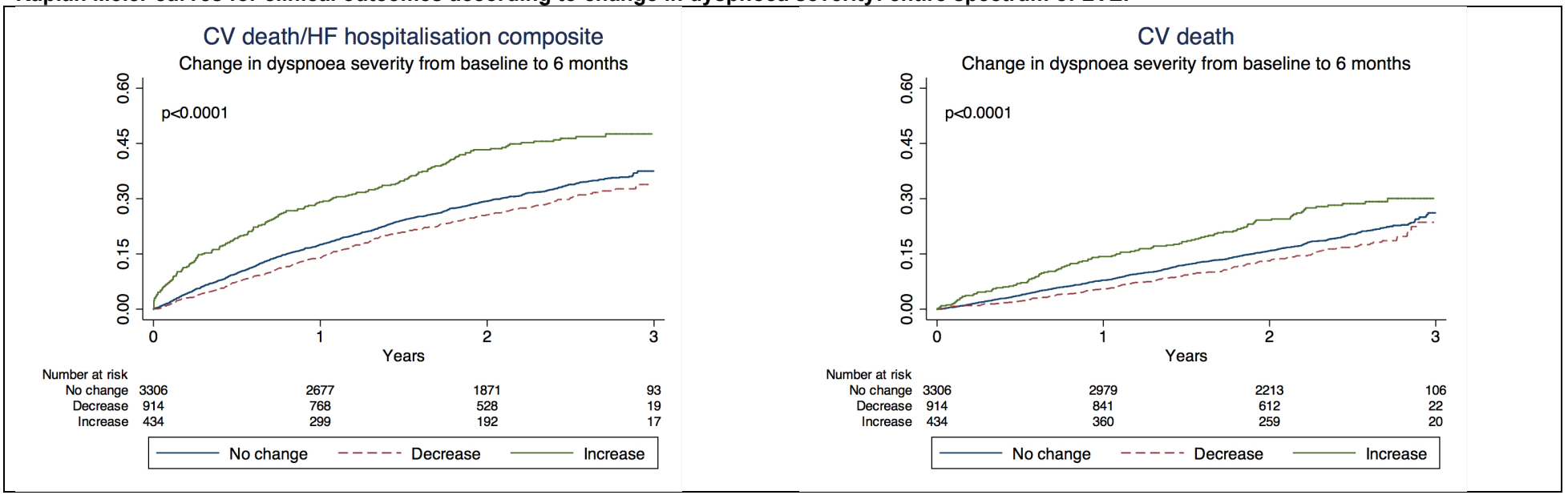
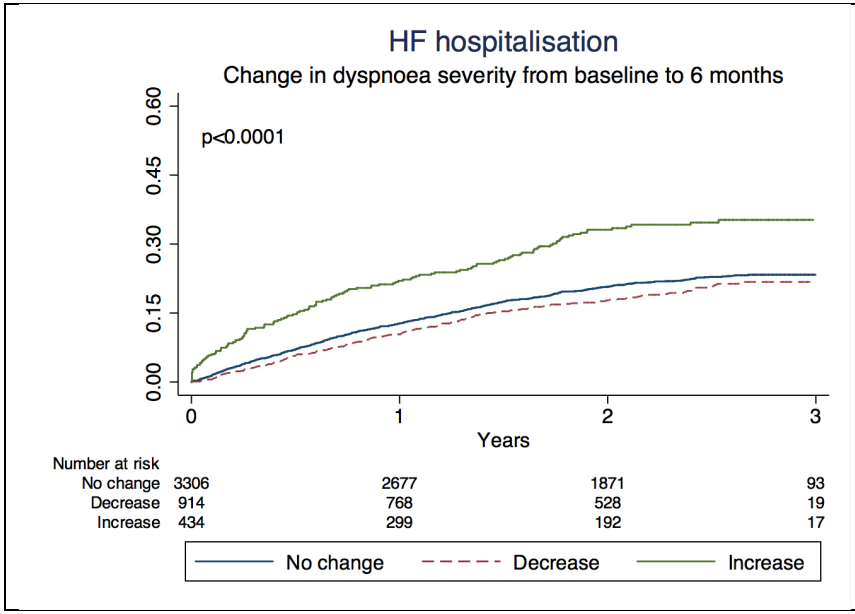
0
1
2
3
Years
Number at risk
No change 3253 2637 1833 97
Decrease 855 716 497 19
Increase 545 390 260 13
No change
Decrease
Increase


All cause death
Change in fatigue severity from baseline to 6 months
p<0.0001
0.00
0.15
0.30
0.45
0.60
0
1
2
3
Years
Number at risk
No change 3253 2943 2192 106
Decrease 855 783 577 23
Increase 545 462 327 19
No change
Decrease
Increase

Kaplan Meier curves for clinical outcomes according to change in dyspnoea severity: entire spectrum of LVEF




HF hospitalisation
Change in dyspnoea severity from baseline to 6 months
p<0.0001
0.00
0.15
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1
2
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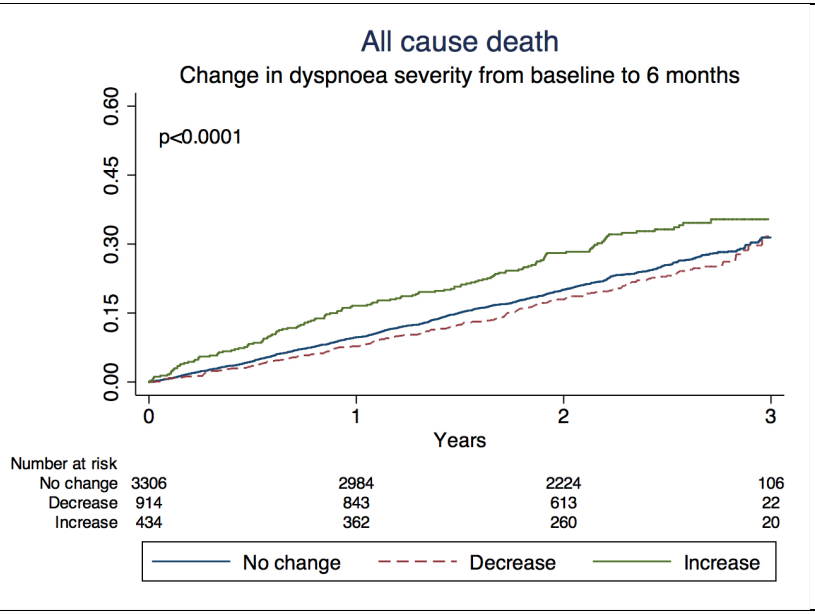
Years
Number at risk
No change 3306 2677 1871 93
Decrease 914 768 528 19
Increase 434 299 192 17
No change
Decrease
Increase


All cause death
Change in dyspnoea severity from baseline to 6 months
p<0.0001
0.00
0.15
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0.45
0.60
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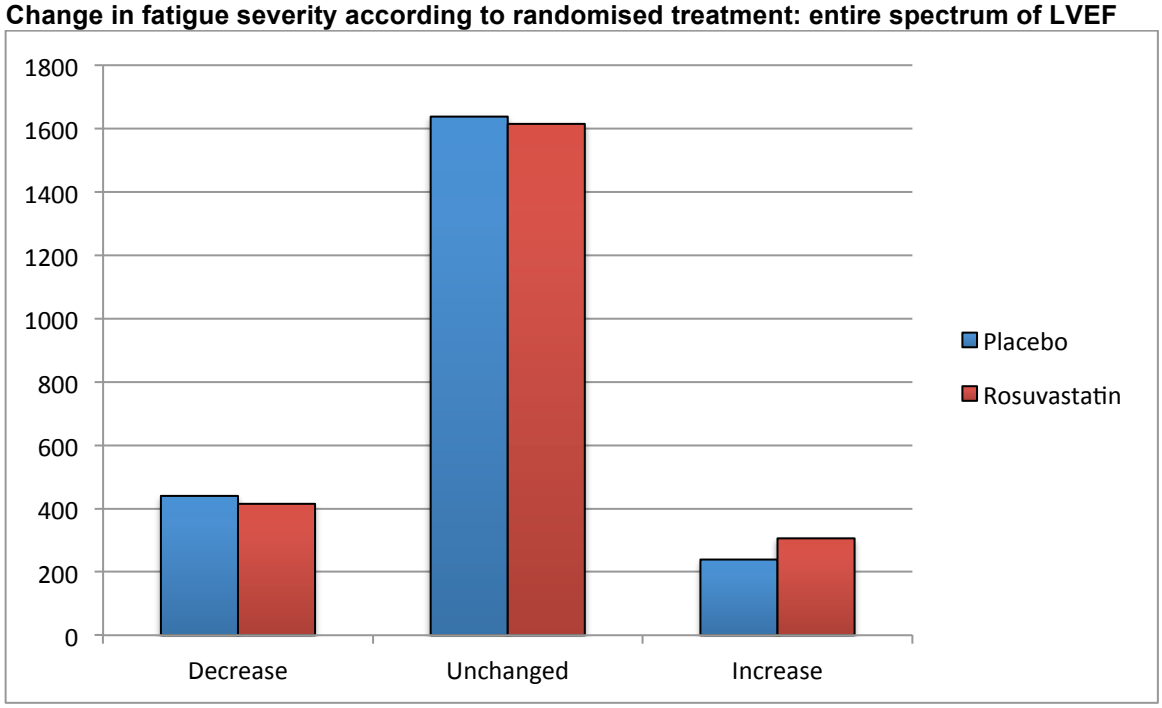
1
2
3
Years
Number at risk
No change 3306 2984 2224 106
Decrease 914 843 613 22
Increase 434 362 260 20
No change
Decrease
Increase

Adjusted HR for change in symptom severity and outcomes: entire spectrum of LVEF

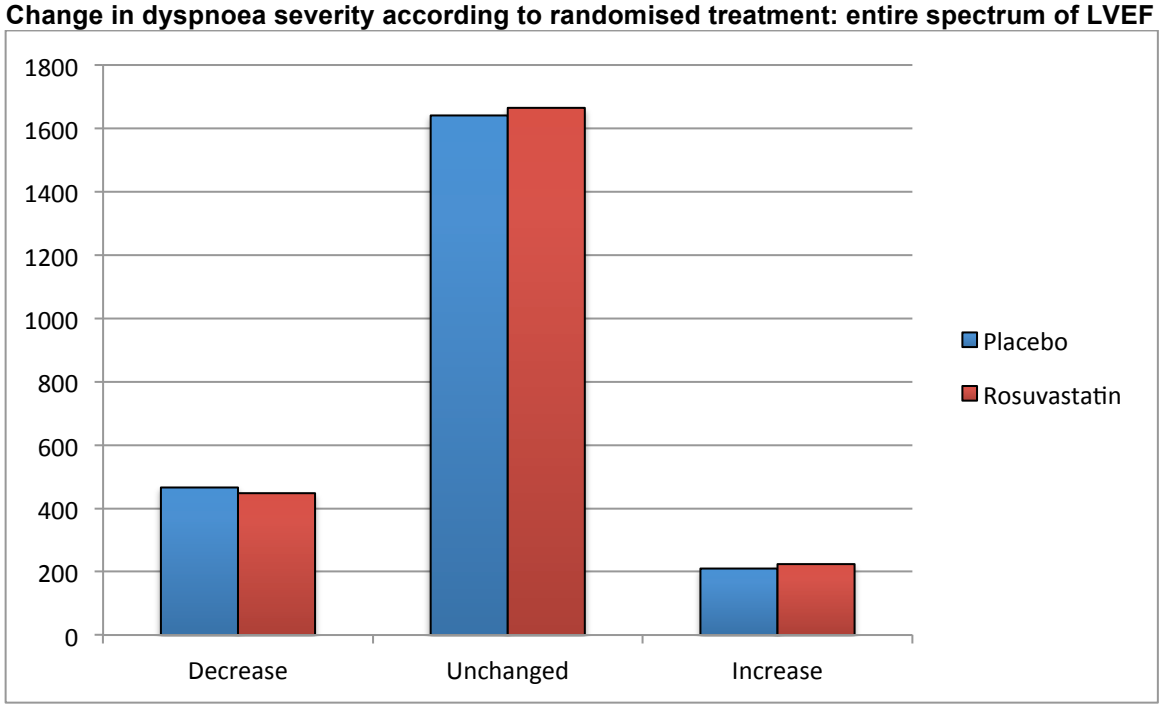
	CV Death/HF hospitalisation HR (95%CI)	P	Cardiovascular death HR (95%CI)	P	HF hospitalisation HR (95%CI)	P	All-cause death HR (95%CI)	P
Change in fatigue								
Decrease	0.73 (0.62, 0.87)	<0.001	0.72 (0.57, 0.91)	0.006	0.71 (0.58, 0.88)	0.010	0.77 (0.63, 0.94)	0.009
Increase	1.60 (1.32, 1.94)	<0.001	1.42 (1.11, 1.83)	0.005	1.87 (1.49, 2.36)	<0.001	1.43 (1.15, 1.78)	0.001
Change in dyspnoea								
Decrease	0.71 (0.60, 0.83)	<0.001	0.66 (0.52, 0.83)	<0.001	0.70 (0.57,0.86)	0.001	0.75 (0.62, 0.90)	0.003
Increase	1.85 (1.51, 2.26)	<0.001	1.41 (1.08, 1.86)	0.011	2.36 (1.86, 2.99)	<0.001	1.25 (0.98, 1.59)	0.074

Adjusted for: age, sex, NYHA class, LVEF, body mass index, systolic blood pressure, heart rate, smoking, myocardial infarction, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter, stroke, intermittent claudication, pacemaker and cardioverter-defibrillator implantations, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, and log NT-proBNP and baseline symptom severity.

Change in fatigue severity according to randomised treatment: entire spectrum of LVEF



Change in dyspnoea severity according to randomised treatment: entire spectrum of LVEF



Adjusted HR for change in symptom severity and outcomes: -including randomised treatment: entire spectrum of LVEF

	CV Death/HF hospitalisation HR (95%CI)	P	Cardiovascular death HR (95%CI)	P	HF hospitalisation HR (95%CI)	P	All-cause death HR (95%CI)	P
Change in fatigue								
Decrease	0.73 (0.61, 0.86)	<0.001	0.72 (0.57, 0.91)	0.006	0.71 (0.57, 0.87)	0.001	0.77 (0.63, 0.94)	0.010
Increase	1.62 (1.34, 1.97)	<0.001	1.42 (1.11, 1.83)	0.005	1.90 (1.52, 2.40)	<0.001	1.44 (1.16, 1.78)	0.001
Change in dyspnoea								
Decrease	0.71 (0.60, 0.83)	<0.001	0.66 (0.52, 0.83)	<0.001	0.70 (0.57, 0.86)	0.001	0.75 (0.62, 0.90)	0.003
Increase	1.86 (1.51, 2.28)	<0.001	1.42 (1.08, 1.86)	0.011	2.38 (1.88, 3.01)	<0.001	1.24 (0.98, 1.59)	0.073

Adjusted for: age, sex, NYHA class, LVEF, body mass index, systolic blood pressure, heart rate, smoking, myocardial infarction, CABG or PCI, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter, stroke, intermittent claudication, pacemaker and cardioverter-defibrillator implantations, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, thyroid stimulating hormone, high-sensitivity C-reactive protein, and log NT-proBNP, baseline symptom severity and randomised treatment

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Publications related to work in this thesis

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