Quality of life and depressive symptoms in patients with heart failure

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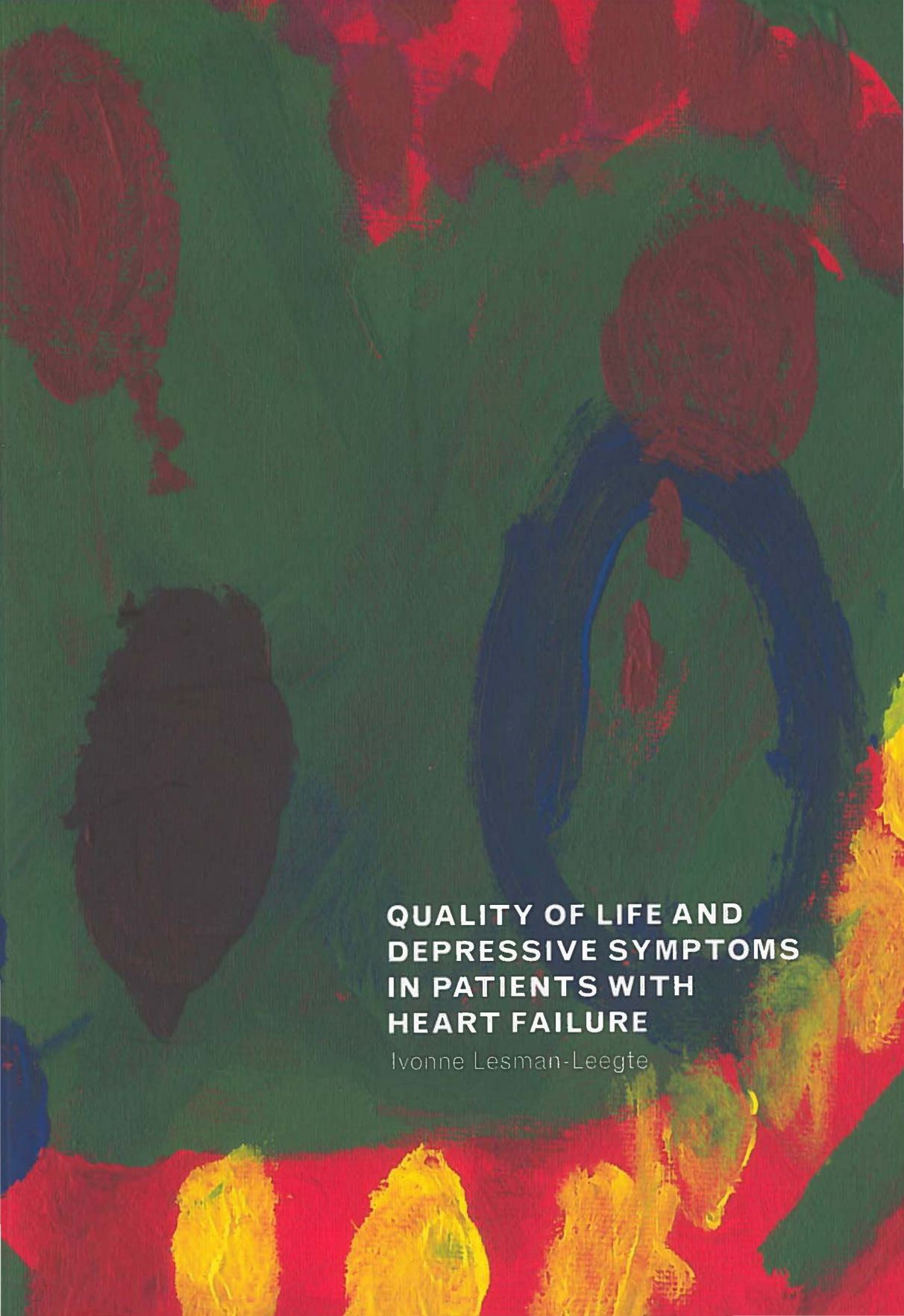

QUALITY OF LIFE AND DEPRESSIVE SYMPTOMS IN PATIENTS WITH HEART FAILURE

Ivonne Lesman-Leegte

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Stellingen

behorend bij het proefschrift:

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Ivonne Lesman-Leegte

1. Hartfalen heeft een negatieve invloed op de kwaliteit van leven, in het bijzonder voor vrouwen en patiënten met comorbiditeit (dit proefschrift).

2. Als er rekening wordt gehouden met symptomen van hartfalen blijkt de score op een meetinstrument voor depressieve symptomen niet drastisch te dalen (dit proefschrift).

3. Vrouwen met hartfalen hebben vaker depressieve symptomen dan mannen met hartfalen (dit proefschrift).

4. Patiënten met hartfalen en ernstige depressieve symptomen worden vaker heropgenomen dan patiënten zonder depressieve symptomen (dit proefschrift).

5. Patiënten met hartfalen en depressieve symptomen hebben een gemiddeld langere opnameduur bij een heropname, dan hartfalenpatiënten zonder depressieve symptomen (dit proefschrift).

6. Voorlichting en begeleiding door hartfalenverpleegkundigen, toegevoegd aan de behandeling van de cardioloog, kan door een lagere drempel en meer interactie, leiden tot meer heropnames (dit proefschrift).

7. Naast het voorkomen van heropnames bij patiënten met hartfalen, is het minstens zo belangrijk om heropnames efficiënt te organiseren.

8. In de dagelijkse praktijk van de zorg aan patiënten met hartfalen, is het van belang om routinematig te screenen op de aanwezigheid van depressieve symptomen.

9. Het ontbreken van eenduidige theoriën en definities van het concept kwaliteit van leven heeft geleid tot een groot aantal operationalisaties van dit begrip en als gevolg daarvan een grote diversiteit aan meetinstrumenten.

10. Vele individuele successen zijn geboekt, toch blijft het COACH team als geheel meer dan de som der delen.

11. Geluk hangt af van wat men kan geven, niet van wat men kan krijgen (Mahatma Ghandi 1917-1985).

12. De meest belangrijke dingen van het leven zijn geen dingen.

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Contents

Voor jou, pap.

CHAPTER 1

General introduction

Parts of this chapter are published in:

Tiny Jaarsma , Martje H.L. van der Wal, Jochem Hogenhuis, Ivonne Lesman-Leegte, Marie Louise Luttik, Nic J.G.M. Veeger, Dirk J. van Veldhuisen. Design and methodology of the COACH study: a multicentre randomised Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure.

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Introduction

Heart failure has emerged as a major public health problem in developed countries and is sometimes described as epidemic.[1,2] It is primarily a condition of the elderly and the 'aging of the population' will lead to an increase in the prevalence of heart failure over time.[3] Additionally, due to improvement in health care in general and in treatment options for cardiovascular diseases, more patients will survive an acute coronary event and might develop heart failure later in their lives. In Europe 1-2% of the adult population and 6-10% of people older than 65 years have heart failure.[1,2,4] In the Netherlands approximately 200,000 adults have heart failure with 50,000 new cases every year.[5]

Heart failure is a clinical syndrome characterized by the inability of the myocardium to pump sufficient amounts of blood to meet the metabolic needs of the body, resulting in typical heart failure symptoms such as breathlessness or fatigue at rest or during exertion.[6] These symptoms significantly affect the health-related quality of life of patients with heart failure.[7] Furthermore, the long-term outcome for patients with heart failure is associated with mortality and readmission rates. Community-based surveys report 5-year mortality rates of 45-67%,[8,9] and these are even higher in hospital-based studies (48-77%).[10]

Despite the increased options for medical treatment since the 1980s (new pharmacological therapies and new devices for heart failure), the prognosis of heart failure patients remains poor and patients experience many adverse effects from both the disease and its treatment.[11]
To improve patient outcomes, heart failure management programmes have been developed and tested over the past twenty years,[12,13] and these now contribute to the heart failure therapy.[6] A number of studies support the use of comprehensive non-pharmacological intervention programmes in patients with heart failure,[14-17] but other studies have not confirmed these positive findings.[18-21] Substantial differences in type and intensity of disease management programmes make it impossible to draw definitive conclusions about the effectiveness, optimal timing and frequency of intervention programmes. It is therefore necessary to identify which programme and the level of intensity of the chosen programme, is most effective in terms of survival, hospital readmission and health-related quality of life. This is the objective of the Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure patients (COACH study). Some of the results of this study will be presented in this thesis, in addition to the main issues of the thesis. Complementary to traditional outcomes such as morbidity and

mortality, health-related quality of life is increasingly used as a measure of outcome in patients with heart failure. It is therefore important to gain more insight into aspects of health-related quality of life in heart failure patients, which is the main focus of this thesis.

Quality of life

Definition and assessment

The constant presence of physical limitations, progressive symptoms, consequences of the complex heart failure treatment regimen and psychological concerns may result in diminished health-related quality of life of patients with heart failure. It is known that the health-related quality of life of patients with heart failure is highly affected and reduced to around one-third when compared to the general population.[22] Therefore improving or maintaining health-related quality of life is one of the primary goals of heart failure management today.[6]

The World Health Organisation has defined quality of life as 'an individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns'.[23] From a health perspective quality of life has been said to refer to the physical, psychological and social domains of health, which are seen as distinct areas that are influenced by a person's experiences, beliefs, expectancies and perceptions. Although there has been some debate about how to define health-related quality of life, an international group of quality of life experts reached agreement upon the fundamental dimensions essential to any health-related quality of life assessment. These should include physical, psychological, and social dimensions, role functioning and the overall life satisfaction and perception of health status.[24] In this thesis we will use the words 'quality of life', when 'health-related quality of life' is meant. Apart from the domains of quality of life, all aspects are considered together when patients are asked to rate 'their overall quality of life'.

Translating the various components of health into a quantitative value that indicates quality of life is a complex task, and disease-specific and generic instruments that measure quality of life have been developed. Disease-specific instruments measure symptoms that are specific for the disease under study, and consequences and are sensitive to subtle disease-specific changes. An example of a disease-specific instrument used in heart failure studies is the Minnesota Living with Heart Failure Questionnaire (MLwHFQ).[25]

When using generic instruments, respondents have to rate their level of functioning or satisfaction with each area of life and indicate the relative importance of each of these to their overall quality of life. The quality of life of the population under study can then be compared with populations with other diseases for instance COPD or cancer. The Medical Outcomes Study 36-item Short Form (SF-36 or the RAND-36) and the Cantril's ladder of life are examples of generic instruments that are frequently used in heart failure patients.[26,27]
In both clinical practice and research into the heart failure population the importance of measuring quality of life is acknowledged, but it is difficult to find instruments that are both suitable and practical.
Thus far, much effort at exploring quality of life in patients with heart failure was made. However most knowledge about quality of life in patients with heart failure is derived from clinical trials with a highly selected heart failure population of younger, male patients without co morbidities. Additionally, data on the quality of life of heart failure populations are often compared with a healthy, general reference population which is not representative of the elderly living in the community, who often suffer from several chronic diseases and have already faced several life events (for example loss of a spouse or retirement) that might effect their quality of life and psychosocial status as well. Therefor a group of elderly heart failure patients is not necessarily comparible with a healthy elderly population.

Depressive symptoms in heart failure patients

Chronic diseases such as heart failure may confront patients with numerous threats including impaired physical and social functioning and changes to future perspectives. One response to this is emotional imbalance and depression. Depressive symptoms, which can be classified under the heading of the psychological functioning of the quality of life domains, may even have a greater impact on an overall quality of life rating than the severity of cardiac function or functional impairment in heart failure patients.[28,29] There is also sufficient proof of the presence of depressive symptoms as risk factor for the future development of heart failure.[30,31] Others suggest that there might be an interaction effect whereby negative emotions and heart failure affect each other in deleterious ways.[32]

Definition of depressive symptoms

It is important to emphasize the difference between depressive symptoms and depressive disorder, since both result in different prevalence rates and differences in outcomes. Depressive symptoms refer to a depressed mood, whereas depressive disorder refers to a psychiatric diagnosis which points to a cluster of signs and symptoms that fulfil stringent criteria. These criteria are described in the international accepted classification system for mental disorders, the Diagnostic and Statistical Manual of Mental Disorder (DSM-IV).[33]

To assess depressive symptoms, questionnaires have been designed to measure the presence and severity of them. Diagnostic interviews are used to assess depressive disorder. As a result, the prevalence of depressive symptoms depends on the definition and instruments used. In this thesis the Center for Epidemiologic Studies Depression scale (CES-D)[34] is used, which is a valid instrument for assessing depressive symptoms in general populations as well as medical patients and is also frequently used to assess cardiac patients.[35,36]

Prevalence of depressive symptoms and related variables

From community-based surveys it is known that depressive symptoms are common in the elderly and in patients with medical illnesses.[37] In studies of heart failure patients high rates of depressive symptoms (14-77%) have been described, but these rates varied with the definition and instruments used and were explored in rather small samples.[38-41]

From the general population it is known that rates of depressive symptoms are associated with characteristics such as age, gender, race, education level, socioeconomic, and marital status. In patients with medical illnesses, the number of chronic conditions and disease severity are related to depressive symptoms.[42,43] The presence of depressive symptoms and their relationship with patient and disease-related factors have also been studied in patients with heart failure, but the results of these studies were not consistent.[44-47] The results are often drawn from secondary analyses of populations used in clinical trials with patient samples selected on strict clinical criteria. The consequence of these highly selected patient samples is the limited generalization of the conclusions. However, to date, studies on the prevalence and determinants of depressive symptoms in a heart failure population representative of the population seen in today's clinical practice are scarce.

Depressive symptoms and outcomes

It is suggested that depressive symptoms could be increasing readmission and mortality among heart failure patients, independent of age, gender and disease severity, but not all studies reveal consistent results.[40,48-50] Some studies suggest a substantially worse prognosis and increased readmission rates for patients with heart failure who have more severe depressive symptoms compared to patients with moderate or without depressive symptoms.[40,50] Others do not confirm this or find worse perspectives for patients with increased depressive symptom severity. These studies varied in the characteristics of the patient populations, and follow up time, and all used small samples. It is useful to examine this objective in a large, representative heart failure population.

Objectives

The literature showed that additional data is needed to gain more insight into quality of life issues and the prevalence of depressive symptoms in an unselected heart failure population. We therefore examined quality of life and depressive symptoms in heart failure patients and a comparable elderly population. Although the roles of demographics and clinical characteristics on depressive symptoms have been investigated in heart failure patients, the results were inconclusive. Furthermore, depressive symptoms have been associated with high rates of readmission and mortality in patients with heart failure. However, this has not been investigated in a large group of heart failure patients representative of the population seen in present clinical practice. To reduce readmission and mortality and to improve quality of life, heart failure disease management programmes are increasingly being implemented. Thus far there are no large multicentre trials in this field nor any studies that compare the intensity of advice and counselling in relation to these patients.

The following aims for this thesis were formulated. To describe:

1. the prevalence of quality of life and depressive symptoms in heart failure patients compared with an age and gender matched population of community dwelling elderly
2. the association between depressive symptoms and demographic and clinical variables in patients with heart failure
3. the prognostic value of depressive symptoms on clinical outcome in patients with heart failure
4. the effect of heart failure management programmes on clinical outcome in an unselected heart failure patient population.

Study populations

Data were gathered from three sources for this thesis: firstly from the COACH study, secondly from an elderly population living in the community and thirdly from a population of heart failure patients from the Rijnland Hospital in Leiderdorp.

The COACH study was the largest study in the world to evaluate the effects of advice and counselling of patients with heart failure. The primary objective of the COACH study was to explore whether advice and counselling would be beneficial to patients with heart failure, as compared to a 'care as usual' group, in terms of prevention of heart failure related mortality and morbidity, as well as quality of life and health care costs. A multicentre, randomized controlled design was used and 1,049 hospitalized patients with heart failure were included. Following confirmation of suitability and informed consent, patients' baseline characteristics were assessed from medical charts, patient interviews and questionnaires, and patients were randomized to either 'care-as-usual', basic support or intensive support. Two different types of interventions were tested and compared to a control group. The control group received follow up treatment from the cardiologist. Both the support groups received additional advice and counselling, follow up interventions, and had telephone access to a heart failure nurse. The extra support that was provided for the intensive support group consisted of two home visits and two consultations with a multidisciplinary team (physiotherapist, dietician, social worker) to optimize the advice for each patient.

Outline

The first aim of this thesis will be accomplished through a study in which quality of life and depressive symptoms in a heart failure population and a population of community dwelling elderly will be compared (Chapter 3). Quality of life will be assessed with different instruments. Two quality of life instruments, and in particularly the relationship between a one-item generic quality of life measure (Ladder of Life) and a multiple-item disease-specific questionnaire (the Minnesota Living with Heart Failure Questionnaire) are described in Chapter 2. In Chapter 4 the prevalence of depressive symptoms in a heart failure population will be assessed and demographic and clinical variables related to depressive symptoms will be described. In Chapter 5, a more in-depth view of depressive symptoms and related factors in men and women will be studied. The third aim of this thesis will be studied by analysing longitudinal data from the COACH study. Chapter 6 examines whether

depressive symptom severity in a heart failure population is associated with readmission and mortality. In Chapter 7, the results of the COACH study will be described. Finally the findings of the studies described in this thesis will be reflected upon in the general discussion in Chapter 8. Recommendations will be made for daily clinical practice and for future research.

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CHAPTER 2

Measuring quality of life in heart failure: one versus multiple items

Tiny Jaarsma, Ivonne Lesman-Leegte, Ger V.J. Cleuren, Carolien M.H.B. Lucas.

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1. Introduction

Heart failure (HF) is a chronic disabling disease with a substantial impact on the quality of life of patients and their family members. This is irrespective of the severity of the disease or whether the patient suffers from systolic of diastolic dysfunction.[1,2] From international data it is known that compared to a general population and compared to patients with other chronic diseases, HF patients have a highly affected quality of life.[2] In several studies in the Dutch population it was found that different domains in the area of quality of life are affected due to their heart failure, for instance physical functioning, HF symptoms and psychosocial adjustment.[3,4] Contrary to what is always expected, both patients with a preserved systolic function or patients with systolic dysfunction have reported a low quality of life.[2]

Measuring quality of life of patients is a challenge. Several aspects have to be considered such as subjectivity versus objectivity, a 'needs' or a 'wants', and disease-generic or disease- specific measurement of quality of life.[5,6] The Word Health Organization has defined quality of life as 'the 'individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concern'.[7] It is considered to be a multidimensional concept with physical dimensions (symptom frequency, physical functioning), psychological dimensions (adaptation, stress, coping, emotion) and social dimensions (family, friendships, work).

To measure quality of life, either a generic instrument or a disease-specific instrument can be used. Instruments that are often used to measure generic quality of life in Dutch HF studies are the Short Form 36 (SF36)/RAND 36[8,9] (or short versions), or the Sickness Impact Profile (SIP)[10] and the Schedule for the Evaluation of Individual Quality of life (SEIQOL)[11] which allows respondents to nominate the areas of life that are most important, rate their level of functioning or satisfaction with each, and indicate the relative importance of each to their overall quality of life.[11] Another generic instrument that is used in HF is Cantril's Ladder of Life.[12] All these questionnaires have been widely used in various clinical and healthy populations and the instruments are reliable and valid. The advantage of using a generic questionnaire is that the scores of the population under study can be compared to populations from other diseases e.g. compare the quality of life of a HF population with that of patients with cancer or COPD. The disadvantage of these generic instruments is that they are often not very sensitive to subtitle disease-specific changes and that disease-specific symptoms or consequences are not measured.

To measure these more disease-specific aspects of quality of life of HF patients the following instruments are used: The Minnesota living with HF

questionnaire (MLwHFQ)[13], the Kansas City Cardiomyopathy Questionnaire (KCCQ)[14] and the Quality of life Questionnaire for severe Heart Failure (QLQ-SHF)[15].
Most HF trials and other studies use the MLwHFQ to measure disease specific quality of life. Since 1998, a Dutch version of this scale is available and it has been tested for reliability and validity.[16] This version of the MLwHFQ has recently been under some critic and it was questioned if it really reflects the concept that it intends to measure.[17] In a study by Hak and colleagues, issues of validity, specificity and sensitivity with regard to the MLwHFQ in patients with severe HF were explored. Their findings suggest that most patients neither read the introduction nor the core question of the instrument. So they answered other questions than those that were intended. If they answered these other questions they responded irrespective of whether these symptoms or handicaps were caused by their HF or prevented them from living as they wanted to live and they did not answer the questions for the last month.[17]
Overall we observed that both in clinical practice and in research in HF more attention is paid to the measurement of quality of life and much energy is devoted to searching for the right instrument to measure this. It is often difficult to find a suitable and practical instrument and in that light a one-item question sometimes seems more attractive then a multiple-item questionnaire. At the same time however, we need to be sure we are measuring the relevant aspects of the concept.
To explore possible equality in a simple and more complex instrument we determined the relationship between a one-item quality of life measure (Ladder of Life) and a multiple-item questionnaire (the Minnesota Living with Heart Failure Questionnaire).

2. Methods

2.1 Design

A cross sectional design is used to explore the relationship between two instruments that are purported to measure quality of life. The sample consisted of HF patients who were admitted to a general hospital (Rijnland Hospital) in the Netherlands. Patients were admitted with symptoms of chronic HF (NYHA class III-IV) to a cardiology ward and were followed in a heart failure outpatient clinic.[18] During hospitalisation, all patients completed the Minnesota Living with Heart Failure Questionnaire (MLwHFQ) and the Ladder of Life. Demographic and clinical characteristics were collected from medical chart and a patient interview carried out by the HF nurse.

LADDER OF LIFE

All of us want certain things out of life. When you think about what really matters in your own life, what are your wishes and hopes for the future? In other words, if you imagine your own future in the best possible light, what would your life look like then, if your are to be happy? Take your time thinking about this.
Now taking the other side to the picture, what are your fears and worries about the future? In other words, if you imagine your future in the worst possible light, what would your life look like then?

Here is a picture of a ladder. The top of the ladder represents the best possible life and the bottom the worst for you. Where on the ladder do you feel you personally stand at the present time?

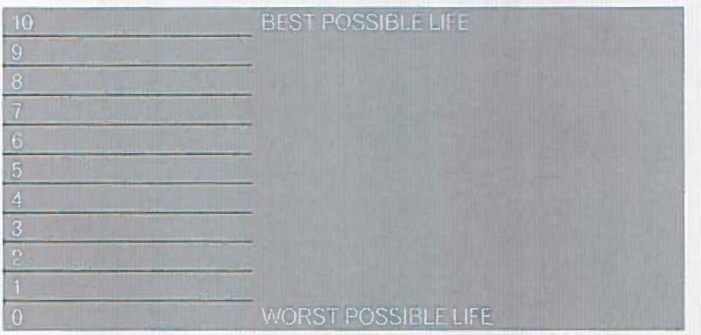

Figure 1. Ladder of life.

2.2 Questionnaires

The MLwHFQ is developed by Rector et al.[13], it is a disease-specific instrument and used commonly in clinical trials and community programs to measure health related quality of life. It is a 21 item scale with a scoring range of zero for no impairment as result of heart failure to 105 for maximum impairment. Three scores can be determined: an overall score (21 items, 0-105), the physical dimension (8 items, 0-40)) and the emotional dimension (5 items, 0-25). Higher scores mean a worse quality of life. Reliability and validity of the MLwHFQ has been documented.
The Ladder of Life was developed by Cantril and published in 1965. It is a single-item instrument that has been used in previous studies to measure global well being.[12] Patients are asked to rate their sense of well-being on a 'ladder' (Figure1) with 10 reflecting the best possible life imaginable and zero reflecting the worst possible life imaginable. Higher scores mean better quality of life.

2.3 Statistical analysis

Pearson correlation coefficients were calculated between the Ladder of Life and the MLwHFQ overall score and the physical and emotional subscale. Ladder of Life scores were compared between MLwHF questionnaires and differences were tested with a non parametric Kruskal-Wallis test. Outcomes were considered significant when $p<0.05$. Values are presented as means ± SD except when stated otherwise.

3. Results

3.1 Patients

There was almost an equal distribution between genders; 47% was female. The mean age was 75 (± 11) years with a range from 30 to 98, 58% of the sample were married, the other 42% were single (3%) or widowed (39%). The mean left ventricular ejection fraction (LVEF) was 40% (± 16). More than half of the patients (73%) had no previous admission due to HF. Ischemic heart disease was the most important cause of HF (60%) (Table 1).

3.2 Quality of life

On average, patients scored a 4 (± 2) on the Ladder of Life. In total 19 patients (8%) scored ≥7. The average score on the MLwHFQ was 59 (± 21) (Table2). Both the emotional subscale of the MLwHFQ and the Ladder of Life were weakly correlated to age ($r=0.16$ and $r= -0.20$, $p <0.05$) and the Minnesota overall and Ladder of Life were correlated to the number of previous HF admissions ($r=0.15$ and $r= -0.15$, $p<0.05$). Only the MLwHFQ was significantly correlated to COPD ($r=0.16$, $p<0.5$) and diabetes ($r=0.13$, $p<.05$). No correlations were found with other demographic and clinical variables.

3.3 Relation Ladder of life and MLwHFQ

The correlation between the Ladder of life and the MLwHFQ was: $r= 0.36$ ($p<0.001$) for the overall MLWHFQ; $r= 0.35$ ($p<0.001$) for the MLwHFQ emotional subscale and $r= 0.32$ ($p<0.001$) for the MLwHFQ physical subscale. If MLwHFQ scores are divided by quartiles (Figure 2), Ladder of Life scores in the lowest quartiles of the MLwHFQ (meaning high quality of life), are higher and this relationship between MLwHFQ and Ladder of Life stays consistent in the other quartiles, with a significant difference between the quartiles ($chi^2 = 32$, $p<.001$). In the scatter plot (Figure 3) a large variation in MLwHFQ score (12-83) is seen in patients who score a relative high overall well being, (>6, relatively good QOL). A large variation in MLwHFQ scores exists (10-105) also exists in patients who score relatively low on the Ladder of Life (<1, low QOL)

Table 1. Demographic and clinical characteristics (n=231)

	n=231
Age (± SD)	75 (± 11)
Female gender:	47%
Married	58%
LVEF (± SD)	40% (± 16)
Aetiology of HF:	
Ischemia	60%
Comorbidities	
Diabetes	29%
COPD	27%
Stroke	14%
Number of previous HF admissions:	
no previous HF admission	73%
1 previous HF admission	16%
> 1 previous HF admissions	11%

Table 2. Scores on the quality of life questionnaires (n=231)

Questionnaire	Theoretical range	mean ± sd
Ladder of life	0 -10	4 ± 2
MLwHFQ overall	0 - 105	59 ± 21
MLwHFQ physical	0 - 40	28 ± 10
MLwHFQ emotional	0 - 25	16 ± 6

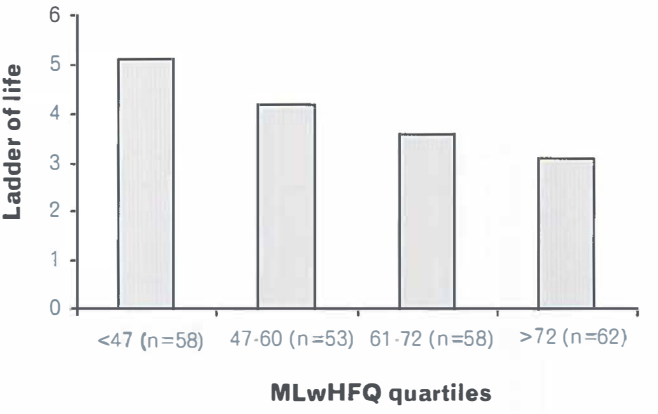

Figure 2. Ladder of life scores (means) divided by MLwHFQquartiles (n=231).

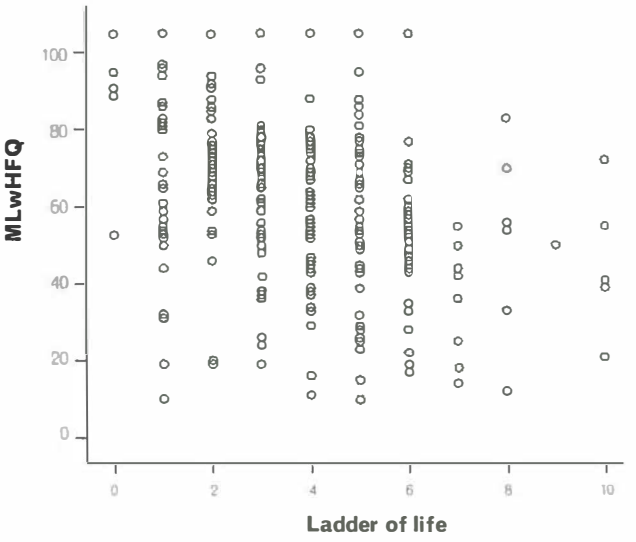

Figure 3. Scatter plot of Ladder of Life and MLwHFQ.

4. Discussion

In his book 'Doctors Dilemma', Lasagna wrote in 1962: 'It would seem important to devote more of the energies of man to improving the qualities of life, so that it may be joyous or noble or creative. Otherwise, existence is nothing but the bored molecular unwinding of a dismal biological clock'.[19] More recently quality of life has become an increasingly important outcome measure in medicine and healthcare, but it often seems difficult to choose the best instrument for the best population. Although in this study we did not assess which instrument is 'best', we did try to gain insight into the relationship between two instruments that both measure quality of life and were administered at the same time, namely during hospitalisation with symptoms of heart failure.

In this study we found that a single item assessment of quality of life with the Ladder of Life does not reveal the same information as the assessment of quality of life with a multiple-item instrument, the Minnesota Living with Heart Failure Questionnaire.

In this study, HF patients had a very low score on the Ladder of Life (mean 4),

compared with other studies in a similar Dutch HF population who scored 6.4 (± 2,2) during admission (20).
Although basic clinical characteristics of these populations are similar, the population we studied in Leiderdorp was an unselected patient population and patients were not recruited for a specific study, leaving a more heterogeneous population, with possibly more severe comorbidity or depression.
Results from other studies show patients rating a 6 before bypass surgery and patients in cardiac rehabilitation scoring an 8.[21,22] The low score confirms the impact a HF hospitalisation can have on a patient's life. Also, the MLwHFQ in our sample was rather high (reflecting a low quality of life); in comparable HF populations in HF clinics, scores between 45 and 63 have been reported.[23,24] Patients with an extremely low score, that is (≤1), did not consequently always score a low quality of life on the MLwHFQ. On the other extreme of the scale, some patients who scored relatively high on the Ladder of Life - stating that their life was close to the best possible life imaginable (>7) - scored a low quality of life on the MLwHFQ. Although there is a relationship between these two instruments, from these data one cannot make a choice for one of them.
Limitation of this study are the use of a cross sectional design and the time of reporting quality of life by the patient. In the Ladder of Life, patients score themselves on their overall quality of life at one particular moment. Hospital admission and staying away from home and loved ones can have a large impact on this score. The multi-item MLwHFQ asks patients to give a more balanced score over the previous month. Although it is not known that patients perceive this as difficult, it does seem to give another reflection of their quality of life.
In choosing the best instrument for our studies we also need to realise that the Dutch MLwHFQ also needs to be interpreted with caution. Earlier research concluded that completing the MLwHFQ requires much from respondents in terms of cognitive effort. In this study we did not measure the cognitive ability of our patients; however, from other studies it is known that HF is associated with a pattern of cognitive impairment that included attention and memory deficits.[25]
In gathering data on quality of life in HF patients it is important to consider what population is under study and what the possible effect of comorbidities might be. In our study we found weak correlations between comorbidity and MLwHFQ. This was confirmed by the study of Hak et al.[17], who also concluded that in completing the MLwHFQ patients need to consider only those restrictions that are caused by their HF.
We therefore like to conclude that although the Ladder of Life and the MLwHFQ do correlate, they do not seem to be interchangeable.
The one-item quality of life score can give clinicians and researchers important

information how the patients assesses their quality of life in a global score, but a more detailed description of emotional and physical aspects of quality of life can be gained with the MLwHFQ. This questionnaire, however, needs to be applied with good instructions. Several newer instruments have been developed for measuring quality of life in HF. The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a promising scale with six domains including symptoms, physical limitations and self-efficacy.[14] This questionnaire is rather new and needs to be tested before it can be used. At the same time there is a broad variety of instruments that are reliable and valid for measuring quality of life, but it is important to realise that they do measure different aspects of quality of life.

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CHAPTER 3

Quality of life and depressive symptoms in the elderly: a comparison between heart failure patients and age and gender matched community controls

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Submitted.

Abstract

Aim

To compare quality of life (QoL) and depressive symptoms of a Heart Failure (HF) population with an age and gender matched sample of community dwelling elderly.

Methods

Data were collected from 781 HF patients (36% female; age 72 ± 9; NYHA II-IV) and 781 age and gender matched community dwelling elderly. Participants completed the RAND-36, the Cantril's Ladder of life, and the Center for Epidemiologic Studies-Depression scale (CES-D).

Results

For both men and women with HF, QoL was reduced and depressive symptoms were elevated when compared to their elderly counterparts (CES-D ≥ 16: 39% versus 21%, $p<0.001$). HF patients had more chronic conditions, specifically diabetes and asthma/COPD. Impaired QoL and depressive symptoms were most prevalent among HF patients with co-morbid conditions. Prevalence was also higher in HF patients in the absence of these conditions.

Conclusion

HF has a large impact on QoL and depressive symptoms, especially in HF women. Differences persist, even in the absence of chronic conditions commonly co-morbid with HF. Results demonstrate the need for studies of representative HF patients with direct comparisons to age and gender matched controls.

1. Introduction

Heart Failure (HF) is a devastating disease with high morbidity and mortality and a lower five year survival rates than many common cancers such as breast and prostate cancer.[1] Additionally, HF is associated with diminished quality of life (QoL) by contributing to severe physical, role, social and functional impairment as well as increased psychological distress.[2,3] Major depression and depressive symptoms are common in patients with HF and even depressive symptoms in the absence of a confirmed diagnosis of depression increases the risk of short term worsening, clinical events and mortality.[4,5] Depressive symptoms may have a stronger association to QoL than severity of cardiac function or functional impairment.[2,6,7]

Most studies of HF patients involve a relatively young cohort of male HF patients, participating in medical clinical trials conducted at specialty tertiary care settings with stringent selection criteria.[8] Referral and selection biases thus yield samples that are not representative of the present HF population with its growing representation of elderly, female patients. Earlier, we showed that survival rates in a community sample of HF patients were worse than the known survival rates in clinical trials, with worse outcomes for males versus females[9], illustrating the importance to recruit samples outside the clinical trial population. Furthermore, assessment of measures of QoL and functioning often involve comparison to a normative population, rather than more comparable elderly living in the community.[10] These community residing elderly often suffer from several chronic diseases and have faced age related life events (e.g. loss of a spouse, retirement) that might affect their QoL and psychosocial status as well.

We are not aware of any published direct comparisons of QoL and depressive symptoms in a HF sample versus an age and gender matched community residing elderly control group. The purpose of the present study is (1) to examining whether there are differences in QoL and depressive symptoms between HF patients and an age and gender matched population of community dwelling elderly and (2) how does taking account chronic health conditions commonly comorbid with HF qualify the answers to this question?

2. Methods

2.1 Study population

2.1.1 HF population

Baseline data of patients hospitalized for HF and participating in the COACH (Coordinating study evaluating Advising and Counselling in Heart failure) study were used. COACH is a randomized clinical trial conducted in 17 centres in the Netherlands and studied the effect of outcome and counselling in HF patients.[11] Patients were included in the COACH-study between October 2002 and February 2005 when they were hospitalized for symptomatic HF confirmed by the cardiologist and had documented underlying heart disease. All patients were admitted for HF (NYHA II-IV). Patients were at least 18 years of age, with evidence of structural underlying heart disease. Patients were excluded if they were enrolled in a study requiring additional visits to research health care personnel. Other reasons for exclusion were invasive intervention (PTCA, CABG, heart transplantation, valve replacement) within the last 6 months or planned during the following 3 months; terminal disease or an active psychiatric diagnosis which hindered them from participating.
A cardiologist and a research nurse approached all patients. After written informed consent, patients completed questionnaires and were interviewed by an independent interviewer not involved in care for these patients. The Central Ethics Committee approved the study and the investigation conforms to the principles outlined in the Declaration of Helsinki.

2.1.2 Elderly population living in the community

Nine local district council offices in different areas in the Netherlands were asked for a random sample of addresses of 500-1,000 subjects of at least 55 years who were not living at the same address. Between July and August 2005, 5,500 questionnaires were distributed accompanied by a letter in which the subjects were invited to complete the questionnaires and return it in a pre-stamped envelope. Anonymity and confidentially was guaranteed. After three weeks a reminder letter was send to everyone, which resulted in a higher response.

2.2 Study measures

2.2.1 Quality of life

QoL was assessed by the Medical Outcome Study 36-item General Health Survey (RAND-36), a self report questionnaire of general health status. It is a well validated generic, 36-item questionnaire which includes nine health concepts that represent dimensions of QoL: physical functioning, role

limitations due to physical functioning, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional functioning, mental health and perceived health change. Each domain has a score between 0-100 and a higher score means better health.[12,13]
Well being was assessed by the Cantril Ladder of life. This is a single item measure that is used to assess global well being. Patients were asked to rate their sense of well being on a ladder, with 10 reflecting the best possible life imaginable and 0 reflecting the worst possible life imaginable. A higher score indicates better well being.[14]

2.2.2 Depressive symptoms

The Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depressive symptoms. The CES-D is a 20-item self-report questionnaire designed to measure depressive symptoms in the general population and has been widely used with the medical ill. A total sum score is used (0-60), with higher scores indicating more depressive symptoms. A cut-off point of 16 is generally used to define patients with clinically significant distress and the need for evaluation for clinical depression.[15,16]

2.2.3 Chronic conditions

In HF patients, data on what were presumed to be chronic conditions commonly co-morbid with HF (Diabetes Mellitus, Hypertension, Rheumatoid Arthritis, Stroke, Asthma/COPD and existing Renal disease) were collected from the medical patients chart. In the community dwelling elderly these were obtained by self reported questionnaires in which information about nineteen active medical problems was provided.

2.3 Statistical analyses

The two populations were matched by age and gender in order to have a fair test of differences.[17] First, descriptive statistics were used to characterize both samples. For continuous variables means and standard deviations and for categorical variables frequencies with percentages were used. Secondly differences on QoL between the two populations were tested by independent samples t- tests. Differences in dichotomized depressive symptoms were analyzed with chi-square test. Third, subgroup analyses were performed for gender. Scores on QoL and depressive symptoms were corrected for differences in age and number of comorbidities. ANOVA techniques for continuous variables and chi square tests for depressive symptoms were used. Because the homogeneity of variance was violated according to the Levine's test, Welch F tests were performed. Furthermore, QoL and depressive symptoms were examined in subjects with and without chronic conditions in general and specifically for subjects with and without diabetes and asthma/COPD. The

relative risk for depressive symptoms in both populations according to gender and chronic conditions were obtained by logistic regression analyses. Outcomes were considered statistically significant when $p < 0.05$.

3. Results

3.1 Response rate

For the COACH study approximately 2,957 patients with HF were screened. A total of 1,049 patients agreed to participate in the study and gave informed consent. From the 5,500 questionnaires distributed among community dwelling elderly, 2,512 were returned. In total 781 HF patients and 781 community dwelling elderly were matched on age and gender. Due to the process of matching, 268 HF patients were not analyzed. These HF patients were younger and more often female and their QoL was slightly worse on social functioning, role limitations due to physical functioning and perceived health change ($p<0.05$). All other domains of QoL including well being and depressive symptoms were similar in both groups.

3.2 Characteristics

Matched samples were on average 72 (± 9) years of age and 36% were women. In the HF population 39% was living alone compared to 30% in the elderly population ($p<0.001$) (Table 1). In patients with HF more chronic conditions are present (Table 2). At discharge, most HF patients were in NYHA functional class II and III (51% and 45% respectively). In total, 43% had ischemic HF. Patients with HF were on regular HF medication at discharge. In total 73% of the HF patients reported more than two chronic conditions while this was 4% in the elderly. Most reported comorbidities among HF patients were hypertension, asthma/COPD and diabetes. In the elderly population most subjects reported hypertension, rheumatoid arthritis or diabetes.

3.3 Quality of life and depressive symptoms

3.3.1 Total population

Without exception, all measures of QoL indicated significantly impairment among the HF patients compared to the matched elderly (Table 3). The largest differences between the two populations occurred in physical functioning and vitality ($p<0.001$). In role limitations due to physical functioning, the HF patients scored very low and the difference in mean score between the two populations was even more pronounced (19 ± 34 in HF patients, versus 66 ± 41 in the community dwelling elderly, $p<0.001$).

Table 1. Clinical characteristics of the Heart Failure population

Clinical characteristics	(n = 781)
NYHA functional class at discharge	
II	51%
III	45%
IV	4%
Ischemic Heart Failure	43%
Medication (at discharge)	
ACE/ARB*	86%
Diuretics	96%
B-blockers	65%
Duration of heart failure (years)	2.7 ± 4.5

*ACE/ARB = ACE inhibitor or angiotensin receptor blocker.

Table 2. Chronic conditions in a HF population and an age and gender matched population of community dwelling elderly.

Chronic conditions	Heart Failure patients (n = 781)	Community dwelling elderly (n = 781)	P value
Hypertension	43%	30%	<0.001
Asthma/COPD	30%	9%	<0.001
Diabetes Mellitus	29%	12%	<0.001
Stroke	11%	2%	<0.001
Rheumatoid Arthritis	7%	18%*	<0.001
Renal disease**	8%	1%	<0.001
Number of chronic conditions			
0	-	50%	
1	100%	33%	<0.001
2	27%	13%	
>2	73%	4%	

*Besides rheumatoid arthritis also other inflammation of the joints were included.
** documented as comorbidity

Table 3. QoL and depressive symptoms of a HF population and an age and gender matched population of community dwelling elderly.

	Heart Failure patients (n = 781)	Community dwelling elderly (n = 781)	P value
RAND-36 domains	m ± sd	m ± sd	
Physical functioning	35 ± 26	67 ± 27	<0.001
Role limitations physical	19 ± 34	66 ± 41	<0.001
Bodily pain	66 ± 33	79 ± 22	<0.001
General health perceptions	44 ± 18	60 ± 19	<0.001
Vitality	40 ± 24	64 ± 19	<0.001
Social functioning	54 ± 31	79 ± 24	<0.001
Role limitations emotional	51 ± 45	77 ± 37	<0.001
Mental health	66 ± 23	75 ± 17	<0.001
Perceived health change	26 ± 24	46 ± 18	<0.001
Well being	6.3 ± 1.8	7.2 ± 1.4	<0.001
Depression			
Depressive symptoms*	39%	21%	<0.001
CES-D	15 ± 10	10 ± 9	<0.001

*CES-D ≥ 16.

As measured with the Ladder of Life, well-being was significantly lower in the HF population versus the community dwelling elderly (6.3 versus 7.2, p<0.001).

In the HF population 39% reported depressive symptoms versus 21% of the community dwelling elderly (p<0.001) (Table 3).

Because living situation was different between the two populations and living alone has been shown to be associated with lower QoL, additional analyses were performed on quality of life and depressive symptoms in which we adjusted for living alone, but differences between the two populations remained the same (results not shown).

Table 4. QoL and depressive symptoms of patients with HF and community dwelling elderly divided by gender.

	Heart Failure men (n=503)	Community dwelling men (n=503)	Heart Failure women (n=278)	Community dwelling women (n=278)	
RAND-36 domains	m ± sd	m ± sd	m ± sd	m ± sd	F test
Physical functioning	38 ± 26	68 ± 26	32 ± 25	60 ± 28	F = 182.2 *†
Role limitations physical	21 ± 35	67 ± 39	20 ± 32	60 ± 42	F = 175.1*
Bodily pain	68 ± 32	79 ± 21	65 ± 24	73 ± 24	F = 19.03*
General health perceptions	45 ± 18	59 ± 19	46 ± 19	58 ± 18	F = 107.46*
Vitality	43 ± 23	65 ± 19	38 ± 24	59 ± 19	F =133.9*
Social functioning	56 ± 30	79 ± 22	55 ± 32	75 ± 27	F = 80.4*
Role limitations emotional	52 ± 45	77 ± 35	54 ± 46	70 ± 40	F = 37.4*
Mental health	69 ± 22	77 ± 16	64 ± 24	70 ± 22	F = 27.1*
Perceived health change	26 ± 23	46 ± 18	26 ± 25	46 ± 19	F = 107.4*
Well being	6.5 ± 1.8	7.2 ± 1.3	6.1 ± 1.9	7.0 ± 1.4	F = 38.8*
Depression					
CES-D	14 ± 10	9 ± 7	16 ± 12	12 ± 9	F = 38.7*
Depressive symptoms[1]	36%	17%	45%	29%	α^2=141.1*

[1] CES-D ≥ 16. * p<0.001. † QoL scores were adjusted for age and number of comorbidities.

3.3.2 Gender

Men with HF had significant impaired QoL compared to their age-matched elderly men. In total 36% in men with HF and 17% of the elderly men reported the presence of depressive symptoms ($chi^2 = 141.1$, $p < 0.001$) (Table 4).
In women with HF all domains of QoL were significant impaired compared to their age-matched counterparts from the community. Depressive symptoms were present in 45% of HF women and in elderly women the presence was 29%.
Men and women with HF had significant lower QoL on all domains and higher depressive symptoms when compared with their elderly gender matched counterparts (Table 4). Within both strata, women had significant

lower QoL on several domains and more depressive symptoms than men. Women with HF had more impaired QoL on physical functioning, vitality, mental health, well being and depressive symptoms than men with HF even when adjusted for age and number of co morbidities.
In both HF men and women, the risk for depressive symptoms is more than doubled of that of their age comparable counterparts resulting in an odds ratio of 2.71 for men with HF compared with their male counterparts and an odds ratio of 2.02 for women with HF compared with elderly women.

3.3.3 Chronic conditions

Diabetes and COPD. The prevalence of asthma/COPD and Diabetes, was much higher in the HF population compared to the non HF population. In HF patients 30% and in the elderly 9% reported asthma/COPD and diabetes was present in 29% of HF patients versus 12% in the elderly living in the community ($p<0.001$). HF patients in the presence of these two co-morbidities had worse QoL than those without. The less impaired HF patients without these chronic conditions were nonetheless worse off than the elderly and specifically those elderly with diabetes or asthma/COPD.

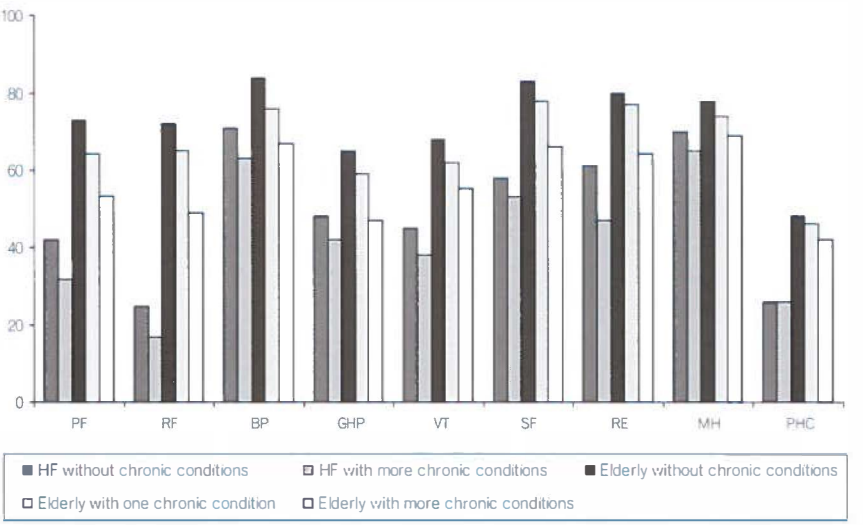

Figure 1. QoL of patients with heart failure and community dwelling elderly according to the number of chronic conditions, adjusted for age and living alone.
(PF= physical functioning; RF=role limitations due to physical functioning; BP=bodily pain; GHP=general health perception; VT=vitality; SF=social functioning; RE=role limitations due to emotional functioning; MH=mental health; PHC=perceived health change).

Table 5. Demographic characteristics, well being and depressive symptoms of patients with HF and community dwelling elderly divided by numbers of chronic conditions.

	HF patients without chronic conditions (n=208)	HF patients with more chronic conditions (n=573)	Community dwelling elderly without chronic conditions (n=392)	Community dwelling elderly with one chronic condition (n=261)	Community dwelling elderly with more chronic conditions (n=128)	
	m ± sd	m ± sd	m ± sd	m ± sd	m ± sd	P value
Age	70.4 ± 9.4	72.9 ± 8.6	72.6 ± 8.9	72.3 ± 8.5	73.8 ± 8.1	0.003
Sex (f)	32%	37%	34%	35%	41%	0.44
Living alone	38%	40%	28%	31%	31%	0.002
Well being **	6.2 ± 1.9	6.4 ± 1.8	7.3 ± 1.3	7.1 ± 1.4	6.8 ± 1.4	<0.001
Depression						
CES-D**	13 ± 9	16 ± 11	8 ± 7	10 ± 8	13 ± 9	<0.001
'Depressive symptoms**	32%	42%	16%	22%	38%	<0.001
† OR depressive symptoms	2.48	3.79	1.0	1.43	3.24	

Chronic conditions studied are: diabetes, stroke, arthritis, hypertension, renal disease, asthma/COPD.
'CES-D ≥ 16. † OR = Odds Ratio.** Adjusted for age and living alone.

Patients with HF both with and without chronic conditions had significant lower QoL on all domains than the cohort of community dwelling elderly (Figure 1). HF patients without additional chronic conditions like asthma/ COPD, Arthritis, Diabetes, Renal disease, Hypertension or Stroke, showed impaired QoL specifically in physical functioning, role limitations, vitality, mental health, social functioning and well being. The QoL of HF patients without chronic conditions was also lower in most QoL domains (physical functioning and role limitations, vitality, social functioning and well being) when compared with the QoL of elderly with several chronic conditions. Depressive symptoms in HF patients with additional chronic conditions were higher compared with elderly without and with one major chronic condition. However, in elderly with two or more chronic conditions, depressive symptoms were more often reported and bodily pain and general health perceptions were more impaired (Table 5). The unadjusted odds ratio for depressive symptoms in HF patients without additional chronic conditions is 2.48 and with additional chronic conditions the odds ratio is 3.79 compared with community dwelling elderly without chronic conditions.

4. Discussion

QoL of HF patients was significant impaired on all dimensions when compared with an age and gender matched community residing sample. Greatest differences in QoL occurred in the area of physical health (physical functioning, role limitations due to physical functioning, vitality), in which HF patients consistently scored significant lower. Women had more impaired QoL compared with their female counterpart and so do men. We found that QoL declines with an increasing burden of comorbidity in both those with and without HF. However patient with HF and comorbidities were worse off than the comparable elderly population with comorbidities.

Our findings are consistent with findings from other studies in which QoL of HF patients was significant more impaired than the QoL of a general population sample,[3,8] a healthy elderly population sample[19] and compared to patients with other chronic disorders[20].

Elevations in depressive symptoms in the HF population were more common and almost double compared to the age and gender matched sample. These higher rates of depressive symptoms in HF patients have been reported earlier[21,23], but in two of these studies[22,23] highly selective patient samples of consecutive HF patients who were severely ill, from University Hospitals were used, which are not comparable with the present HF population. The strength of our study was that the HF sample used was recruited from 17 hospitals,

with broad selection criteria, reducing referral bias so that the sample is more representative of the HF population living in the community. The present results are comparable to some of our earlier findings among HF patients from a community sample. We found that they were low on various QoL measures and remained at that level after the disease develops.[24]

Overall the substantial impact of HF on QoL is more pronounced in women: women with HF are more impaired in physical health, mental health and well being than men with HF and report more depressive symptoms. Friedman and colleagues[25] previously found that women were more impaired by HF than men especially in physical functioning but the patients under study were recruited from an acute care setting. Riedinger and colleagues[26] studied QoL in women compared to a normative group and patients with other chronic conditions. But the results of this study are limited by the origin of its respondents who were recruited from medical trials (i.e. SOLVD) In a prospective study in which data before onset of the disease were available as well as QoL data after the onset, we saw clear gender differences, indicating that females were worse off compared to males, both at baseline (before onset) as well as after the onset.[24]

The present study allowed some differentiation of the effects of HF versus commonly co-morbid conditions. When additional chronic conditions are present, QoL is impaired in both HF patients and matched controls. The risk for depressive symptoms in both HF patients and matched elderly with more chronic conditions is more than three times higher than in elderly without chronic conditions. HF patients with asthma/COPD have reduced QoL presumably of the toll of dyspnoea. HF patients with diabetes are more likely to have other late effects of diabetes like neuropathy, with negative implications for QoL and depressive symptoms. Nonetheless, in the absence of asthma/COPD and diabetes, HF patients have lower QoL and more depressive symptoms than age and gender matched controls. This differentiation of the effects of HF and commonly associated co-morbid conditions is a distinctive feature of the present study. Despite the high prevalence of these co-morbid conditions, patients suffering from them are often excluded from the clinical trials that serve as data base for our understanding of HF.

Hospitalisation could be of influence on QoL of this HF population, however HF patients have to deal with these sometimes frequent and frightening exacerbations during the course of HF. There is evidence that QoL in general improves as time from discharge increases.[27] However, despite improving after hospital discharge, QoL remains poor and is worse than that seen in most patients with other chronic and cardiac diseases.[28]

High scores of depressive symptoms were seen in both women with HF and in the elderly population. These elevated scores occur in the context

of considerable disease burden. It may be necessary to adjust the standard cut point for the CES-D, if a substantial portion of the increase in scores due to this burden, does not correspond directly to increased risk of major depressive disorder, but rather to some degree mainly represents an elevation of less specific distress and depressive symptomatology.

There were two limitations to the assessment of chronic conditions in this study. First, the list was not intended as an overall measure of chronic health conditions. The list was by no means exhaustive, but limited to conditions likely to have substantial comorbidity in the HF population and were documented as co-morbidity in the chart. While these conditions are relevant to sorting the effects of HF on QoL and depressive symptoms from the effects of comorbid conditions, the conditions underestimate the total disease burden for both HF patients and community controls. A second limitation is that whereas the comorbid conditions in HF patients were assessed by chart review, assessment in the community dwelling elderly population were derived from self reported questionnaires. However, a number of studies indicate a good correspondence between medical records and physician reports versus adult respondent self-reports.[29]

Conclusion

Our data demonstrate the burden of HF on all components of QoL in a clinical representative HF sample and provide direct comparisons to age and gender matched controls living in the community. The burden is related to the common presence of comorbid conditions but also occurs in the absence of them. HF guidelines acknowledge the impact of HF on QoL since improving QoL is the main goal in the treatment of chronic HF. The study also showed the high amount of depressive symptoms in HF women and patients with more chronic conditions. Results underscore the need to detect symptoms of depression in an early stage and for the subgroup which is clinically depressed, ensure appropriate treatment according to established guidelines. However, the quite high rates of depressive symptoms relative to age and gender matched community comparisons suggest the possible need to re-validate the standard cut off for the CES-D for use in an elderly HF population.

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CHAPTER 4

Depressive symptoms are prominent among elderly hospitalised heart failure patients

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Abstract

Background

There are limited data on the prevalence of depressive symptoms in hospitalised elderly heart failure (HF) patients and demographic and clinical characteristics associated with depressive symptoms are not known.

Methods

A sample of 572 HF patients (61% male; age 71 ± 12; LVEF 34% ± 15) was recruited from 17 Dutch hospitals during HF admission. Depressive symptoms were assessed by the CES-D. Demographic, clinical variables and HF symptoms were collected from patient chart and interview.

Results

Forty one percent of the patients had symptoms of depression with women significantly more often reporting depressive symptoms than men 48% vs. 36% ($chi^2 = 8.1$, $p<0.005$). HF patients with depressive symptoms reported more clinical HF symptoms than patients without depressive symptoms. Even after deleting HF related symptoms (sleep disturbances and loss of appetite) from the CES-D scale, 36% of the patients were still found to have symptoms of depression. Multivariable logistic regression analyses revealed that depressive symptoms were associated with female gender (odds 1.68, 95% CI 1.14-2.48), COPD (odds 2.11, 95% CI 1.35-3.30), sleep disturbance (odds 3.45, 95% CI 2.03-5.85) and loss of appetite (odds 2.61, 95% CI 1.58-4.33).

Conclusions

Depressive symptoms are prominent in elderly hospitalised HF patients especially in women. Depressive symptoms are associated with more pronounced symptomatology, despite the fact that other indices of severity of left ventricular dysfunction are similar.

1. Introduction

Despite advances in medical treatment, the prognoses of Heart Failure (HF) remains poor.[1] HF is a chronic disease, which may confront patients with numerous threats including impaired physical functioning and changes in future perspectives. Response to this can be emotional misbalance and depression. Studies that have reported on the prevalence of depression in HF patients mostly evaluate the risk on morbidity and mortality[2-5]; however, only a few studies investigated the relation between patient or clinical characteristics and depressive symptoms. The few studies that have investigated the demographic and clinical factors related to depressive symptoms have used various diagnostic tools for assessing depressive symptoms. The Beck Depression Inventory scale (BDI) is most often used in these studies. The BDI is known to focus substantially on somatic items and therefore may be inadequate as an instrument to screen for depressive symptoms in HF patients.[2] In some studies the Center for Epidemiologic Studies Depression Scale (CES-D) is used. It has only two somatic items that are similar to the somatic symptoms in HF patients and is therefore a reliable and well-validated questionnaire to screen for depressive symptoms in HF patients.[3-7] The studies describing depressive symptoms in HF have used relatively small sample sizes and rather young patient samples: the mean age in most studies was below 65 years of age. Focusing on these 'relatively young' patients may not be representative for the present 'real life' HF population. Finally most of the studies about HF and depression or depressive symptoms were performed in the United States[4,5,8-14], only a few have been performed in Europe[15-17].

It is hard to diagnose depression in diseases in which symptoms of the disease are similar to symptoms of depression.[18] In HF patients, symptoms like fatigue, sleeplessness, loss of appetite, feelings of worthlessness and low energy are common. The same symptoms are used to diagnose depression.[19] This is why it is difficult to distinguish depressive symptoms from worsening HF.

To carefully look at symptoms of depression in HF patients we assessed the occurrence of depressive symptoms in hospitalised, elderly HF patients and explored related demographic and clinical factors.

More specifically the following research questions are addressed:

- What is the prevalence of depressive symptoms in elderly hospitalised HF patients?
- Which demographic and clinical variables are related to depressive symptoms in elderly hospitalised HF patients?
- What is the relationship between depressive symptoms and symptoms of HF?

2. Methods

2.1 Participants

Patients in the present study were included in a multi centre HF trial (Coordinating study evaluating Outcomes of Advising and Counselling in HF patients-COACH) conducted in the Netherlands.[20] Data on depressive symptoms that are reported in this study were collected from baseline interviews, before any intervention took place. The study design has been described elsewhere.[20] A summary of the inclusion and exclusion criteria used, is as follows. All patients were admitted for HF (NYHA II-IV). Patients were at least 18 years of age, with evidence of structural underlying heart disease. Patients were excluded if they were enrolled in a study requiring additional visits to research health care personnel. Other reasons for exclusion were invasive intervention within the last 6 months (PTCA, CABG, HTX, valve replacement) or planned during the following 3 months; being in an end stage of another life threatening disease or having a psychiatric diagnosis. In total, 572 patients (of the included 737 patients) having complete data sets of CES-D and HF symptoms were included in the analysis. The Central Ethics Committee approved the study and prior to the announcement of the investigation all patients provided written informed consent. The investigation conforms with the principles outlined in the Declaration of Helsinki.

2.2 Study measurements

2.2.1 Depressive symptoms

The definition of depressive symptoms used in this study is taken from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorder-Fourth Edition (DSM-IV). Depression due to a general medical condition (e.g. heart failure), is defined as: patient's clinical presentation which is dominated by a mood disorder that persists and is characterized by either or both depressed mood or markedly decreased interest or pleasure in nearly all activities, or mood that is elevated, expansive or irritable.[14,19]
The Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depressive symptoms of the patients under investigation. The CES-D is a 20-item self-report questionnaire designed to measure depressive symptomatology in the general population and in the medical ill.[6,7] The scale is purported to measure the presence of depressive mood by asking respondents to rate how often they have experienced each of the 20 symptoms during the past week. Each item is scored on a four-point scale: (0) 'rarely or non of the time' (less than once a week), (1) 'some or a little of the time' (1-2 days of the week), (2) 'occasionally or a moderate amount of time' (3-4 days a week), or (3) 'most or all of the time' (5-7 days a week).

The total score for a respondent consists of a sum score to the responses to all 20 items, ranging from 0-60, with higher scores indicating more symptoms of depression (weighted by the occurrence during the past week). A cut off point of 16 is generally used to define patients who are at risk for clinical depression.[3,21] The CES-D is a valid instrument to identify high-risk groups and to study the relationships between depressive symptoms and many other variables, which has been established in cardiac and non-cardiac patients.[23,24,26]

2.2.2 Demographic and clinical data

During admission to the hospital, data on demographics: age, sex, living situation and education level were collected from patient interview. Left ventricular ejection fraction (LVEF), NYHA functional class at admission, aetiology, duration of HF and the presence of comorbidities (hypertension, COPD, Type II diabetes mellitus, peripheral vascular disease, renal dysfunction, arthritis and stroke) was collected from medical records.

2.2.3 Symptoms of heart failure

Symptoms of HF were assessed from an interview comprising ten structured questions. During this interview, patients were asked whether they had experienced the following symptoms during the last month: ankle oedema during the day, ankle oedema when getting out of bed in the morning, sleep disturbance, fatigue, breathlessness at rest and during exertion, orthopnoea, coughing, dry cough or loss of appetite. These ten symptoms were clustered in six symptom indexes: oedema, sleep disturbance, fatigue, dyspnoea, coughing and loss of appetite. A total HF symptom score was obtained from the sum of the six symptom indexes.

2.3 Statistical analyses

Descriptive statistics were used to characterize the study population. Means, medians and standard deviations are presented for depressive symptoms, demographic and clinical data and HF symptoms.
Student's *t*-tests and Mann Whitney tests for continuous variables and chi square tests for categorical variables were performed to compare demographic and clinical characteristics and HF symptoms between patients with or without depressive symptoms. A multivariable logistic regression analysis was utilized to define the independent association between depressive symptoms and demographic and clinical characteristics and HF symptoms. The multivariate model was built by entering those variables that had a univariate p value < 0.15 (e.g. sex, LVEF, hypertension, COPD, arthritis, number of HF symptoms, dyspnoea, fatigue, sleep disturbance and loss of appetite) and retaining those variables with $p < 0.05$ in the final model.

Table 1. Patient characteristics and univariate differences between patients with and without depressive symptoms.

	total group n=572 mean ± sd	non-depressive symptoms n=339 mean ± sd	depressive symptoms n=233 mean ± sd	P value
Demographics				
Age	71 ± 12	71 ± 12	70 ± 12	0.16
Sex (female)	39%	33%	43%	0.004*
Living with a partner	61%	62%	57%	0.24
Educational level				
at least six years of primary school	55%	55%	55%	
diploma secondary school	30%	28%	32%	0.77
higher education or university	15%	16%	13%	
Clinical characteristics				
LVEF (%)	34 ± 15	33 ± 14	34 ± 15	0.52
LVEF < 40%	32%	71%	63%	0.07
NYHA II, III, IV (at admission %)	6, 51, 43	6, 50, 44	6, 52, 42	0.60
Serum creatinine (mmol/L)	122 ± 45	120 ± 41	124 ± 50	0.31
Serum sodium (mmol/L)	139 ± 4	139 ± 4	139 ± 5	0.24
Haemoglobin (mmol/L)	8.3 ± 1.2	8.4 ± 1.2	8.3 ± 1.2	0.49
Aetiology (%) Ischaemic	43%	45%	40%	0.24
Non-ischemic	57%	55%	60%	
Atrial fibrillation	42%	42%	43%	0.89
Medication at admission				
Diuretics	62%	62%	62%	0.89
ACE-inhibitors/ARB	56%	55%	56%	0.85
Beta blockers	42%	41%	43%	0.58
Digoxin	19%	17%	21%	0.18
Spironolactone	16%	15%	17%	0.50

Table 1. Continued.

Comorbidities				
Hypertension	35%	33%	39%	0.14
COPD	25%	22%	29%	0.06
Type II diabetes	20%	20%	19%	0.79
Peripheral vascular disease	16%	16%	18%	0.60
Renal disease	8%	8%	8%	0.95
Stroke	8%	8%	8%	0.95
Arthritis	7%	5%	9%	0.10
Mean number of comorbidities	1.1 ± 1.0	1.0 ± 1.0	1.2 ± 1.1	
No comorbidities	34%	36%	31%	0.16
1-2 comorbidities	56%	54%	59%	
2-6 comorbidities	10%	10%	10%	
Duration of heart failure (y)	2.5 ± 4.8	2.8 ± 5.6	2.0 ± 3.3	0.19
Heart Failure symptoms				
Mean number of HF symptoms	4.0 ± 1.3	3.9 ± 1.3	4.6 ± 1.4	<0.001*
No symptoms	2%	0.3%	0.4%	
1-2 symptoms	10%	14%	5.4%	
3-4 symptoms	41%	48%	30%	
5-6 symptoms	47%	37%	66%	
Dyspnoea	95%	93%	97%	0.017
Fatigue	87%	82%	95%	<0.001*
Coughing	70%	68%	73%	0.17
Oedema	64%	62%	67%	0.20
Sleep disturbance	62%	51%	79%	<0.001*
Loss of appetite	51%	40%	68%	<0.001*
Depression				
Mean CES-D total score (range: 0-60)	15.6 ± 11	8 ± 4.5	26 ± 8.3	<0.001*
Symptoms of depression (CES-D ≥16)	41%	0%	100%	

* $p<0.05$.

3. Results

3.1 Participants

Between November 2002 and April 2004, 737 patients who met the criteria for the COACH study, agreed to participate and gave informed consent. Six hundred and eighty one of these patients filled out the CES-D questionnaire; however, 109 of these patients did not complete the structured interview about the ten HF symptoms. Therefore, 572 HF patients were included in this sub-study. There were no significant differences in basic demographics (age, sex) and clinical variables (LVEF, NYHA class) between patients with or without complete data sets.

On average patients were 71 ± 12 years of age and most patients (62%) were male (Table 1). The majority of patients had a low educational level, were living with a partner and had suffered from HF for more than two and a half years. On admission, most patients were in NYHA functional class III (51%) and IV (43%). The mean LVEF was 34% ± 15. On average patients had one medical comorbidity (range 0 – 6). One third of patients were hypertensive (35%), Chronic Obstructive Pulmonary Disease (COPD) was present in 25% of the patients and type II diabetes was present in 20%. All patients were on standard medical treatment regimen with ACE-inhibitors, beta blockers and diuretics.

3.2 Symptoms of heart failure

Patients reported on average four symptoms of HF; less than two percent of the patients reported no symptoms, 30% had five symptoms and 17% had six symptoms of HF at the time of measurement. Most reported symptoms of HF were dyspnoea (95%) and fatigue (87%). More than two third of the patients had coughing, oedema and sleep disturbance. Fifty one percent of patients had loss of appetite (Table 1).

3.3 Prevalence of depressive symptoms

The mean score on the CES-D in this study population was 15.6 ± 11 (0-60) (Figure 1). More than 41% of the patients had depressive symptoms (score CES-D ≥ 16) (Table 1). Importantly, on all 20 items of the CES-D significant differences were found between patients with and without depressive symptoms, including the somatic items like loss of appetite and sleep disturbance.

Loss of appetite and sleep disturbance are two common somatic symptoms in HF patients as well as in patients with depression. Of the non-depressed HF patients 40% reported loss of appetite and 51% have sleeping difficulties. But patients with depressive symptoms more often report loss of appetite (68%) and sleeping difficulties (79%) (Table 1). Although sleep disturbance and loss of appetite are both symptoms of HF and symptoms of depression, patients with

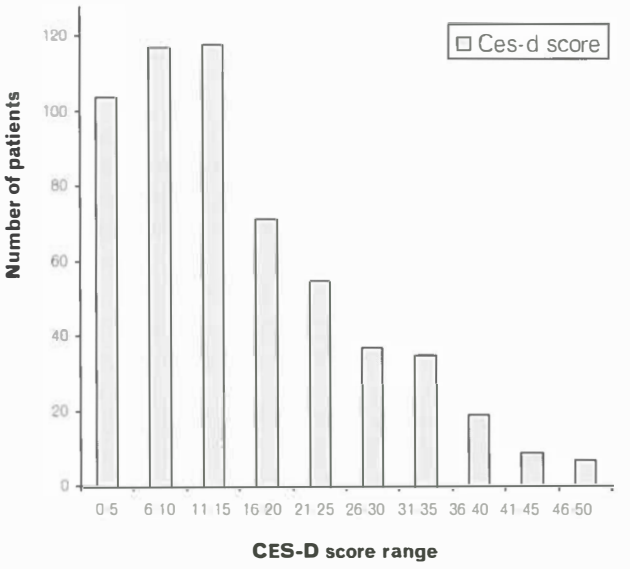

Figure 1. CES-D total score in population (n=572).

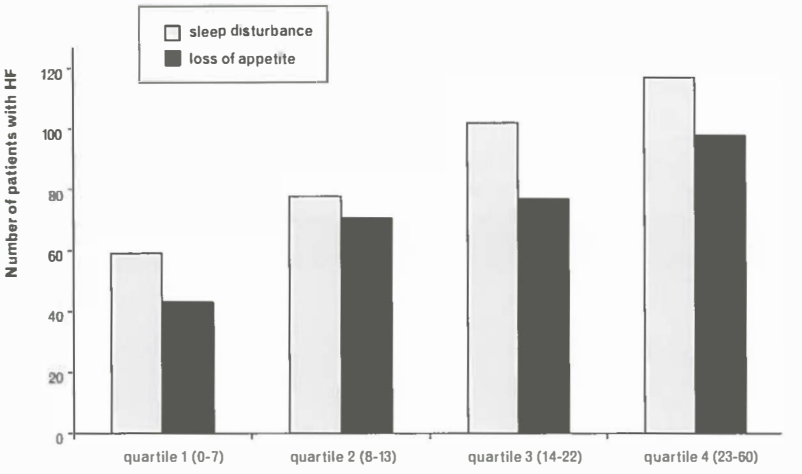

Figure 2. Number of patients (n=572) with sleep disturbance and loss of appetite among the 4 quartiles of the CES-D score.

depressive symptoms score significant worse on these two items (Figure 2). When these two items were removed from the CES-D, 36% of the HF patients still reported depressive symptoms (CES-D ≥16).

3.4 Differences in demographic and clinical characteristics between patients with and without depressive symptoms

Based on the CES-D score, we compared patients without (score <16) or with (score ≥16) depressive symptoms. Univariate analyses among patients with or without depressive symptoms indicated that more women than men suffered from depressive symptoms: 48% versus 36% (chi square = 8.1, $p < 0.05$) (Table 1). No significant differences were found between patients with and without depressive symptoms according to age, living with a partner and educational level.

With respect to clinical characteristics, like LVEF, NYHA functional class at admission, aetiology, duration of HF and the number and nature of medical comorbidities, no significant differences were seen between the two groups (Table 1).

3.5 Relation between depressive symptoms and HF symptoms

Compared to patients without depressive symptoms, patients with depressive symptoms had more symptoms of HF ($z = -7.1$ $p < 0.01$). Also the nature of these symptoms was different between the two groups. Patients with depressive symptoms more often reported dyspnoea ($p < 0.01$), fatigue, sleep disturbance and loss of appetite ($p < 0.01$). In a multivariable logistic regression analysis female sex, COPD, sleep disturbances and loss of appetite were all independently associated with depressive symptoms (Table 2).

Table 2. Summary statistics for multivariable logistic regression model of depressive symptoms and demographic and clinical variables.

Variable	Odds ratio	95% CI	P value
Female sex	1.68	1.14 – 2.48	0.009
COPD	2.11	1.35 – 3.30	0.001
Sleep disturbance	3.45	2.03 – 5.85	0.001
Loss of appetite	2.28	1.58 – 4.33	0.001

CI = confidence interval; COPD = chronic obstructive pulmonary disease.

4. Discussion

4.1 Depressive symptoms

In this study we found a very high prevalence of depressive symptoms among a group of hospitalised, elderly HF patients. This is consistent with findings in several other studies. Recent studies have shown that depression is common in HF patients with prevalence rates in outpatients ranging from 11% to 25%.[9,15] In our study of hospitalised elderly patients we found that 41% of patients with HF reported depressive symptoms. This is comparable to some other smaller studies that found rates of 14-77%.[4;5;8;13;17;22;23] One reason for the wide range of prevalence rates reported across studies is the use of different definitions.[23] If depression is defined as a clinical diagnosis, listed in a patient record as an active problem, the prevalence will be low. Faris[15] reports that this is an underestimation of the prevalence of depressive symptoms. Sometimes the term depression is defined as 'major depression' as defined by DSM-IV. If this is the case, lower incidence rates for depression are also found (9-26%).[23] If depression is defined as mild or moderate or as having depressive symptoms then the incidence is much higher. In our study, we defined depression as having depressive symptoms.

It has also been reported in other studies, that patients with HF suffer more frequently from moderate to severe depression than patients with other chronic diseases (e.g. type II diabetes, cancer). In a study of 203 older patients with type II diabetes (mean age: 67 years) only 10% were depressed[24]. A Dutch study of 475 patients with cancer (mean age: 58.6), 19.7 % had CES-D score ≥16 [7;25] and in a community based sample of elderly people in the Netherlands[3], 15% were found to be depressed. The high rate of depressive symptoms in HF patients may be due to the worse functional status[26;27], decrease in quality of life[28,29] the high level of psychological distress[30;31] and biological abnormalities[10;32].

In our study female sex, COPD, sleep disturbances and loss of appetite were associated with depressive symptoms. Gottlieb et al.[9] also reported that women are more likely to experience depression. In their study among 155 outpatient HF patients 64% of the women are depressed compared to 44% of the men. It is also known that in physically healthy subjects, women are twice as likely to be diagnosed with depressive symptoms than men.[7;25;33] None of the other demographic and clinical parameters were associated with depressive symptoms in this study population.

COPD is a common comorbidity in HF patients and in our study an independent risk factor associated with depressive symptoms. Symptoms like dyspnoea and fatigue experienced by HF patients with COPD do interact with each other and can lead to increased frequency and severity of symptoms of HF, which in turn can lead to symptoms of depression.

There seems to be a considerable overlap between depressive symptoms and symptoms of HF. For example fatigue, low mood, lost of interest in usual activities and sleeplessness are common in both.[15,18,34] In our study, we found that sleep disturbances and loss of appetite were both independently associated with depressive symptoms. The connection between these symptoms of depression in HF patients may lie in shared mechanisms in HF and depression. Both in HF patients and depressive patients activation of the sympathetic nervous system, elevated levels of cytokines, a decreased heart rate variability (HRV) and rhythm disturbances have been described.[10,32,35,37] For example in both patients with HF and patients with depression a higher level of tumor necrosis factor alpha (TNF-α) has been found[35,36], which is linked to cardiac cachexia[35,36]. Sleep disturbance is a symptom also often seen in both depressive and HF patients. The shared factor in this can be the low HRV in both groups of patients.[10,18,21] Despite the overlap of symptoms, we found a significant difference in the amount and nature of HF symptoms between patients with and without depressive symptoms. In further analyses only two somatic items of the CES-D had an overlap with the questions about HF symptoms in the structured interview. If these two somatic items (sleep disturbance and loss of appetite) were removed from the CES-D, a lot of HF patients (36%) still reported depressive symptoms (CES-D ≥16). Furthermore for these two items, patients with depressive symptoms score significantly worse on both the CES-D and the structured interview.

In conclusion: In the present study we assessed the occurrence of depressive symptoms in elderly HF patients and studied the relation with demographic and clinical characteristics and HF symptoms. Depressive symptoms are very prominent in hospitalised, elderly HF patients, especially in women and in those with more pronounced symptomatology. Several studies have suggested that depression and depressive symptoms in HF patients are linked to adverse outcomes. Therefore, treatment of depression or depressive symptoms, especially if they continue after discharge, is important as these symptoms may hamper successful treatment of HF and have an adverse impact on the lives of elderly, hospitalised HF patients.

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CHAPTER 5

Determinants of depressive symptoms in hospitalised men and women with heart failure

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Abstract

Aim

Depressive symptoms are prominent and related to an increased risk on cardiovascular disease outcomes and all cause mortality in HF patients. To intervene effectively, factors related to depressive symptoms in men and women should be identified.

Methods

Depressive symptoms of 921 hospitalised HF patients (61% male; age 71 ± 11; LVEF 33% ± 14, NYHA II-IV) were assessed by the Center for Epidemiologic Studies-Depression scale (CES-D).

Results

Overall 40% of the patients had depressive symptoms (CES-D ≥ 16), which were more common in women than in men (47% versus 36%, $p < 0.001$). Multivariable analysis in men revealed that depressive symptoms were related to age (OR 0.84, 95% CI 0.71-0.98, p=0.03, per 10 years), physical health (OR 0.76, 95% CI 0.71-0.83, $p < 0.001$, per 10 units) and HF symptoms. In women depressive symptoms were also related to NYHA II-III versus IV (OR 0.60, 95% CI 0.37-0.95, $p < 0.03$) and COPD (OR 2.33, 95% CI 1.20-4.53, $p<0.012$).

Conclusion

Depressive symptoms are more common in women than in men. In both men and women depressive symptoms are related to age and physical health. For clinical factors: in men only HF symptoms, but in women also NYHA and COPD were related to depressive symptoms.

1. Introduction

Depression is common in heart failure (HF) patients. Depression rates of 11-77% have been reported and it predicts poor outcomes such as readmissions, mortality and increasing health care costs.[1,3]
Several demographic and clinical risk factors have been reported to be related to depressive symptoms in the general population and in medical ill patients. In these populations, risk factors described are female gender and younger age[4], lack of social support and physical illness[5]. It is known that more women than men experience periods of depressive symptoms or more and longer periods of major depression. Despite the higher prevalence of depression in the general population in women compared to men, only few studies have found this in patients with HF.[6,7] Gottlieb and colleagues[7] found that in women with HF more depressive symptoms were reported compared to men with HF. In a study of Freedland and colleagues[6] female gender remained as a significant predictor to depression in the multivariate analysis. However, the underlying reasons for this difference between men and women is not clear. A review on gender differences in HF patients showed that HF men and women differ in their life situation (e.g. age and marital status) and in several HF related factors (e.g. aetiology, HF symptoms, LVEF and comorbidities).[8] Ekman[9] reported that women and men with HF experience similar symptoms, but that these symptoms are perceived in different ways. Considering these differences between men and women with HF, it is useful to identify related factors of depressive symptoms not in HF patients as one group but study these in men separately from women. To the best of our knowledge no study has examined depressive symptoms and related factors in HF men separately from HF women.
The purpose of this study is to explore the presence of depressive symptoms and its relationship with demographic and clinical factors in a cohort of hospitalised *men* with HF and separately in hospitalised *women* with HF.

2. Methods

2.1 Participants

All patients in the present study were part of the Coordinating study evaluating Outcomes of Advising and Counselling in heart failure (COACH study). This study was designed to determine the effects of two levels of intensity in heart failure disease management programs on the combined endpoint of heart failure readmission and mortality. Baseline data (prior to

randomisation) of these patients were analysed. The design of the COACH study is described in detail elsewhere.[10] In short, patients were included in the COACH study between October 2002 and February 2005 when they were hospitalised for symptomatic HF (NYHA II-IV) and had documented underlying heart disease. Patients were at least 18 years of age. Patients were excluded if they were enrolled in a study requiring additional visits to research health care personnel. Other reasons for exclusion were invasive intervention (PTCA, CABG, heart transplantation, valve replacement) within the last 6 months or planned during the following 3 months; a terminal disease or an active psychiatric diagnosis which hindered them from participating.
A cardiologist and a research nurse approached all patients. After written informed consent, patients completed questionnaires and were interviewed by an independent interviewer not involved in the care for these patients. The Central Ethics Committee approved the study and the investigation conforms to the principles outlined in the Declaration of Helsinki.

2.2 Study measurements

2.2.1 Depressive symptoms

The Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depressive symptoms. The CES-D is a 20-item self-report questionnaire designed to measure depressive symptoms in the general population and in the medical ill.[11,12] The scale measures the presence of depressive mood by asking respondents to rate how often they have experienced each of the 20 symptoms during the past week. A total sum score is used (0-60), with higher scores indicating more depressive symptoms. A cut-off point of 16 is generally used to define patients at risk for clinical depression.[13]

2.2.2 Demographics and clinical variables

During admission to the hospital, data on demographic and clinical characteristics were collected by interviews and medical records. Demographics under investigation are age, gender, marital status (living alone versus not living alone), educational level (no education/primary school, secondary school, higher education/university) and physical health. Physical health was assessed by the RAND-36 physical health domain, which reflect a sum score of 10 items on physical health. Higher scores reflect better physical health.
Clinical variables studied were Left Ventricular Ejection Fraction (LVEF), NYHA functional class (II-III versus IV; at admission), presence of anaemia, duration of HF, number of comorbidities (0, 1, ≥ 2 out of: COPD, diabetes, rheumatoid arthritis, stroke, renal disease and hypertension; from medical

chart), presence of COPD and number of HF symptoms (0-2, 3-4, 5-6: assessed by patient interview by asking their experience, during the last month, with dyspnoea, fatigue, loss of appetite, oedema, sleep disturbance and cough). COPD was entered separately as comorbidity because earlier research showed an association with depressive symptoms.[14]

2.3 Statistical analyses

Descriptive statistics were used to characterise the total sample and to describe demographic and clinical characteristics of men and women with and without depressive symptoms. Univariate and multivariable logistic regression analyses were used in men and women separately. Firstly univariate analyses were performed to explore which demographic and clinical variables were related to depressive symptoms in men or women. In addition, four separate multivariable logistic regression analyses were performed to explore an independent contribution of demographic and clinical factors separately for men and women. Different models were performed because of the possible overlap of variables such as physical health with NYHA functional class and number of HF symptoms.

Although living alone was not significantly different between patients with and without depressive symptoms, it was forced in the multivariable logistic regression analyses for demographic characteristics in men and women, because of its known association with depressive symptoms.

In women, the multivariable logistic regression analyses were adjusted for age, because of the age difference between women with and without depressive symptoms.

A p value of < 0.05 was considered statistical significant. SPSS for windows 12.0 was used for all statistical analyses.

3. Results

3.1 Demographic and clinical variables

For the COACH study, 2,957 patients with symptomatic HF were screened. A total of 1,049 patients met the criteria of the study, agreed to participate in the study and gave informed consent. In total 921 patients had complete data for all relevant variables (CES-D, marital status, physical health, NYHA functional class, HF symptoms and comorbidities). There were no significant differences in age, gender, NYHA functional class or LVEF between the 921 patients included in the analyses and the 128 patients that were not included. Patients were on average 71 years of age, 63% were men and 39% lived alone. The average LVEF was 33% and in total 40% had ischemic HF (Table 1).

Table 1. Demographic and clinical characteristics of the total HF population.

	Total group n= 921
Demographics	
Age (years)	71 ± 11
Gender (female)	37%
Living alone	39%
Education level	
No education / primary school	34%
Diploma secondary school	56%
Higher education / University	11%
Physical health (theoretical range 0-100)	35 ± 26
Clinical characteristics	
LVEF[a] (%)	33 ± 14
NYHA (at admission)	
II-III	55%
IV	45%
Laboratory	
Serum creatinine (micromol/L)	125 ± 59
Serum sodium (mmol/L)	138 ± 5
Anaemia[b]	29%
Ischemic heart failure	40%
Atrial Fibrillation	30%
Duration of Heart Failure (years)	2.6 ± 4.5
Medication at admission	
Diuretics	63%
ACE-inhibitors/ARB[c]	57%
Beta-blockers	42%
Digoxin	18%
Spironolactone	16%
HF symptoms	
0-2	4%
3-4	41%
5-6	48%
Comorbidities	
No comorbidities	40%
One comorbidity	37%
Two or more comorbidities	23%
COPD[d]	26%
Diabetes Mellitus type II	20%
Renal dysfunction	7%
Stroke	10%

[a]LVEF= left ventricular ejection fraction; [b]anaemia is defined as in women: haemoglobin <7.5 mmol/ltr; in men haemoglobin < 8.1 mmol/ltr; [c]ARB=angiotensin receptor blocker; [d]COPD=chronic obstructive pulmonary disease.

3.2 Depressive symptoms

In total 47% of the women and 36% of the men reported depressive symptoms (CES-D ≥ 16) at admission ($p < 0.001$).
For both men and women, patients with depressive symptoms were slightly younger and their physical health was more impaired. In both men and women, symptoms of HF and numbers of comorbidities were more frequently observed when depressive symptoms were present. Women with depressive symptoms more often had lower NYHA functional class and COPD when compared with women without depressive symptoms ($p=0.02$ and $p=0.01$, respectively). Educational level, LVEF and duration of HF were not related to depressive symptoms (Table 2).

3.3 Factors related to depressive symptoms in women

Age, physical health, NYHA functional class (II-III), more HF symptoms, more comorbidities and the presence of COPD were univariate variables related to depressive symptoms. Age and physical health were independently associated to depressive symptoms. The clinical variables independently associated with depressive symptoms were NYHA functional class (II-III vs IV) (OR 0.60, 95% CI 0.37-0.95, $p<0.03$), a higher number of HF symptoms (5-6 vs 0-2) (OR 6.11, 95% CI 2.34-15.97, $p<0.001$), (3-4 vs 0-2) (OR 2.66, 95% CI 1.00-7.08, $p=0.05$) and the presence of COPD(OR 2.33, 95% CI 1.20-4.53, $p<0.012$) (Table 3).

3.4 Factors related to depressive symptoms in men

In men age, physical health and HF symptoms were univariate associated with depressive symptoms. All variables again were entered in two separate multivariable analyses. Lower age (OR 0.84, 95% CI 0.71-0.98, $p = 0.03$, per 10 years) and impaired physical health (OR 0.76, 95% CI 0.71-0.83, $p < 0.001$, per 10 units) were independently associated with depressive symptoms. Within the model of clinical variables a higher number of HF symptoms (5-6 vs 0-2) (OR 7.33, 95% CI 3.49-15.40, $p < 0.001$), (3-4 vs 0-2) (OR 2.15, 95% CI 1.00-4.60, $p = 0.047$) was independently associated with depressive symptoms. Living alone, NYHA functional class, total numbers of comorbidities and the presence of COPD were not independently related to depressive symptoms (Table 4).

Table 2. Differences in demographic and clinical variables by depressive symptoms for men and women.

	Men (n=582)		Women (n=339)	
	depression yes n=208	depression no n=374	depression yes n=158	depression no n=181
Demographics				
Age (years)	69 ± 11	70 ± 11	71 ± 13	73 ± 11
Living alone	30%	25%	56%	61%
Education level				
No education /prim. school	30%	27%	41%	46%
Diploma secondary school	54%	60%	56%	49%
Higher education /university	16%	13%	3%	5%
Physical health (0-100)	28 ± 22	44 ± 28	24 ± 19	34 ± 27
Clinical characteristics				
NYHA (at admission)				
II-III	56%	54%	61%	49%
IV	44%	46%	39%	51%
LVEF(%)[a]	32 ± 13	32 ± 14	36 ± 16	35 ± 15
Duration of Heart Failure (y)	2.6 ± 4.6	2.7 ± 4.8	2.5 ± 4.3	2.5 ± 4.3
HF symptoms				
0-2 HF symptoms	4%	11%	4%	14%
3-4 HF symptoms	29%	50%	31%	46%
5-6 HF symptoms	67%	34%	65%	39%
Comorbidity				
No comorbidities	38%	42%	39%	41%
One comorbidity	37%	37%	34%	38%
Two or more comorbidities	25%	25%	27%	21%
Presence of COPD[b]	33%	28%	27%	16%

[a]LVEF= left ventricular ejection fraction; [b]COPD = chronic obstructive pulmonary disease.

Table 3. Two separate models with univariate and multivariable logistic regression analysis for demographic factors and clinical factors associated with depressive symptoms in women with HF.

	Univariate OR (95% CI)	Multivariate OR (95% CI)	P-value
	Model 1		
Demographic variables[a]			
Age (per 10 years)	0.84 (0.70-1.00)	0.77 (0.63-0.97)	0.018
Living alone	0.79 (0.51-1.22)	0.99 (0.62-1.60)	0.98
Physical health[b]	0.83 (0.75-0.91)	0.81 (0.73-0.89)	<0.001
	Model 2		
Clinical variables[a]			
NYHA II-III vs IV	0.61 (0.40-0.94)	0.60 (0.38-0.96)	0.032
HF symptoms			
0-2	1	1	<0.001
3-4	2.53 (0.97-6.57)	2.66 (1.02-7.08)	0.050
5-6	6.29 (2.46-16.06)	6.11 (2.34-15.97)	<0.001
Comorbidity			
No comorbidities	1	1	0.86
One comorbidity	1.05 (0.64-2.08)	0.86 (0.50-1.50)	0.59
Two or more comorbidities	1.53 (0.89-2.64)	0.95 (0.47-1.90)	0.89
Presence of COPD	1.96 (1.15-3.33)	2.33 (1.20-4.53)	0.012

OR = odds ratio; CI= confidence interval. [a]Increase in depressive symptoms per 10 units of physical health on RAND-36; [b]multivariable analyses for clinical variables are age adjusted.

Table 4. Two separate models with univariate and multivariable logistic regression analysis for demographic factors and clinical factors associated with depressive symptoms in men with HF.

	Univariate OR (95% CI)	Multivariable OR (95% CI)	P-value
	Model 1		
Demographic variables			
Age (per 10 years)	0.94 (0.81-1.10)	0.84 (0.71-0.98)	0.03
Living alone	1.31 (0.90-1.92)	1.22 (0.82-1.81)	0.33
Physical health[a]	0.77 (0.71-0.83)	0.76 (0.71-0.83)	<0.001
	Model 2		
Clinical variables			
NYHA II-III vs IV	1.10 (0.78-1.54)	0.94 (0.65-1.34)	0.73
HF symptoms			
0-2	1	1	<0.001
3-4	2.18 (1.02-4.64)	2.15 (1.00-4.60)	0.047
5-6	7.48 (3.57-15.66)	7.33 (3.49-15.40)	<0.001
Comorbidity			
No comorbidities	1	1	0.82
One comorbidity	0.84 (0.53-1.33)	0.84 (0.51-1.39)	0.49
Two or more comorbidities	1.17 (0.78-1.77)	1.07 (0.66-1.74)	0.79
Presence of COPD	1.31 (0.91-1.89)	1.07 (0.66-1.73)	0.77

OR = odds ratio; CI= confidence interval, [a] Increase in depressive symptoms per 10 units of physical health on RAND-36

4. Discussion

In men with HF, depressive symptoms were associated with younger age, impaired physical health and more HF symptoms whereas in women additional variables such as NYHA functional class and the presence of COPD were associated with depressive symptoms. Although there have been few studies on factors related to depressive symptoms in HF patients, it remained unclear which factors were related to depressive symptoms in hospitalised HF men and which in women. In the present study we explored which demographic and clinical characteristics were associated with depressive symptoms separately in hospitalised women with HF and in hospitalised men with HF.

4.1 Prevalence of depressive symptoms

Depressive symptoms are common in hospitalised and outpatient HF patients.[2,6,14-17] Our finding that more women than men with HF reported depressive symptoms is consistent with findings in healthy samples[12,13] and in HF patients[6]. The difference in depressive symptoms between the two genders could be a reflection of the nature in depressive symptoms. Some previous studies suggest that men report lesser somatic symptoms as well as report lesser impairment of their depression compared to women.[18] This might implicate that men to a lesser extent pass the threshold of having depressive symptoms on the CES-D. Furthermore it is reported that women are more exposed to risk factors for depression than men for instance by life events (losing their partner) and by their social role in every day life.[19] Although this was reported in a study on quality of life, this could be of influence in developing depressive symptoms. Finally, women are described to cope inadequately physically and psychosocially with diseases and have more psychosomatic symptoms.[20]

4.2 Demographics and psychosocial factors associated with depressive symptoms

In both women and men with HF, depressive symptoms are associated with age and physical health. From other studies in HF patients it is known that depressive symptoms are more present in younger patients, because they have more difficulties to adapt to HF than the elderly.[7] Reasons for this could be the inability to work, not capable to do activities as travelling, social activities or other activities they have planned to do after retirement, due to HF. Surprisingly marital status and education level were not related to depressive symptoms in our study. Van Jaarsveld et al.[21] also concluded that marital status and educational level were non significant covariates for psychological

functioning for either male and female patients. Reverse results have been published by Murberg.[22] He concluded that close family members such as spouses and children had significant impact on depression in 119 clinical stable HF patients. The fact that marital status was not related to depressive symptoms in our study could be due to the way marital status was measured, which might not be sensitive enough to pass the threshold to have depressive symptoms.

4.3 Clinical factors associated with depressive symptoms

As expected, in both men and women a higher number of HF symptoms were associated with depressive symptoms. This might be due to the possible overlap of symptoms of HF and somatic symptoms of depression. However, the CES-D is a well-known and often used questionnaire measuring depressive symptoms in patients with HF. Furthermore in a previous study we reported that depressive symptoms were common even when somatic symptoms from the CES-D were deleted from the analyses.[16] The causal relationship between depressive symptoms, functional impairment and being more symptomatic is still unclear. Some studies reported that symptomatic HF patients have a higher risk in developing depressive symptoms[23], while other studies suggest that depressive symptoms in HF patient exaggerate HF symptoms by physiological mechanisms such as inflammation and heart rate variability.[24] The high prevalence of depressive symptoms is also seen in older patients with other illnesses, but it is documented that HF patients suffer more.[25] In women, compared to men NYHA functional class (II/III) and COPD, besides symptoms of HF, were other clinical factors associated with depressive symptoms. The presence of COPD together with HF due to the symptom similarity (dyspnoea), may have quite an impact on functional capabilities of women, which probably could explain why these factors were associated with depressive symptoms in women. Lower NYHA functional class was also associated with depressive symptoms in women with HF. It is possible that traditional gender roles place conflicting demands on women in NYHA functional class II and III, because sometimes they are able to perform household activities and sometimes not.[26] These women are often confronted with their limitations due to HF. Role expectations by themselves and by their social network can not always be fulfilled, which could be an explanation of the association with depressive symptoms. Women in NYHA functional class IV are to ill to fulfil their role expectations and possible accept more easily their limitations due to HF.

Interesting in our study was that in men, only the number of HF symptoms and no clinical factors like LVEF, presence of anaemia or duration of HF, were related to depressive symptoms. Others too, found that disease severity

accounted only for a small extend to depressive symptoms. Depressive symptoms correlate with indices of functional severity of heart disease such as NYHA functional class, but not with physiological markers of heart disease severity such as LVEF.[27] Social factors and health status are more predictive for developing depressive symptoms in HF patients.[28]

One of the limitations in our study is its cross sectional design, so no causal inferences can be drawn. Data on the course of depressive symptoms and its related factors have to show if these demographic and clinical related factors are predicting depressive symptoms in elderly HF men and women. Furthermore, depressive symptoms were assessed in hospitalized patients with advanced HF. Although it is previously reported that depressive symptoms are common in hospitalised patients and in patients from outpatient clinics, one must be careful to generalise the findings of this study to other than hospitalised HF patients.

4.4 Conclusions and implications

From our research it can be concluded that depressive symptoms are prominent in hospitalised HF patients and more common in women. Depressive symptoms in HF men are related to age, physical health and HF symptoms, but in women a slightly different pattern was observed.
It is important for health care providers to be aware that HF patients are at risk for developing depressive symptoms, especially women. It is recommended that evaluation of depressive symptoms among HF patients becomes a routine procedure and HF patients need to be treated according to the established guidelines.
Longitudinal data are necessary to further unravel the complex interplay between the course of depressive symptoms and its related factors. Furthermore, research about the treatment and adherence to medical treatment (medication compliance) of HF patients with depressive symptoms is needed, because thus far no promising results in the treatment of depressive symptoms in HF have been published.

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CHAPTER 6

Relationship between severity of depressive symptoms and outcomes in patients with heart failure

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Abstract

Background

Depression is common in heart failure (HF) patients, but little is known about the consequences of depressive symptoms for patient outcomes. We studied the independent prognostic value of depressive symptoms on readmission and mortality in patients with heart failure in a large sample of hospitalised HF patients.

Methods

A sample of 958 HF patients who where admitted to the hospital with symptoms of heart failure (NYHA II-IV) were prospectively followed for the Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure patients (COACH study). Depressive symptoms were measured at baseline by means of the Center for Epidemiologic Studies Depression Scale (CES-D). Secondary analyses with data from the COACH study were performed. Cox proportional hazards regression analyses were used to examine the association of depressive symptom severity on the combined endpoint of time to rehospitalisation for heart failure or death during 18 months follow up.

Results

Mean age was 71 years, 37% of patients were female: 49% had moderate to severe heart failure at discharge. At baseline 377 (39%) patients reported depressive symptoms (CES-D≥ 16), of whom 200 (21%) patients had severe depressive symptoms (CES-D ≥ 24). During the study 386 patients (40%) were readmitted for heart failure or died from any cause; 39% in both groups without and with moderate depressive symptoms and 45% in patients with severe depressive symptoms. Severe depressive symptoms was a risk factor for the combined endpoint independent of age and sex (HR 1.32, 95% CI 1.03-1.69; p=0.03). For patients with severe depressive symptoms, days in hospital for heart failure were doubled (8 versus 4 days) compared to patients without depressive symptoms (p<0.001).

Conclusion

If patients reported severe depressive symptoms the chance of being readmitted or dying was 32% higher compared to patients without depressive symptoms and duration of heart failure readmission was significantly higher.

1. Introduction

Heart failure (HF) is a clinical syndrome that is increasing in incidence worldwide and results in high morbidity, mortality and a marked decrease in quality of life and functional status.[1,2] This high rate of mortality and readmission is confirmed in the Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure patients (COACH study) in which 40% of patients were readmitted or died within 18 months of follow up.[3,4]
However, it is yet not studied in the COACH, which HF patients are vulnerable to adverse events.
It is described that depressive symptoms are common in HF patients[5] and in previous studies it is suggested that depressive symptoms could be related to adverse events in terms of survival and hospitalisation. In some studies with HF patients, an association between depressive symptoms and readmission and mortality, independent of age, sex and disease severity, is described[1,6-8] while others did not confirm this.[8-10] Additionally, there not only seemed to be an association between adverse events and the presence of depressive symptoms but also the severity of the depressive symptoms should be taken into account.[7,8,10]
In one of our previous studies, we found an association between depressive symptoms and the number of comorbidities. In both a heart failure population and a population of community dwelling elderly, the prevalence of depressive symptoms was higher in patients and elderly with chronic conditions, compared with patients and elderly without chronic conditions and higher in HF patients with comorbidities compared with HF patients without comorbidities.[11] Other factors described to be associated with depressive symptoms and outcomes in heart failure patients are age, sex and disease severity in terms of NYHA classification.[6-8,12]
At this moment, an increased risk rate of depressive symptoms in HF patients has only been studied with relatively small samples, which were marginally powered to detect clinical significant effects over shorter time intervals.[13] Furthermore, the populations studied were not representative for today's clinical practice, while this is of interest because in earlier research it is found that survival rates in a community sample of HF patients were worse than the known survival rates in clinical trials.[14] Since depressive symptoms may be preventable and treatable, to know if depressive symptoms are associated with adverse events in patients with HF may have important clinical implications. Therefore, the following objectives were formulated.

1. To describe the relation between depressive symptom severity and the combined endpoint of HF readmission and all cause mortality in patients with HF over 18 months follow up;
2. To describe the relation between depressive symptom severity and the individual components: HF readmission and death from any cause.

2. Methods

2.1 Study design

Data were collected in the COACH (Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure) study. This was a multicenter, randomised trial designed to compare basic support and intensive support to standard treatment in patients with heart failure. The methodology of the trial was described in detail before.[4] Summarized, patients were recruited during a period of 28 months from October 2002 to February 2005. All patients had been admitted to the hospital with symptoms of heart failure, New York Heart Association (NYHA) functional classification II-IV. Patients were > 18 years of age and had evidence of structural underlying heart disease. Major exclusion criteria were: concurrent inclusion in another study or in a heart failure clinic, inability to complete the questionnaires; any invasive procedure or cardiac surgery intervention within the last 6 months or planned during the following 3 months; ongoing evaluation for heart transplantation; and inability or unwillingness to give informed consent.
During hospitalization patients were randomized to (1) basic support, (2) intensive support or (3) a control treatment. All patients were treated from hospital discharge until 18 months after hospital discharge.

2.2 Assessment of depressive symptoms

The Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depressive symptoms experienced during the previous week. It is a 20-item self-report questionnaire designed to measure depressive symptoms in the general population and in the medical ill.[15,16] A total sum score is used (0-60), with higher scores indicating more depressive symptoms. For purposes of this study, the CES-D is divided into three categories. A cut-off point of 16, which is generally used to define patients at risk for clinical depression was used to distinguish between heart failure patients with depressive symptoms (CES-D ≥ 16) and patients without depressive symptoms (CES-D < 16).[15] A third category was created based on the median score of the patients with a score of CES-D ≥ 16, which was 24. This resulted in the following three categories: no depressive symptoms (CES-D score range 0-15); a moderate level of depressive symptoms (CES-D score range 16-23) and a severe level of depressive symptoms (CES-D score ≥ 24). In creating this third category a graded effect of depressive symptoms can be examined. Furthermore, it is shown that subjects with a confirmed diagnosis of clinical depression had a higher mean score on the CES-D questionnaire compared to patients with minor depression.[17] Other investigators already advise a higher cut-off score which seems to be more useful for screening medical ill patients for depression than the standard cut-off score.[18-20]

2.3 Readmission and mortality

The primary and secondary endpoints used in this sub study were the same endpoints that were used in the COACH study.[3] The primary endpoint was a composite of heart failure rehospitalisation or death from one cause or other. A hospitalisation for heart failure was defined as an unplanned overnight stay in a hospital due to progression of heart failure or directly related to heart failure. The secondary endpoints were the two individual components of the combined endpoint: death from one cause or other and hospitalisation for heart failure. Data on readmission and mortality were collected from the patient's medical record and by interviews with the patient during follow up. The reason for readmission, the cause of death and the date of the event were adjudicated by a central end-points committee.

2.4 Demographic and clinical data

Demographic and clinical variables known from the literature that would be potentially important as covariates in the relation between depressive symptom severity and adverse events in HF patients were identified. Demographic covariates included age, sex, living situation and educational level and were assessed by patient interview during index hospitalization. Clinical covariates included medical history, duration of HF, the number and presence of comorbidities (asthma/COPD, diabetes, rheumatoid arthritis, renal disease, stroke and hypertension), NYHA functional class, number of HF symptoms (total sum score of the following symptoms: oedema, sleep disturbance, fatigue, dyspnoea, coughing or loss of appetite) which were collected from medical record and by patient interview.

2.5 Statistical analyses

Characteristics of patients according to the severity of depressive symptoms were compared using one way ANOVA for continuous variables and chi square tests for categorical variables. Kaplan-Meier curves were constructed for the different in time to event (hospitalisation for heart failure or death from any cause) evaluations and differences between the groups were tested by the log rank test. Cox proportional hazards regression models were used to examine the association of depressive symptoms with time to mortality or HF readmission during the 18 month follow up study. To evaluate a possible effect-modifying role of potential risk factors with regard to HF readmission or mortality, Cox regression analyses were performed with the risk factors of interest, that were significant different at a level of $p<0.10$ between the groups at index hospitalisation, their product term, age and sex in the model. A significant relative risk for the product term was considered effect modification by that risk factor. To assess whether the associations of depressive symptom severity with the combined or individual endpoints were

independent, Cox regression analyses were adjusted for all risk factors that were statistically significant in initial analyses. Outcomes were considered statistically significant when $p<0.05$.

3. Results

3.1 Study sample

For the COACH study, 2,957 patients with HF were screened for study eligibility. In total 1,049 patients met the inclusion criteria, and of these, 1,023 patients were discharged alive.[3] Analyses were performed on patients with a complete CES-D score, resulting in a final sample of 958 patients. There were no significant differences between patients who completed the questionnaires and patients who did not with regard to age, gender, readmission rate and mortality.

Patients had a mean age of 71 years (± 11), 37% were female, 39% were living alone and most patients had a low education level. The mean LVEF was 34% (± 14) and at discharge most patients had a NYHA functional class II or III (Table 1).

At baseline, 377 patients had depressive symptoms (CES-D ≥ 16), of whom 177 (18%) patients had a moderate level of depressive symptoms (CES-D 16-23) and 21% (200 patients) had a severe level of depressive symptoms (CES-D ≥ 24). Patients with moderate and severe depressive symptoms were more often female, had a higher NYHA functional class at discharge, more HF symptoms, more comorbidities, more often asthma/COPD and hypertension compared to patients without depressive symptoms (Table 1). Although hypertension and the number of HF symptoms were significant different between the three groups, these potential risk factors were not significant associated with the combined endpoint. The number of comorbidities, NYHA functional class and asthma/COPD were significant associated with the combined endpoint, but their product term was not, implicating that these risk factors were confounding the relation between depressive symptoms and readmission or death and therefore have to be adjusted to the model.

3.2 Association between severity of depressive symptoms and the time to HF readmission or death from any cause

During the 18 month study period, 386 out of 958 patients (40%) reached the primary endpoint (HF readmission or death): 227 (39%) patients without depressive symptoms; 69 (39%) patients with moderate depressive symptoms and 90 (45%) patients with severe depressive symptoms. Analyses of the time to first event (HF readmission or death) (Figure 1),

Table 1. Baseline characteristics according to severity of depressive symptoms

Patient characteristics	Total group n=958	No depressive symptoms n = 581	Moderate depressive symptoms n = 177	Severe depressive symptoms n = 200	P value
Demographic variables					
Age in years (m ± sd)	71 ± 11	71 ± 11	71 ± 12	69 ± 12	0.12
Sex (f)	37%	33%	40%	45%	0.01
Living alone	39%	37%	40%	42%	0.45
Education level					
At least six years of primary school	55%	54%	55%	56%	0.69
Diploma secondary school	29%	30%	25%	32%	
Higher education or university	16%	16%	20%	12%	
Clinical variables					
LVEF (%)(m ± sd)	33 ± 14	32 ± 14	34 ± 16	34 ± 16	0.22
NYHA (at discharge)					
II	51%	56%	51%	38%	<0.001
III	46%	42%	47%	56%	
IV	3%	2%	2%	6%	
Cause of HF					
Ischemic aetiology (%)	43%	45%	40%	41%	0.42
Presence of comorbidities					
Asthma/COPD	27%	26%	36%	37%	0.01
Diabetes	28%	28%	26%	30%	0.72
Stroke	10%	9%	12%	13%	0.17
Renal disease	8%	7%	7%	11%	0.25
Rheumatoid arthritis	7%	6%	9%	6%	0.38
Hypertension	43%	40%	48%	50%	0.02
Number of comorbidities					
no comorbidities	28%	30%	23%	24%	0.01
1 comorbidity	34%	36%	33%	31%	
≥2 comorbidities	38%	34%	44%	45%	
HF symptoms (m ± sd)	4.2 ± 1.4	3.9 ± 1.4	4.6 ± 1.2	5.0 ± 1.0	<0.001
0-2 symptoms	11%	16%	5%	3%	<0.001
3-4 symptoms	42%	49%	40%	23%	
5-6 symptoms	47%	35%	55%	74%	
Medication at discharge					
ACE/ARB*	87%	87%	86%	87%	0.96
Diuretics	96%	96%	98%	94%	0.20
B-blockers	66%	66%	67%	67%	0.97
Anti depressant medication	7%	5%	11%	12%	<0.001

Table 1. Continued

Patient characteristics	Total group n=958	No depressive symptoms n = 581	Moderate depressive symptoms n = 177	Severe depressive symptoms n = 200	P value
Duration of heart failure (days) (median, inter quartile range)	109 (21-1399)	102 (21-1417)	111 (22-1192)	129 (21-1501)	0.94
Support					
Care as usual	33%	35%	29%	32%	
Basic support	33%	34%	32%	35%	0.21
Intensive support	34%	32%	39%	34%	
Depressive symptoms					
Mean CES-D total score (m ± sd)	15 ± 10	8 ± 4	19 ± 2	32 ± 7	<0.001

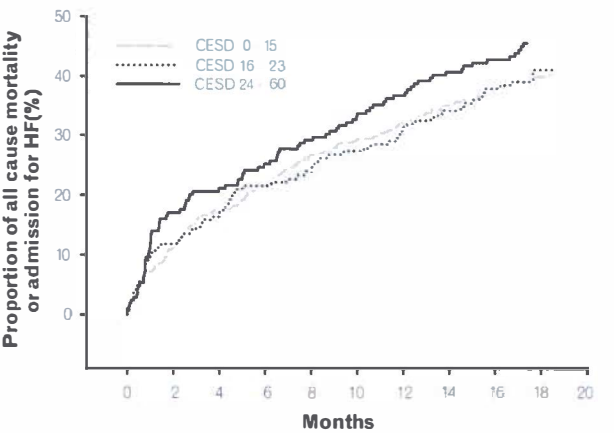

Figure 1. Kaplan Meier curves for time to death or HF readmission in patients with HF without depressive symptoms, with moderate depressive symptoms and severe depressive symptoms.

adjusted for age and sex, showed hazard ratios (HR) of 1.02 (95% confidence interval [CI] 0.78-1.34, p= 0.87) for patients with moderate depressive symptoms and HR 1.32 (95% CI 1.03-1.69, p=0.03) for patients with severe depressive symptoms versus patients without depressive symptoms. After further adjustment for the number of comorbidities, which had the strongest association with the primary endpoint, the HR was decreased to 1.22 (95% CI 0.95-1.56, p=0.12) in patients with severe depressive symptoms. Additional adjustments for the other confounding factors (e.g. NYHA functional class and asthma/COPD) further decreased the HR of patients with severe depressive symptoms (Table 2).

3.3 Association between depressive symptom severity and readmission

3.3.1 Heart failure readmission

More patients with severe depressive symptoms (32%) were readmitted for HF compared to patients with moderate or without depressive symptoms ($chi^2 = 4.49$, p=0.11). These readmissions for HF were significantly longer for patients with severe depressive symptoms compared to patients without depressive symptoms (8 days versus 4 days, p<0.001) or patients with moderate depressive symptoms (8 days versus 5 days, p=0.01).
Cox proportional hazard regression analyses on the relationship between severity of depressive symptoms and time to readmission for HF (Figure 2), showed that patients with severe depressive symptoms had 41% higher risk to be readmitted for HF in 18 months compared to the patients without depressive symptoms (p < 0.04), adjusted for age and sex. This was not different for patients with a moderate level of depressive symptoms when compared with patients without depressive symptoms.
The fully adjusted model (adjusted for age, sex, number of comorbidities, NYHA functional class and asthma/COPD), showed that patients with severe depressive symptoms had a 17% higher risk on HF readmission over 18 months, compared to those without depressive symptoms, however this was not statistically significant (Table 2).

3.3.2 All cause and non cardiovascular readmission

In addition, the analyses were repeated for all cause readmission and gave similar results. For all cause, a total of 64% of the patients with severe depressive symptoms were readmitted during 18 months of follow up, compared to 53% of patients without and 55% of the patients with moderate depressive symptoms ($chi^2= 6.87$, p=0.03).
Patients with severe depressive symptoms also had a significant longer duration of all cause readmission compared to patients without and with

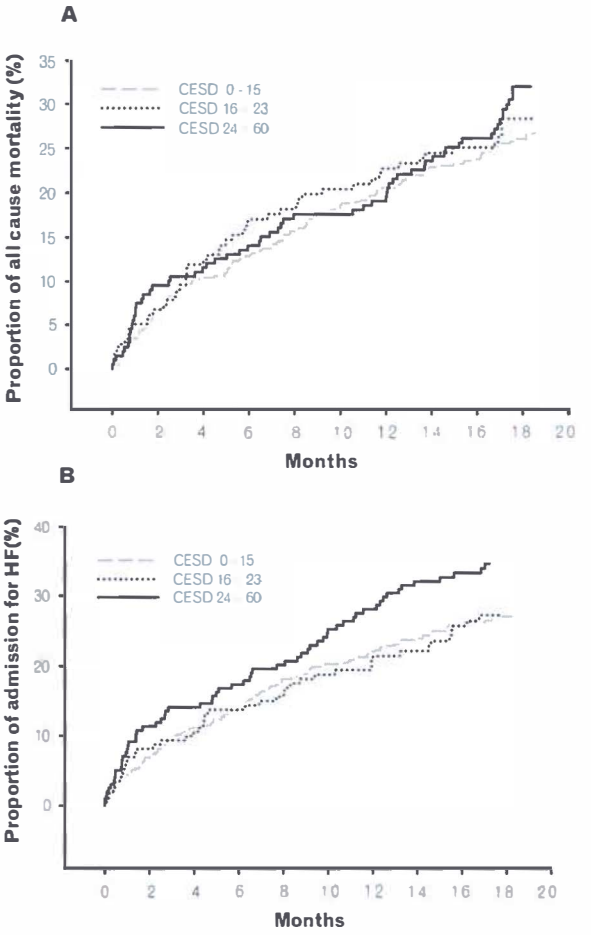

Figure 2.
a. Kaplan Meier curves for mortality among patients with HF without depressive symptoms, moderate depressive symptoms and severe depressive symptoms
b. Kaplan Meier curves for HF readmission among patients with HF without depressive symptoms, moderate depressive symptoms and severe depressive symptoms

moderate depressive symptoms (20 days versus 11 days, p< 0.001) and (20 days versus 14 days, p=0.04), respectively. After adjusting for age and sex, patients with severe depressive symptoms had a 35% higher risk (p<0.005) for a readmission over 18 months, compared to patients without depressive symptoms. After further adjusting for the number of comorbidities,

Table 2. Univariate and multivariate Hazard Ratios of time to all cause mortality and readmission due to HF.

	Moderate depressive symptoms		Severe depressive symptoms	
	HR (95% CI)*	P-value	HR (95% CI)*	P-value
	Model 1		**Model 1**	
HF readmission or death	1.02 (0.78-1.34)	0.87	1.32 (1.03-1.69)	0.03
HF readmission	1.01 (0.72-1.42)	0.98	1.41 (1.04-1.91)	0.03
Mortality	1.09 (0.79-1.52)	0.60	1.34 (0.99-1.80)	0.06
	Model 2		**Model 2**	
HF readmission or death	0.96 (0.73-1.26)	0.77	1.22 (0.95-1.56)	0.12
HF readmission	0.94 (0.67-1.33)	0.73	1.29 (0.95-1.75)	0.10
Mortality	1.03 (0.75-1.44)	0.82	1.24 (0.91-1.68)	0.17
	Model 3		**Model 3**	
HF readmission or death	1.01 (0.77-1.33)	0.95	1.14 (0.88-1.46)	0.33
HF readmission	0.97 (0.69-1.38)	0.87	1.17 (0.86-1.59)	0.33
Mortality	1.09 (0.78-1.52)	0.61	1.14 (0.84-1.56)	0.39

*Hazard Ratio (HR) for comparison with the patients without depressive symptoms. CI indicates confidence interval.
Model 1: adjusted for age and sex.
Model 2: model 1 + adjusted for numbers of comorbidities.
Model 3: model 2 + adjusted for NYHA functional class and asthma/COPD.

NYHA functional class and asthma/COPD, patients with severe depressive symptoms showed a 16% higher risk on all cause readmission over 18 months compared to patients without depressive symptoms (ns).
Repeating the analyses for non cardiovascular readmissions showed slightly different results. In contrast to HF and all cause readmission, the number of patients readmitted for a non cardiovascular reason was not different between the three groups: (non depressed 24%; moderate depressed 31% and severe depressed 27%, p=0.12). When adjusted for age and sex, patients with moderate and severe depressive symptoms had higher hazard ratio: HR 1.41 (95%CI 1.03-1.92) and HR 1.32 (95% CI 0.97-1.79), but again, when adjusting for possible confounders (e.g. number of comorbidities, NYHA functional class, asthma/COPD), the HR decreased and was no longer statistically significant.

3.4 Association between severity of depressive symptoms and mortality

A total of 257 patients died (27%) in 18 months follow up, with the highest mortality rate in patients with severe depressive symptoms (31%) and lowest mortality rate in patients without depressive symptoms (26%) ($chi^2 = 1.79$, p=0.40). Figure 2 showed the time to mortality over 18 months according to the level of depressive symptoms. Cox proportional hazard regression analyses showed that although patients with a severe level of depressive symptoms had a 34% higher risk to die in 18 months (HR 1.34; 95% CI 0.99-1.80, p=0.06) compared to patients without depressive symptoms, the difference was not statistically significant and the HR decreased when adjusted for other confounding factors (Table 2).

4. Discussion

In this large sample of heart failure patients, no independent association between severity of depressive symptoms and the combined endpoint of heart failure rehospitalisation and all cause mortality was found. However, we did find a significant increase in readmissions in patients with severe depressive symptoms compared to patients without or with moderate depressive symptoms. For patients with depressive symptoms, independent of severity, the duration of a readmission was on average 6 days longer compared to patients without depressive symptoms. The duration of a HF readmission even doubled in patients with severe depressive symptoms compared to patients without depressive symptoms. With reference to mortality no significant association with severity of depressive symptoms was found.

Our results do not confirm earlier findings that describe that depressive symptoms are independently related to readmission and mortality.[6,21,24] This difference might be explained by differences in patient samples. Our patients might be more representative for the real life HF patient population which is older and include more female patients and patients with comorbidities. It is described that a more representative heart failure population have more depressive symptoms and worse survival rates, compared to the population of clinical trials.[14] Moreover, Jiang and colleagues[7] showed in a population of 357 hospitalised heart failure patients (26% female), with LVEF < 35%, an independent association between depression and poor prognosis, while Koenig[10] found no independent association in 107 older heart failure patients in which 52% were female. Furthermore, most studies in which an

independent association between depressive symptoms and adverse events were found, had longer follow up time of up to 6 years.[22,23,25]
The trend we found regarding an increased readmission rate in increasingly severe depressive symptoms was similar to the findings of Jiang et al.[7], and Vaccarino et al.[8] But in contrast with their findings, our association was not strong and did not concern mortality. A possible explanation for this difference could be the different definitions used for the most severe depressed patients. Major depression was assessed with a diagnostic interview and severe depressed patients by a score of more than 10 symptoms on the Geriatric Depression Scale, respectively. We defined severe depressive symptoms by a CES-D score of more than 24.
Furthermore, patients with severe depressive symptoms had more comorbidities and had a higher NYHA classification what explained most of the association between depressive symptoms and adverse events.
The patients with severe depressive symptoms also had a longer duration of readmission either due to heart failure or for other reasons. It might be possible that this vulnerable group of patients is less well treatable or more vulnerable for deterioration. It is shown that patients with depressive symptoms have lower adherence rates with medication or life style recommendations such as inactivity and smoking[26,27]. Shared physiologic mechanisms, such as activation of sympatric nervous system, elevated levels of cytokines and lower heart rate variability [28,30], have been identified, which also could explain the increased readmission rates in patients with severe depressive symptoms and longer duration of readmissions.

Although we did not find an independent association between depressive symptoms severity and readmission and mortality, our results were not contradictive to earlier findings.
The data used in this sub study were derived from the COACH study, which was not designed to determine the association between depressive symptoms severity and the combined endpoint of readmission and death, which might explain the non significant results.
In earlier studies, an association between depression and mortality was found when depression was defined as 'major depression', implicating that a diagnosis of depression was established. In our study we used a self reported questionnaire (CES-D) and the measure of moderate and severe depressive symptoms was based on not officially determined cut off scores. The cut of scores of 16 and 24 on the CES-D are not necessarily equivalent to a clinical diagnosis of depression. However previous studies[15-18] have indicated that these cut off scores were a reasonable approximation of a clinical diagnosis of depression.

To conclude, the present study is one of the largest studies on the relation between depressive symptom severity and adverse events in hospitalised HF patients. Patients with moderate and severe depressive symptoms have higher readmission rates and stayed longer in the hospital compared to patients without depressive symptoms. The risk for readmission over 18 months independent of age and sex, is higher in patients with severe depressive symptoms compared to patients without depressive symptoms. Recognition and treatment of depressive symptoms in this population is important. Whether treatment of depressive symptoms can reduce readmissions and mortality must be explored in further research.

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CHAPTER 7

Effect of moderate or intensive disease management program on outcome in patients with heart failure. The Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure (COACH)

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Abstract

Background

Heart failure (HF) disease management programs are widely implemented, but data regarding effect on outcome have been inconsistent so far.

Methods

The Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure (COACH) study was a multicenter randomized controlled trial, in which 1023 patients were enrolled after hospitalization for HF. Patients were assigned to one of three groups: a control group (follow-up by cardiologist), and two intervention groups with additional basic, or intensive support by a HF nurse. Patients were studied for 18 months. Primary endpoints were time to death or rehospitalization for HF, and the number of days lost to death or hospitalization.

Results

Mean age was 71 years, and 38% were female; 50% of patients had mild, and 50% had moderate to severe HF. During the study 411 patients (40%) were readmitted for HF or died from any cause: 42% in the control group, and 41% and 38% in the basic and intensive support groups, respectively (hazard ratios [HR] 0.96 and 0.93, resp., both p=NS). The number of days lost to death or hospitalization was 39,960 in the control group, and was 15% lower in the intervention groups combined (p=NS). All-cause mortality occurred in 29% of the control group, and there was a trend toward lower mortality in the intervention groups combined (HR 0.85; 95%, p=0.18). On the other hand, there were slightly more hospitalizations (p=NS) in the two intervention groups.

Conclusions

Neither moderate nor intensive disease management by a HF nurse reduced the combined endpoint of HF hospitalizations and mortality compared to standard follow-up. There was a nonsignificant, potentially relevant reduction in mortality, accompanied by a slight increase in the number of short hospitalizations in both intervention groups.

1. Introduction

Heart failure is one of the largest medical problems of our time, and despite significant advances in its treatment, morbidity and mortality remain high.[1,2] In recent years, various forms of disease management programmes have been examined and in some favorable effects on morbidity (hospitalizations) and even mortality were reported.[3-6] As a result, in many hospitals special disease management programmes are implemented, such as a heart failure clinic in which specialized nurses provide additional care.[7]

Although most studies have reported favorable effects of a variety of these disease management programmes, not all have shown positive findings.[8-10] Recent meta-analyses also reported effectiveness of heart failure disease management programmes in reducing mortality and hospital readmissions and potential improvements in quality of life and cost savings.[11,12] Although some factors have been identified to be important for a successful program[13], it has remained largely unclear which components of these programmes are mainly responsible for the observed favorable effect and how intensive such a program should be.

The present study was therefore designed to examine the effect of a nurse-led disease management program in a sufficiently large population, with an assumed relatively high event-rate. The Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure (COACH) was designed to determine the effects of two levels of intensity in heart failure disease management programmes on the combined endpoint of heart failure readmission and mortality. Patients who were eligible for COACH had been hospitalized for heart failure, and were then randomized to one of three treatment arms and studied for 18 months.

2. Methods

COACH was a multicenter, randomized, open trial with blinded endpoint evaluation, designed to compare basic support and intensive support in patients with chronic heart failure to a control group receiving "usual" care, as described in detail before.[14] Patients were recruited during a period of 28 months (October 2002 to February 2005) and all patients were followed for a fixed time period of 18 months. The Medical Ethics Committee approved the study protocol and all patients provided written informed consent.

2.1 Patient population

All patients had been admitted to the hospital with symptoms of HF, New York Heart Association (NYHA) functional classification II-IV[14]. The diagnosis was made by a combination of typical signs and symptoms, for which a hospitalization was considered necessary, including the need of intravenous medication. All 17 sites were experienced HF centres, who had participated in multicenter HF trials. Patients were >18 years and had evidence of structural underlying heart disease, as shown by cardiovascular imaging. Both patients with an impaired and those with a preserved left ventricular ejection fraction could participate. Before discharge from the hospital (i.e. before inclusion into the study), patients had to be stable on standard medication for HF. The decision to enroll a patient into the study was made at the participating center. Major exclusion criteria were: concurrent inclusion in another study or HF clinic, inability to complete the questionnaires; invasive procedure or cardiac surgery intervention <6 months, or planned <3 months; ongoing evaluation for heart transplantation; and inability or unwillingness to give informed consent.

2.2 Randomization

During hospitalization patients were randomized to (1) basic support, (2) intensive support or (3) a control treatment. The computer-generated randomization scheme used random permuted blocks of six patients stratified per center to ensure balanced assignment of patients to each of the three groups in each of the participating 17 centers.

2.3 Intervention strategies

There were two types of interventions and a control treatment[14]. Figure 1 depicts the intensity of contacts with the cardiologist and HF nurse during follow-up. All patients received usual routine management by their cardiologist. This included an outpatient visit <2 months after discharge and then every 6 months. Since 17 hospitals were involved, with potential differences in follow-up intensity, a standard follow-up schedule was developed. Patients in the two support groups were visited by a HF nurse during admission for education and support and were scheduled for extra visits to the outpatient clinic.

Patients in the *basic support* group were scheduled for extra visits to the HF nurse at the outpatient clinic. Patients were educated following a protocol and behavioral strategies were used to improve adherence. In addition, patients were instructed to contact the nurse if there was a change in their condition.

Patients in the *intensive support* group received a similar intervention as the basic support group, except that they had contact with the nurse routinely on a monthly basis. In the first month after discharge, weekly telephone contacts

were made and the patient was visited at home by the HF nurse. Furthermore, telephone calls, two home visits and a multidisciplinary advice (by physiotherapist, dietician and social worker) were part of the intensive support intervention. In addition to providing information to patients, HF nurses were trained to increase self-efficacy of patients. Materials used in the intervention included a patient diary, brochures on HF and its management, and samples of sodium restricted seasonings. Patients in both intervention groups were instructed to seek help if symptoms increased of if they gained weight. Patients in the *control* group did not receive any other treatment besides standard management by their cardiologist. All nurses were trained and the quality of the two study interventions was maintained by monthly site visits of the research team to confirm adherence to the protocol.

2.4 Follow-up and data collection

All patients were studied from hospital discharge for 18 months.[14] Data on mortality and number of readmissions were collected from medical record and patient interview. Reason for readmission, cause of death and date of the event was adjudicated by a central end-points committee whose members were blinded to the group assignment.

2.5 Endpoints

The study had two primary endpoints[14]. The first primary endpoint was a composite of HF hospitalization or death from any cause. A hospitalization for HF was defined as an unplanned overnight stay in a hospital due to progression of HF or directly related to HF. Patients had to have typical signs and symptoms, and hospitalizations were classified as "HF" if admission was primarily for its treatment or when HF became a became a major component of the patient's hospital admission, according to a predefined Manual of Operations for COACH, using standard criteria. Evidence of worsening HF was also classified using standard clinical criteria[15]. The other primary endpoint was the number of unfavorable days which was defined as the number of days lost to death or hospitalization during the 18 months follow-up period. Major secondary endpoints were the two individual components of the composite end point — death from any cause and hospitalization for HF — and the number of all cause hospitalizations per patient.
All reported deaths and hospital admissions were referred to and adjudicated by an independent Clinical Event Committee (see appendix), who were blinded to the allocation of the interventions.

2.6 Sample size

We assumed a 40% event-rate for the primary endpoint (readmission for heart failure or mortality) in the control group within the first year.[14] A 25%

decrease of events in the basic support group was considered as both realistic and clinically relevant. With a power of 90%, and an alpha of 0.05, 349 patients were required in each of the three groups.

2.7 Statistical Analysis

All analyses were conducted according to the intention-to-treat principle.[14] There were two primary endpoint comparisons: time to first major event (heart failure hospitalization or death) and the number of days lost to death or hospitalization. Kaplan–Meier curves were constructed for the different time to event evaluations and groups were compared with the use of log-rank tests. To estimate the size of the effect, Hazard Ratio's with 95 percent confidence intervals were calculated with the use of unadjusted Cox regression models. The number of days lost to death or hospitalization during the 18 months follow-up period and the number of hospitalizations per patient were calculated and tested between groups by means of the Mann-Whitney-U tests. All analyses were prespecified; reported P values are two-sided and have not been adjusted for multiple testing. Dependency of multiple hospitalizations within one patient have not been taken into account in testing differences in heart failure hospitalization incidences and heart failure hospitalization durations. A $p < 0.05$ was considered to indicate statistical significance. Statistical analyses were performed by using SPSS (version 12.0, SPSS) and SAS software (version 9.1, SAS Institute).

3. Results

During the study period 2957 patients were hospitalized with symptomatic heart failure and structural underlying heart disease (Figure 1). A total of 1908 patients were excluded. Of these, there were 1117 patients who did not meet the inclusion criteria (already enrolled in heart failure clinic or other trial: n=336, not able to follow the study protocol due to dementia, other psychiatric illness or deafness: n=328, planned or recent invasive procedure or surgery: n=292, or judged as terminal illness or being in palliative phase n=125, or who died prior to randomization: n=36). There were 282 patients who refused to participate, and in 509 patients there were other usually logistic reasons (hospital admission too short to be included, no transportation to the hospital available, etc.). Patients who participated were on average 4 years younger and more often male (63% versus 51%) compared to the non participants. A total of 1049 patients were randomized during heart failure hospitalization of which 1023 were discharged alive and followed for 18 months; this latter group forms the study population that was analyzed.

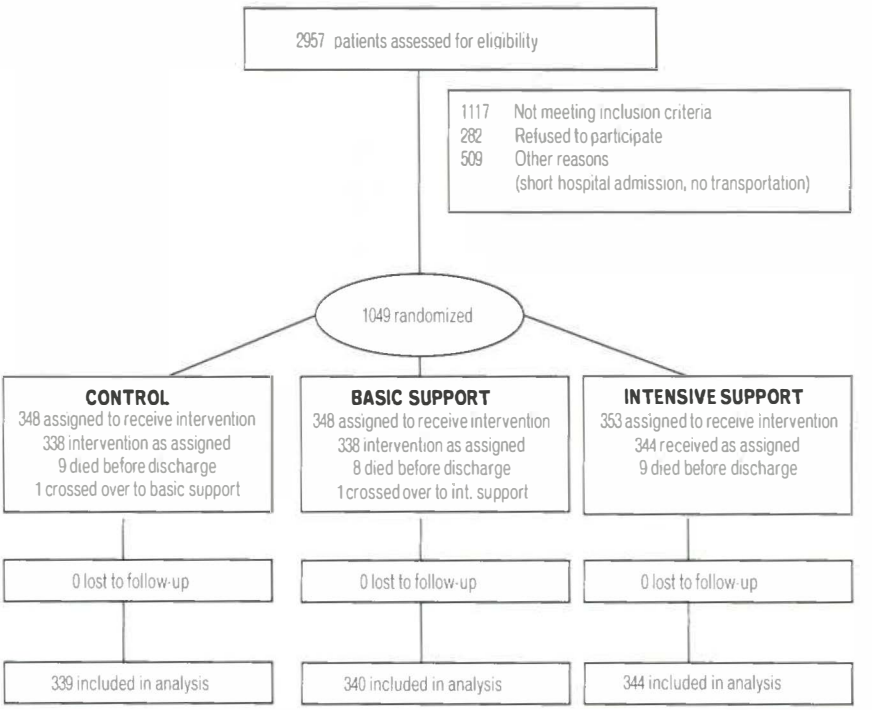

Figure 1. Flow of participants through the trial

7

3.1 Baseline characteristics

The baseline characteristics of the three groups were comparable. The mean age was 71 years (range 23-93), 62% were male and 61% were married (Table 1). While virtually all patients were in NYHA functional class III-IV at the time of admission, at discharge 50% of patients was classified in NYHA class II and 50% in NYHA III/IV. Both patients with decreased left ventricular ejection fraction (LVEF) and preserved LVEF were included, and the mean LVEF was 34%.

3.2 Intervention

There was a substantial difference in contacts with health care providers in all three groups compared to the planned protocol (Figure 2). Control patients were only supposed to visit the cardiologist four times, and to have no contact with a heart failure nurse. According to this schedule, a total of 858 visits to

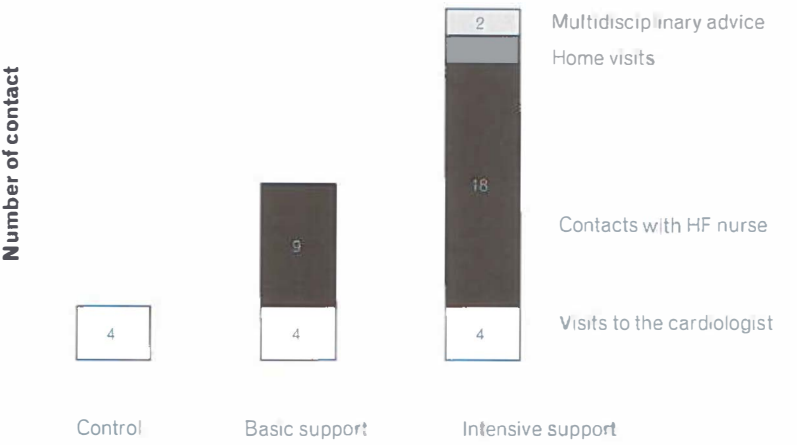

Figure 2. Protocol for contacts with care providers in the three groups.

the cardiologist should have taken place, but an actual total of 1,144 visits to the cardiologist were made (+286 visits, or +33%). In the basic support group, a total of 2,347 visits and phone calls were originally planned, but 3,302 (+40%) were actually made. In the intensive support group a total of 5,868 visits and phone calls were planned and 6469 (+10%) were made. The time investment of nurses in the basic intervention was estimated at 20 hours per patient and for the intensive intervention at 40 hours per patient. Two patients crossed over (one from the basic support to intensive support and one patient from control group to basic support). These cases were analyzed as randomized (intention to treat).

3.3 Outcomes

3.3.1 Primary endpoints

During the 18 months study period, 411 of 1,023 patients (40%) reached the primary endpoint (heart failure hospitalization or death): 141 patients (42%) in the control group, 138 patients (41%) in the basic support group and 132 patients (38%) in the intensive support group. Analysis of the time to first event showed hazard ratios (HR) of 0.96 (95% confidence interval [CI] 0.76-1.21, p=0.73) and 0.93 (95% CI 0.73 -1.17, p=0.53) for the composite of heart failure hospitalizations or death in the basic and intensive support groups respectively, vs. the control group (Figure 3a).

The total number of days lost to death or all cause hospitalization during the 18 month study period (the other primary endpoint) was 39,960 days in the control

Table 1. Baseline characteristics of patients at discharge according to the assigned treatment (n=1023).

	All (n=1023)	Control (n=339)	Basic Support (n=340)	Intensive Support (n=344)
Mean age – yr	71 ± 11	72 ± 11	71 ± 11	70 ± 12
Female sex - no. (%)	384 (38%)	136 (40%)	115 (34%)	133 (39%)
LVEF %	34 ± 14	34 ±14	34 ±14	33 ±15
NYHA class - no. (%)				
II	513 (50%)	177 (54%)	171 (51%)	165 (48%)
III	461 (46%)	139 (42%)	159 (47%)	163 (48%)
IV	34 (4%)	13 (4%)	8 (3%)	13 (4%)
Mean SBP – mm Hg	118 ± 21	119 ± 22	118 ± 20	117 ± 21
Mean DBP – mm Hg	68 ± 12	68 ± 12	69 ± 13	68 ± 12
Mean HR at discharge (beats/min)	75 ± 14	75 ± 14	75 ± 13	74 ± 14
Prior admission for Heart Failure- no. (%)	334 (32%)	120 (35%)	122 (36%)	106 (31%)
Comorbidities				
Hypertension – no. (%)	439 (43%)	157 (46%)	152 (45%)	130 (38%)
Atrial Fibrillation - no. (%)	372 (36%)	121 (36%)	122 (36%)	129 (37%)
Diabetes - no. (%)	289 (28%)	103 (30%)	98 (29%)	88 (26%)
Stroke - no. (%)	105 (10%)	37 (11%)	35 (10%)	33 (9%)
COPD – no. (%)	268 (27%)	84 (25%)	87 (26%)	97 (28%)
Etiology				
History of Myocardial Infarction no. (%)	436 (43%)	149 (44%)	144 (42%)	143 (42%)
Median Index hospital stay –days	10 (7-16)	11 (7-16)	10 (7-16)	11 (7-17)
Living alone - no. (%)	396 (39%)	139 (42%)	136 (41%)	121 (35%)
Mean Body Mass Index -kg/ m^2	27 ± 5	27 ± 5	27 ± 5	27 ± 5
Median length of disease yr	1 (0-34)	1 (0-34)	1 (0-29)	1 (0-22)
Mean eGFR - ml/min/1.73m^2	55 ± 21	52 ± 20	57 ± 19	57 ± 23
Medication				
ACE/ARB - no. (%)	847 (83%)	277 (82%)	290 (85%)	280 (81%)
Beta-blockers - no. (%)	677 (66%)	221 (65%)	239 (70%)	217 (63%)
Diuretics* - no. (%)	980 (95%)	325 (96%)	330 (97%)	325 (95%)
Digoxin - no. (%)	309 (30%)	100 (30%)	108 (32%)	101 (29%)
Calcium Antagonists - no. (%)	162 (16%)	60 (18%)	57 (17%)	45 (13%)
Nitrates - no. (%)	324 (32%)	109 (32%)	101 (30%)	114 (33%)
Statins– no. (%)	388 (38%)	126 (37%)	141 (42%)	121 (35%)
Laboratory values				
Median (IR) BNP -pg/dl	493 (730)	530 (986)	478 (657)	478 (634)
Median (IR) NT-proBNP - pg/dl	2528 (4291)	2677 (5251)	2404 (3903)	2505 (4274)
Mean Serum sodium - mg/dl	139 ± 4	139 ± 4	139 ± 4	139 ± 4
Mean Haemoglobin - mmol/l	8.2 ± 1.2	8.0 ± 1.2	8.2 ± 1.3	8.2 ± 1.2

COPD: Chronic Obstructive Pulmonary Disease; eGFR= estimated Glomerular Filtration Rate; NYHA= New York Heart Association functional class; SBP = systolic Blood Pressure; DBP; diastolic Blood Pressure; HR = Heart Rate, ACE/ARB= Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker, AF= Atrial Fibrillation, BNP= B-type Natriuretic Peptide; NT pro BNP = N-terminal pro B-type Natriuretic Peptide. * Loopdiuretics, thiazides and aldosterone-antagonists

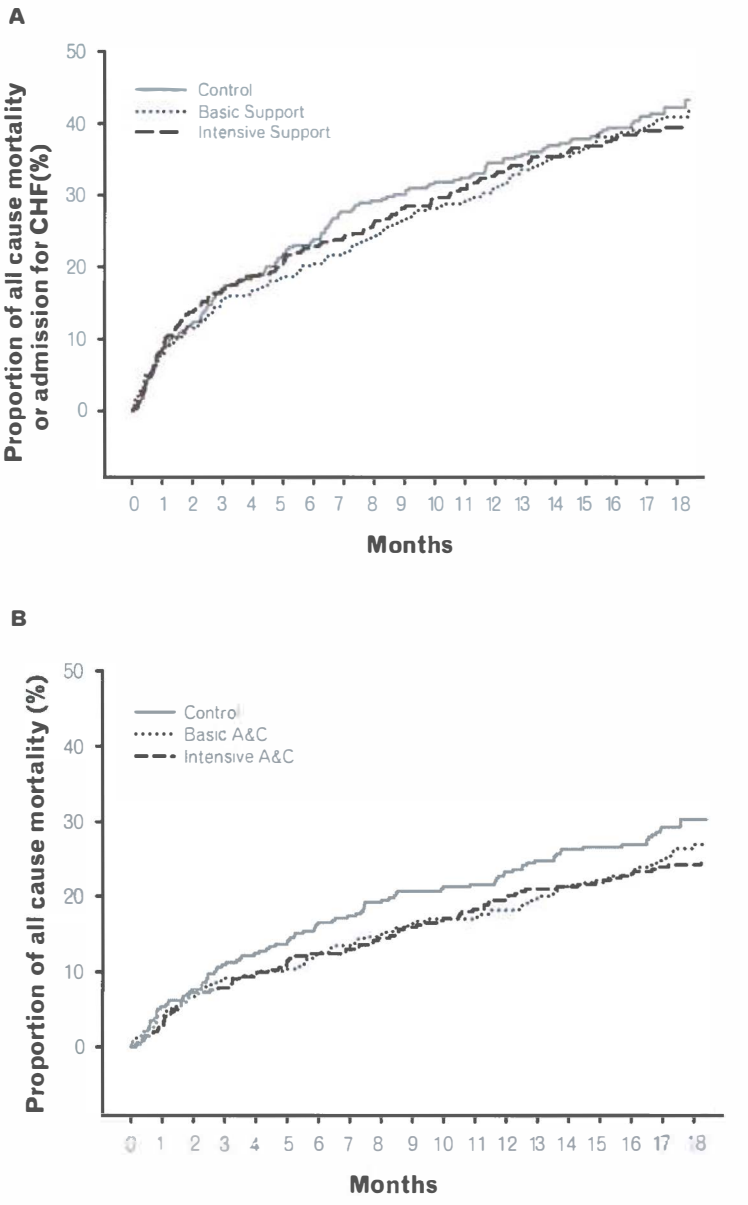

Figure 3.
a. Kaplan Meier curve for time to the first hospitalization for heart failure or death (primary endpoint)
b. Kaplan Meier curve for all-cause mortality (major secondary endpoint)

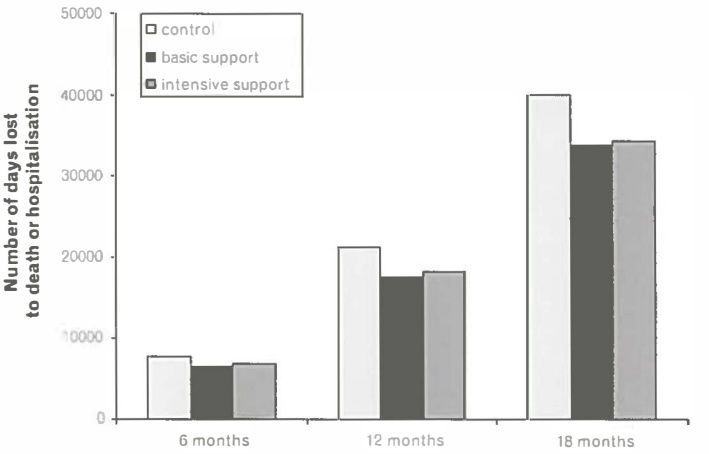

Figure 4. The number of days lost to death or hospitalization during 18 months (co primary endpoint).

group, compared to 33,731 days for the basic support group, and 34,268 for the intensive support group (Figure 4). Per patient the median days lost to death or all cause hospitalization were 12.0 days in the control group (Q1-Q3: 0.0-173.0 days), 9.0 days in the basic support group (Q1-Q3 0.0-88.0 days, p=0.81 versus the control group) and 7.5 days in the intensive support group (Q1-Q3: 0.0-86.5 days, p=0.49 versus the control group).

3.3.2 Secondary endpoints

Mortality

All-cause mortality was 29% in patients in the control group, 27% in the basic support group and 24% in the intensive support group (Figure 3b). The 12% and 19% reduction in mortality over the 18 months were not statistically significant, with HRs of 0.88 (95% CI 0.66-1.18, p=0.39) and 0.81 (95% CI 0.60 -1.08, p=0.15). For the two intervention groups combined, the HR was 0.85 (95% CI 0.66-1.08, p=0.18).

Hospitalizations

Of all patients, 55% were hospitalized at least once, for any cause during the 18 months, resulting in a total of 1,161 hospitalizations (Table 3). A total of 64% (746) of these hospitalizations were attributed to cardiovascular causes but only 32% (375) were related to heart failure. There were slightly more hospitalizations for heart failure in the intensive support group (134 versus 120) compared to the control group. Taking into account a total cumulative follow up duration of

Table 2. Outcomes in patients according to intervention strategies.

	Total (n=1023)	Control (n=339)	Basic Support (n=340)	Intensive Support (n=344)
Primary endpoints				
Mortality/HF hospitalization	411 (40%)	141 (42%)	138 (41%)	132 (38%)
Days lost in 18 months	107,959	39,960	33,731	34,268
Median days lost per patient (Q1-Q3)	10.0 (0.0-109.0)	12.0 (0.0-173.0)	9.0 (0.0-88.0)	7.5 (0-0.0-109)
Other events				
Hospitalizations				
Number of patients with				
All cause hospitalization	567 (55%)	181 (53%)	192 (57%)	194 (56%)
Cardiovascular	433 (42%)	143 (42%)	143 (42%)	147 (43%)
Heart Failure	260 (25%)	84 (25%)	84 (25%)	92 (27%)
Number of hospitalizations				
All cause	1161	376	377	408
Cardiovascular	746	255	236	255
Heart Failure	375	120	121	134
Mortality				
All - no. (%)	272 (27%)	99 (29%)	90 (27%)	83 (24%)
Cardiovascular	219 (21%)	72 (21%)	76 (22%)	71 (21%)
Non Cardiovascular	38 (4%)	19 (6%)	10 (5%)	9 (3%)
Unknown	15 (2%)	8 (2%)	4 (1%)	3 (1%)
Median length in days				
Heart Failure hospitalization (Q1-Q3))	9.0 (5.0-17.0)	12.0 (5.0-19.5)	8.0 (4.0-14.0)	9.5 (5.0-17.0)

429.02 years for the intensive support and 409.27 years for the control group, incidence rates of 0.31 and 0.29 per follow-up year were calculated for the intensive support and control group, respectively, with an incidence rate ratio of 1.07 (95%CI 0.83 - 1.37, p=0.616). However, the median durations of heart failure admissions in the both support groups (8.0 days in basic support, and 9.5 days in intensive support groups, respectively) were shorter when compared with the control group (12.0 days; basic support versus control p=0.010, and intensive support versus control group p=0.294 (Table 2).

4. Discussion

The main findings of this randomized controlled study, which is one of the largest in the field of heart failure disease management so far, do not support the concept that adding either a basic or an intensive nurse-led management program to standard care of a cardiologist, reduces the combined endpoint of heart failure rehospitalization and death. We did however observe a non-significant, but potentially clinically relevant, 15% decrease in all-cause mortality, which was accompanied by slight increase in (shorter) hospitalizations in both intervention groups.

Disease management programmes are implemented on a large scale in many countries and recent guidelines advocate the use of an organized system of specialist HF care to improve symptoms and reduce hospitalizations (class IA) and to increase survival (class IB).[1,2] In the present large study, in 17 centres, we did not find an effect on the composite endpoint of HF hospitalizations and death. Given the existing data, this finding is unexpected and it will impact on the role of disease management programs for HF, and on guidelines for HF. It is therefore important to identify factors that may have led to this outcome.

The two most obvious explanations for the absence of a difference in the event rate between the control and intervention groups are, that either patients in the control group were managed well enough already, thus making it difficult to further improve outcomes, or that the quality of the intervention, did not improve treatment. We believe that particularly the first explanation may play an important role in the present study due to a lower than expected event rate in the control group which is often seen in clinical trials. In earlier studies, patients in the control group did not receive any structured specialized follow-up, which might more frequently have led to undetected deterioration and higher hospitalization rates and mortality.[11,12] In our study, however, control patients were seen by a cardiologist which is usual care in the health care system in the Netherlands. Moreover, the 339 patients in the control group made an additional 286 visits to their cardiologist which was often related to an increase in symptoms. It is very likely that these visits "upgraded" the control group, and led to better adherence to medication, which is known to be associated with a better outcome.[16] Although patients in the two intervention groups also had more visits than planned, it is conceivable that this surplus in visits specifically had the largest effect in the control group. While specific measures were taken during the study to avoid extra contacts[14] and we discouraged local investigators to have these unplanned visits, we often could not prevent them, since in case of deterioration, the cardiologist intensified contacts. The alternative explanation for the absence of a contrast between the groups might be that the additional

support in the two intervention groups was not successful enough in educating and counselling patients. Although this cannot be proven, we believe that this latter explanation is not very likely since significant time and effort was spent by specially educated and experienced workers, to improve knowledge about the disease and its treatment, which is well known to be important in this population.[17]

A comparable increase in the number of hospital admissions in combination with a decrease in mortality has been reported before with intervention programs in patients with heart failure.[9,18] Cleland et al. reported the highest proportion of days spent in hospital in those patients who were monitored most intensively (by a nurse and telemonitoring)[18]. Health care providers might be forced to realize that (HF) readmissions are part of the need of these severely ill patients and should not always labeled as negative. The present study showed that a 'one-size-fits-all' model of disease management does not reduce readmssions in every hospital, and institutions may differ significantly in their organization expertise in the treatment of HF.

While the number of hospitalizations in the present study was not favorably affected, there was a 15% (non-significant) reduction in mortality which was consistent throughout the follow-up and confirms previous meta-analyes.[11,12] This reduction is comparable to proven pharmacological interventions in this population and although the study was not powered to examine mortality, it is substantial. Remarkably, we found that the separate components of the composite endpoint moved in an opposite direction, reflected by a higher readmission rate and a lower mortality rate. Patients in both intervention groups may have had low-threshold access to the care providers, resulting in relatively easy hospital admissions. For this reason, hospitalizations being part of a primary endpoint may not have been ideal, and we might have powered the study for mortality alone. Also, while hospitalizations may possibly be affected by subjective factors, such an effect is unlikely when assessing mortality and the present finding may thus be genuine.

Most if not all of the previous studies that evaluated the effect of programs in a similar –clinical- setting as COACH were relatively small and mostly in one or only a few sites[11,12]. While COACH is the largest study in this clinical setting, there are two even larger studies, but both had a completely different design and examined the effect of (additional) telephone intervention[19,20]. Galbreath et al.[19] studied 1069 HF patients in one single center and showed that initial weekly and later monthly telephone intervention led to a borderline statistically significant reduction in all-cause mortality during an 18-month study period. In another study from Argentina[20], 1518 outpatients with HF were enrolled and the investigators found a statistically significant, 29% reduction in hospital admissions for HF, but no effect on mortality. Two other studies, which were more similar to COACH, and which reported the most pronounced favorable

effects, were conducted in only two to three very dedicated and experienced hospitals[4,21]. Favorable effects observed in other studies may also be attributed to the other components in the programs, but also to a direct involvement of the researchers conducting the study, in delivering of care. Lastly, it can also not be excluded that "positive" studies were published more often than "negative", leading to a publication bias.

Implications

The findings of this present large study at first glance appear to be in contrast with earlier similar studies, but we believe, that they should not lead to abandoning the concept of disease management programs for HF, but rather must lead to more precise definitions of how such programs should be implemented. The data will contribute to the discussion about optimal design and execution of disease management in HF patients and indicate that one model does not fit all patients or/and all health care systems.Hospital admissions contribute to a significant part (60-70%) to costs of HF patients, and in our study the threshold may have been too low to admit patients. Organizing these short hospitalizations effectively is one of the major challenges in the near future.

The observed effect on mortality, albeit not statistically significant, is promising, since mortality is pivotal clinical endpoint in heart failure patients. It suggests that this non-pharmacological intervention may have been successful in preventing progression of disease.

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Appendix:

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CHAPTER 8

General discussion

General discussion

The main focus of this thesis was to gain greater insight into aspects of quality of life in heart failure patients. We were specifically interested in the prevalence, related variables and prognostic value of depressive symptoms in an unselected heart failure population. Therefore the thesis addressed the following four objectives. To describe:

1. the prevalence of quality of life and depressive symptoms of heart failure patients compared with an age and gender matched population of community dwelling elderly
2. the association between depressive symptoms and demographic and clinical variables in patients with heart failure
3. the prognostic value of depressive symptoms on clinical outcome in patients with heart failure
4. the effect of heart failure management programmes on clinical outcome in an unselected heart failure patient population

Having performed the studies that examined these objectives, and described them in the previous chapters, where do we now stand? In this final chapter the main findings of the preceeding chapters regarding these objectives will be discussed. Some methodological strengths and weaknesses will be addressed and possible implications for daily practice and future research will be explored.

Main findings

1. **Depressive symptoms are prevalent in well over one-third of patients with heart failure, and their quality of life is significantly impaired when compared with a similar elderly population living in the community.**

What was already known:

- Heart failure has a substantial impact on the quality of life of patients and their families.[1 4]
- The presence of depressive symptoms in patients with heart failure ranges from 25% to 77%. This large variation can be attributed to the subset of patients examined, and the instruments and definition of depression used in studies.[5 7]
- Most results on quality of life and depressive symptoms are derived from studies in which relatively young male heart failure patients are included based on stringent selection criteria, whereas the heart failure population in daily clinical practice is characterized by a growing number of elderly, female patients and patients with several chronic conditions.

What is the added value of our study:

In our study, we examined quality of life and depressive symptoms in heart failure patients, using a large elderly population residing in the community, matched by age and gender as a control group. Importantly, our clinical sample is thought to be representative for patients treated in outpatient heart failure clinics and the results will therefore provide greater insight into the prevalence of depressive symptoms in this group of patients. This control group enabled us to draw conclusions about the true association of heart failure with depressive symptoms and quality of life. Depressive symptoms were more present in heart failure patients (39%) than in the elderly control population (21%). Even when shared symptoms of heart failure and depressive mood were removed from the CES-D questionnaire, 36% of the heart failure patients still showed depressive symptoms.

We also found that heart failure patients had a significantly lower quality of life compared to the control population in the other domains of quality of life. The largest differences in quality of life between patients with heart failure and these elderly people were observed in domains which reflected physical health, such as physical functioning, role limitations due to physical functioning, and vitality.

Reflection

Symptoms of heart failure such as fatigue, dyspnoea, coughing and sleep disturbances have a large impact on the wellbeing of patients with heart failure. Patients are often limited in their ability to perform daily activities, such as work, household activities or travel.[8] Furthermore, their role in the family or other social contexts changes and future perspectives are altered, which might lead to diminished quality of life and depressive symptoms in particular.

This is reinforced by treatment and lifestyle recommendations. For example, a frequently reported disadvantage of taking diuretics is its limiting effect on social activities.[9]

Patients with heart failure have to adjust to the restrictions of this disease which occur as physical, mental and social impairments. Not every one is capable of adapting to this disease, and this might also lead to diminished quality of life or depressive symptoms.

2. Depressive symptoms and low quality of life are more prevalent in female heart failure patients and heart failure patients with comorbidities.

What was already known:

- In the general population, and after a Myocardial Infarction women are more prone to develop depressive symptoms than men.[10,12]
- Results from studies of the relationship between depressive symptoms and demographic and clinical characteristics are inconclusive.[13,14]
- The presence of comorbidities are common in patients with heart failure and contribute both to a greater decline in daily functioning and lower well being and might be related to an increase in depressive symptoms.[15]

What is the added value of our study:

In our unselected heart failure population, we found that depressive symptoms were more common in women than in men. Furthermore, women in our population with heart failure had a twofold increased risk of depressive symptoms compared to women living in the community. Factors that were independently related to depressive symptoms and gender were age, physical health, NYHA functional class, heart failure symptoms and the presence of chronic obstructive pulmonary disease. Furthermore, women with heart failure also showed lower quality of life with respect to physical functioning and vitality compared with men with heart failure and also in relation to an age and gender matched control group. Depressive symptoms and lower quality of life were also associated with comorbidity. More than 70% of our heart failure population had two or more chronic conditions. A more than threefold

increased risk of depressive symptoms was found in heart failure patients with comorbidities, compared to elderly in the community without comorbidities, while quality of life was lower on all components. However, we did not find an independent relationship between depressive symptoms and other variables that were related to disease severity such as left ventricular ejection fraction.

Reflection

Women

Depressive symptoms and lower quality of life are more common in women than in men, not only among heart failure patients but also in patients after myocardial infarction and in the general population. In addition, women are older when diagnosed with heart failure and are often living alone at the time of diagnosis. It could be that these women have already been more exposed to life events such as losing a partner. Furthermore, women more often reported having lower physical functioning, more insecurity and worthlessness and were more likely to feel themselves to be a burden to those around them.[16-18] These factors might result in a greater decrease in quality of life and increased depressive symptoms in women. Another explanation could be that women might experience a higher burden of heart failure due to a traditional role pattern. Despite having a chronic illness or reaching old age, women, more than men, continue to perform activities related to the household or care giving and therefore the interference with everyday tasks may be more obvious to women than men.[8]

Comorbidities

Comorbidities play an important role in the quality of life of patients with heart failure and especially in the relationship to depressive symptoms.[19] The medical regimen and lifestyle recommendations for heart failure patients are already very complex. Additional treatment and lifestyle recommendations which accompany comorbidities, can further limit patients in their functional capabilities and social functioning, and might increase depressive symptoms. The presence of more chronic diseases at the same time restricts the extent to which patients perceive themselves as being in control of their disease. This loss of functioning of the body and a more negative view of themselves might lead to depressive symptoms.

We also found that chronic obstructive pulmonary disease (COPD) has a prominent role as a comorbid condition in heart failure patients. COPD is a common comorbid condition present in probably one-third of heart failure patients, but precise data are lacking.[20] However, dyspnoea, whether it is a symptom of heart failure or COPD, is a frightening experience directly affecting the quality of life of heart failure patients and may be due to an increase in depressive symptoms.[21]

It is often thought that the quality of life of patients with left ventricular systolic dysfunction is lower than patients with preserved left ventricular function. However, in our large heart failure population, which had a considerable number of patients with a preserved systolic function, we showed that patients with heart failure, independent of left ventricular systolic function have an impaired quality of life.[22]

3. Patients with severe depressive symptoms have worse clinical outcomes compared to patients without depressive symptoms

What was already known:

- Higher readmission rates, higher mortality, low quality of life, higher health care utilization and higher health care costs are known consequences of heart failure.[3,19,23,27]
- Studies reported contradictory results regarding the prospective value of depressive symptoms in relation to adverse events.[5,28,32]
- It is suggested that an increase in depressive symptoms accounts for an increase in readmission rates and mortality in patients with heart failure.[5,29,33]
- However, these studies had small sample sizes and varied in patient characteristics, depressive assessment and follow-up time, so no firm conclusions on the association between depression and adverse events can be drawn as yet.[7]

What is the added value of our study:

We found that the association between depressive symptom severity and a combined endpoint of heart failure readmission and all-cause mortality was independent of age and sex but not independent of the number of comorbidities or NYHA functional class. The risk of heart failure readmission and mortality after 18 months, independent of age and sex, is higher in patients with severe depressive symptoms, compared with heart failure patients who have no depressive symptoms. This association was also found with heart failure readmission as a separate endpoint, but not with mortality as a separate endpoint.

Patients with severe depressive symptoms were readmitted significantly more often than patients without or with moderate depressive symptoms. For patients with depressive symptoms, independent of the severity of the symptoms, the length of hospital stay was significantly longer than for patients without depressive symptoms.

Reflection

Why depressive symptoms in patients with heart failure may be linked to adverse events might be explained by physiological factors such as lower heart rate variability (HRV), increased inflammation and metabolic syndrome, or behavioural factors such as non- adherence.

Physiological factors

Depressive symptoms and adverse events can be interlinked with physiological changes in patients with heart failure, which might hasten the progression of heart failure and worsen prognosis.[34] Reduced HRV in both heart failure patients and patients with depression suggests less protection from arrhythmias and might partly account for the deleterious effects of depressive symptoms on prognosis in heart failure. Secondly, inflammation factors are elevated in patients with heart failure and in patients with depressive symptoms. This might contribute to the progression of heart failure and might be predictive of more severe disease and mortality. Finally, the metabolic syndrome of both heart failure and depression showed some shared mechanisms, such as neurohormonal activation and physiological stress, which could increase the risk of myocardial ischemia and therefore might be predictive of more severe disease and ultimately might have an effect on prognosis.[15,34,37]

Non-adherence

Another possible explanation of the relation between heart failure, depressive symptoms and adverse events could be a decrease in medication adherence among heart failure patients.[38,40] In previous work on the COACH population we found that patients with depressive symptoms perceived significantly more barriers to taking medication and changing diet and fewer benefits to medication. Patients with depressive symptoms also reported feeling worried when checking their feet and legs for oedema.[9] Schiffer et al.[41] recently reported that patients with a distressed mood (Type-D) were also reluctant to report their heart failure symptoms to a health care provider. All of these personal health care behaviours are needed for an optimal management of heart failure and prevention of deterioration and thereby improving outcomes.

4. **Heart failure disease management programmes led by a heart failure nurse, in addition to follow-up by a cardiologist, does not reduce hospitalization or mortality in an unselected heart failure population.**

What is already known:

- Disease management programmes have been shown to be effective in reducing mortality and hospital readmissions, and lead to potential improvements in quality of life and cost savings.
- These programmes varied in components and it is not clear which characteristics of the programmes are responsible for it being effective.
- Substantial differences in the intensity of these disease management programmes make it difficult to draw definitive conclusions about the effectiveness, optimal timing and frequency of interventions.
- Most of these often nurse led interventions were single-centre studies, examined small samples and were not developed specifically for heart failure patients with depressive symptoms.[42 44]

What is the added value of our study:

From the COACH study, it is concluded that adding either a basic or and intensive nurse-led heart failure management programme to the standard care of a cardiologist, does not lead to a reduction in readmissions and mortality. However, a non-significant but potentially clinically relevant decrease in all-cause mortality as well as shorter, though slightly more hospitalizations were seen in both intervention groups.

Reflection

Different explanations can be given for the non-significant effect of a nurse-led disease management programme in this unselected heart failure population. First, in most of the studies in which an effect of a disease management programme is found the control group did not receive any structural follow-up by a cardiologist, while in our study patients visited a cardiologist at least twice a year. This could imply that patients from the control group were managed well enough already, making it difficult to further improve outcomes. In the intervention groups, patients had regular contact with a heart failure nurse, at least every three months. Nurses could have detected worsening heart failure at an early stage or new medical problems, which might have led to prompt interventions and consequently resulted in more, but shorter, readmissions.

Another explanation could be that the main focus of the intervention in our study was on lifestyle changes, while optimizing medical treatment by heart failure nurses was not prominent. The latter however, might be a successful

component of a heart failure disease management programme.[45,46] A 'one-size-fits-all' intervention does not seem to work in every health care system or for every patient. To date, what constitutes the optimal disease management programme in heart failure patients is not clearly determined. Furthermore, the content of the interventions in the COACH study was not specifically developed for patients with depressive symptoms. Therefore, we could not evaluate exactly which components were of special significance to patients with depressive symptoms. However, the COACH study will provide more data to investigate which patients benefited most from a disease management programme. Furthermore, in subsequent analyses we might be able to examine which components are beneficial for heart failure patients and which are not, as well as which are beneficial for heart failure patients with and without depressive symptoms.

Critical reflection on study populations and instruments

In the previous chapters, methodological considerations specific for that particular study were described. In this section of critical reflection on some methodological issues of this thesis will be undertaken.

Analyses

We explored the relationship between depressive symptom severity and outcomes in a secondary analyses setting. The COACH study was not primarily designed to investigate the prevalence of depressive symptoms and the association between depressive symptoms and clinical outcome: readmission and mortality. Hence, the increase in readmissions and mortality seems to be clinically relevant and is a significant issue for further investigation.

Measuring depressive symptoms

Our measure of depressive symptoms was based on a CES-D score of 16 or more, which is not equivalent to a clinical diagnosis of depression. However, previous studies have indicated that a score of 16 or more on the CES-D is a reasonable approximation of a clinical diagnosis of depression.[47-49] Additionally, one of the criticisms of using the CES-D in a sample of hospitalized heart failure patients is the possible overlap of somatic symptoms of heart failure and depression. It might be possible that the CES-D not only measured depressive symptoms, but also indicated a worsening heart condition. However, in Chapter 2 we concluded that only two questions assessed the

somatic symptoms of depression and when these questions were removed from the analyses, a significant number of heart failure patients still reported depressive symptoms.

Study population

The COACH study is one of the largest studies in the world that evaluates the role of advice and counselling in heart failure patients, in which a total of 1,023 patients were randomized and followed for 18 months. The selection criteria for this heart failure population were broad, resulting in a population of elderly patients with several comorbidities and both preserved systolic function and diastolic dysfunction. Our heart failure population is representative of the heart failure population seen in clinical practice and outpatient departments and results can be generalized to the clinical heart failure population. In the study in which quality of life was described in the heart failure population and a comparable elderly population, the two populations were matched by age and gender. This enabled us to make valid comparisons between patients and a reference group regarding quality of life and depressive symptoms. It also enabled us to draw firm conclusions on the impact of heart failure on quality of life and depressive symptoms.

Implications for practice

Attention and identification

There is a lack of attention paid to depression in the medical community at large and in relation to heart failure patients in particular. This is confirmed by the observation that recognition and treatment of depression in heart failure patients is not addressed in the current Dutch multidisciplinary guidelines.[30,31] Findings from this thesis underline the importance of attention to and identification of depressive symptoms in heart failure patients as the prevalence is high and the impact on quality of life and outcomes considerable. Indeed, it is difficult to recognize depressive symptoms in the context of a medical illness because some symptoms of depression are similar to increasing heart failure. Both patients and physicians may attribute depressive symptoms to the medical condition rather than independently to an underlying mood disorder, which might lead to difficulties in recognizing and adequately treating depressive symptoms in patients with heart failure.[34] In future guidelines this topic needs to be addressed and health care providers should be trained to recognize depressive symptoms in heart failure patients. They should also be aware of an increased prevalence of depressive symptoms, particularly in women and in patients with more comorbidities.

Screen for depressive symptoms

It is recommended that routine screening for depressive symptoms among patients with heart failure be undertaken in heart failure clinics. To prevent a time consuming and complicated approach, we suggest a stepwise approach. By asking the two questions mentioned below (derived from the main symptoms of depressive disorder as defined by the DSM-IV), health care providers discern the mental health status of heart failure patients.

1. During the past month, have you often been bothered by feeling down, depressed or hopeless?
2. During the past month, have you often been bothered by little interest or pleasure in doing things?[51]

If patients answer positively, then a questionnaire which focuses on other depressive symptoms should be administered, such as the CES-D for instance, or in the case of the elderly the Geriatric Depression Scale. If patients have a score that indicates they are at higher risk of clinical depression, a diagnostic interview should be undertaken to establish a diagnosis of depression.

Treat depressive symptoms

Under-diagnosis and under-treatment of depressive symptoms in heart failure patients remains a constant problem. Just a small number of heart failure patients with psychological distress see a mental health professional or are prescribed antidepressants (7.9%).[53,54] Our results confirmed these findings in that only 12% of the heart failure patients with depressive symptoms had antidepressant medication.[55] To further optimize care for heart failure patients with depressive symptoms, it is important to treat this group according to the established guidelines.

Integration with heart failure regimen

Although non significant, an important finding of this thesis was the potentially clinically relevant reduction in mortality and a slight increase in the number of hospitalizations with a shorter duration in patients with heart failure, due to the support of heart failure nurses and care by the cardiologist. This implies that a multidisciplinary approach could play an important role in the treatment of heart failure patients. In particular, the heart failure nurse may have an important role to play in the care of heart failure patients, coordinating several medical and lifestyle recommendations offered by diverse medical professionals, as well as acting a case manager. To support patients in managing their disease by improving self-efficacy and self-control might have positive consequences for treatment adherence, health-promoting behaviour and quality of life and might prevent or reduce depressive symptoms. Furthermore, the strength of heart failure nurses is their holistic approach

and easy accessibility. Discussing quality of life and more specific mental health issues, can help in the detection of problems at an early stage, and might prevent depressive symptoms. In addition, some interventions may be considered at this early phase such as education and providing advice to and reassurance for the patient and their partners or key family members.[56]
In the context of the multidisciplinary approach found in most heart failure clinics, heart failure nurses can also play an important role in referral to a clinical psychologist or a psychiatrist. Another approach might be to include a psychiatric nurse or nurse practitioner in the heart failure management team,[57] which might enhance early identification and treatment of depressive symptoms.
Recently, the Netherlands Heart Foundation recognized the importance of psychosocial aspects in the care of patients with heart failure. In 2006 they published a report on the psychosocial care of patients with heart disease in general and patients with heart failure specifically. In this report, limitations and changes in future perspectives due to the disease, psychosocial problems, psychopathology, problems involving partners and interventions are described. The recommendations at the end of this report will be used to develop a new programme called 'Heart for people' which aims to improve the psychosocial care of patients with heart disease. This is a step forward in the development of good quality of care for patients with heart failure and depressive symptoms.[58]

Implications for future research

Critical reflections on populations and instruments have been made and several suggestions to improve treatment and care of heart failure patients with depressive symptoms have been described. From this information the following suggestions for future research can be formulated.

Relationship between depressive symptoms and heart failure

Using longitudinal research, it is important to further unravel the complex interplay between depression and heart failure in elucidating the physiological or behavioural mechanisms by which depressive symptoms cause poor outcomes. Furthermore, further study of the course of depressive symptoms during follow-up is required, because it is possible that sustained depressive symptoms, have a greater impact on clinical outcome than incidental depressive symptoms.

Effective interventions

Disease management programmes for heart failure patients might need to develop a specific approach for patients with depressive symptoms. It might be worthwhile to examine which components in existing disease management programmes work well in these vulnerable patients. Finding optimal interventions for depressive heart failure patients is still a challenge and needs careful evaluation. Recently we learned from the Myocardial Infarction and Depression Interventional Trial (MIND-IT) that antidepressant treatment did not improve cardiac prognoses compared to the 'care as usual' in which patients were not informed about their research diagnosis and additional psychiatric treatment was not offered.[59] Also, cognitive behavioural treatment combined with antidepressant medication has not been proven to decrease the risk of all-cause mortality and reinfarction in patients with myocardial infarction and depression.[60] Although both studies were performed on myocardial patients, they teach us how difficult it is to effectively treat depression in cardiac patients.
A possible direction that could be taken, is a tailored intervention with attention to adherence, effective coping strategies and cognitive behavioural therapy.[61]

Instruments

It would be useful to revalidate the cut off scores used to define patients with heart failure who are at risk of clinical depressions. It might well be the case that a substantial portion of the increase in depressive symptom scores in heart failure patients does not directly correspond with the increased risk of depression but rather represents an elevation of less specific depressive symptoms.

To conclude, in this thesis we gained more insight into the quality of life and the prevalence, related variables and the prognostic value of depressive symptoms in an unselected heart failure population. The thesis stressed the importance of addressing this topic in future guidelines and the important role of health care providers, in particular heart failure nurses and physicians, in recognizing, identifying and treating depressive symptoms. Special attention must be paid to female heart failure patients and heart failure patients with comorbidities.

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SUMMARY

Summary

This thesis is written as part of the COACH trial (Coordinating study evaluatig Advising and Counselling in Heart Failure). All chapters except chapter 2 used data from the COACH trial. The COACH study is a randomized multi-centre trial on the effects of advising and counselling in heart failure patients.

The number of patients with heart failure is rising. This increase is, due, *inter alia*, to the improvement in medical technical care and treatment options for patients with cardiovascular diseases, with the result that more patients with a heart disease will survive and live longer. In addition, the population of the Western world is 'aging' and more people will develop cardiovascular diseases among them is heart failure.

Heart failure is defined as a complex of symptoms and complaints as a result of a failing pumping capacity of the heart. Patients with heart failure often suffer from breathlessness or fatigue, either at rest or during exertion, and/or oedema. These symptoms have a major impact on the daily lives of patients. In addition, treatment, life-style changes and insecure prognosis have a major influence on their quality of life and depression or depressive symptoms can develop. Depressive symptoms are often described among patients suffering from a chronic condition and are also present in patients with heart failure. Studies in patients with heart failure suggest that the presence of depressive symptoms is associated with an increase in readmission and mortality rates and is therefore seen as an important problem.

Thus far no sufficiently large studies, with a relatively unselected sample of heart failure patients, are available that examine the relationship between depressive symptoms and demographic and clinical characteristics.Very few studies have been performed yet, that examine the relationship between depressive symptoms and outcomes in terms of readmission and mortality in large, for daily clinical practice representative groups of heart failure patients. To reduce readmissions and mortality international studies have been performed to examine different disease management programmes. To date, the most optimal way of advising and counselling in patients with heart failure so as to reduce hospital admission and mortality remained largely unclear.

The following aims for this thesis were formulated. To describe:

1. the prevalence of quality of life and depressive symptoms in heart failure patients compared with an age and gender matched population of community dwelling elderly
2. the association between depressive symptoms and demographic and clinical variables in patients with heart failure
3. the prognostic value of depressive symptoms on clinical outcome in patients with heart failure
4. the effect of heart failure management programmes on clinical outcome in an

unselected heart failure patient population.
In ***Chapter 1***, general introduction, the background and concepts of this thesis are described. ***Chapter 2*** presents a study of the measurement of quality of life in heart failure patients. In this study the relationship between a one-item quality of life instrument (Ladder of Life) and a multiple-item questionnaire (the Minnesota Living with Heart Failure Questionnaire: MLwHFQ) is determined. Data from 231 patients with heart failure from the Rijnland Hospital in Leiderdorp were gathered and analysed. The results show that although both quality of life measurements correlate, there is a large variation in the MLwHFQ scores in patients who score relatively low as well as relatively high on the Ladder of Life. From the results it can be concluded that although the Ladder of Life and the MLwHFQ do correlate, they do not seem to be interchangeable. The one-item instrument can give clinicians and researchers important information on how patients assess their quality of life in a global score, but a more detailed description of physical and emotional aspects of quality of life can be obtained by the MLwHFQ. In the COACH (Coordinating Study evaluating Outcomes of Advising and Counselling in Heart Failure) study, the results of which will be discussed later in this thesis, instruments with both one-item and multiple items have been used to describe the quality of life of patients with heart failure.
The quality of life of patients with heart failure often involves comparison with a normative healthy population. However, older people often suffer from several chronic conditions and most have faced age-related life events. This might affect their quality of life and psychosocial status and therefore a group of elderly heart failure patients is not necessarily comparable with a healthy elderly population. In ***Chapter 3***, the impact of heart failure on the quality of life and depressive symptoms of patients from the COACH study is compared with the quality of life and depressive symptoms of a Dutch population of community residing elderly. Both groups, 781 COACH patients and 781 elderly with diverse chronic conditions, were matched on age and gender. The results showed that more than one-third (39%) of patients with heart failure had depressive symptoms compared to 21% of the elderly. Quality of life was significantly impaired on all dimensions of the RAND-36 and the Ladder of Life in patients with heart failure when compared with elderly without heart failure, and is in women more impaired than in men. The substantial impact of heart failure is most pronounced in the domains that reflect physical health, such as physical functioning, role limitations due to physical functioning and vitality. This study also showed that the quality of life of patients and elderly with co-morbid conditions is more impaired and depressive symptoms are more often present when compared to the groups without or with one chronic condition. It can be concluded that the burden of heart failure has a negative impact on the quality of life, and women and elderly with comorbid conditions are at higher risk.

Depressive symptoms are relatively common in patients with heart failure. On the one hand this can be due to the impact of the disease, on the other hand it can be related to the shared symptoms of heart failure and depression such as fatigue, sleeplessness, loss of appetite, feelings of worthlessness and loss of energy. As far as we are aware, only a few studies have examined the relationship between demographic and clinical variables and depressive symptoms. ***Chapter 4*** therefore describes the relationship between depressive symptoms (assessed by the Center for Epidemiologic Studies Depression Scale: CES-D) and demographic and clinical factors and the relationship between depressive symptoms and symptoms of heart failure (assessed by an interview with patients with heart failure). Depressive symptoms were present in 41% of 572 patients with heart failure. When somatic items that were present in both the CES-D questionnaire and the interview questions (loss of appetite and sleeplessness) were removed from the CES-D questionnaire, 36% of the heart failure patients still showed depressive symptoms. More women (45%) than men (36%) reported depressive symptoms but no differences were found between patients with and without depressive symptoms according to age, living alone or education level. In this study, no differences were found between patients with and without depressive symptoms according to the left ventricular ejection fraction, NYHA classification, etiology, duration of heart failure, and the number of comorbidities. The results showed that women with heart failure, heart failure patients with COPD, and heart failure patients with complaints about sleeplessness and loss of appetite reported depressive symptoms more often than patients without these characteristics.
From studies in the general population it is known that women are more prone to develop depressive symptoms than men and that women and men differ in the way they cope with diseases. ***Chapter 5*** describes the determinants of depressive symptoms in heart failure men and women separately. In 582 heart failure men and 339 heart failure women, the demographic factors related to depressive symptoms in men and women are age and physical health. In both men and women it is shown that depressive symptoms are related to more heart failure symptoms. In women it is also shown that NYHA functional class and COPD are associated with depressive symptoms. After describing the results of the prevalence and determinants of depressive symptoms, in ***Chapter 6*** the relationship between depressive symptoms and outcomes in terms of readmission and mortality is examined. The data of 958 patients with heart failure from the COACH study were analysed. In total, 39% of the patients showed depressive symptoms (CES-D ≥ 16), of whom 200 (21%) patients had severe depressive symptoms (CES-D ≥ 24). During the 18-month follow up study, 40% of 958 patients were readmitted for heart failure or died from one cause or other. In the group of patients with severe depressive symptoms this was 45%. Having severe depressive symptoms was a risk factor for the

combined endpoint of heart failure readmission and mortality independent of age and sex (HR 1.32, 95% CI 1.03-1.69; p=0.03). This was not independent of NYHA functional class and the number of comorbidities. Furthermore, patients with severe depressive symptoms had more and longer hospital admissions when compared with patients without or with mild depressive symptoms. This thesis also examined whether a general nurse leading the intervention, which was not specifically designed for patients with depressive symptoms, was effective in reducing readmission and mortality in heart failure patients. ***Chapter 7*** presents the results of the COACH study. In this study, two interventions that differed in intensity (basic support versus intensive support by a heart failure nurse) were compared to a 'care as usual' group (visit to the cardiologist). It was hypothesized that interventions including advising and counselling by a heart failure nurse affect morbidity and mortality during an 18-month follow-up. In total, 1,023 patients from 17 hospitals, who were discharged after hospitalization were studied. During the 18 months, 40% of the patients were readmitted for heart failure or died: 42% in the 'care as usual', 41% in the basic intervention and 38% in the intensive intervention. The results showed that neither the basic nor the intensive intervention led to a significant reduction in heart failure readmission or mortality when compared to follow-up by the cardiologist. However, a non-significant but potentially clinically relevant decrease in all-cause mortality as well as shorter, though slightly more hospitalizations were seen in both intervention groups. The number of days in hospital or died in the 'care as usual' group was in total 39.960. This was 15% lower in both the intervention groups, but the difference is not statistically significant.

Finally in ***Chapter 8***, the most important findings of this thesis are summarized and discussed, including implications for daily practice and further research. This thesis has provided more insight into different aspects of the quality of life of patients with heart failure. Our attention was specifically drawn towards the prevalence, determinants and prognostic value of depressive symptoms in a relatively unselected heart failure patient population. For daily clinical practice it is important that depressive symptoms are recognized, identified and treated according to the established guidelines. Furthermore, it is important that healthcare providers are aware of an increased prevalence of depressive symptoms in patients with heart failure, particularly in women and in patients with more comorbidities (such as COPD). It is recommended that depressive symptoms be routinely screened for to enhance early recognition and treatment of depressive symptoms. This thesis argues that this subject be addressed in the current multidisciplinary guidelines and for a multidisciplinary approach to patients with heart failure.

In the near future it will be important to further unravel the complex interplay between heart failure, depressive symptoms and consequences in terms of

readmission and mortality. Mechanisms, both physiological and behavioural, by which depressive symptoms cause poor outcomes must be elucidated by longitudinal research. Studies are needed to find optimal interventions for heart failure patients with depressive symptoms. Finally, it will be useful to re-validate cut-off points in measurement instruments used for depressive symptoms to define patients with heart failure at risk of depressive symptoms.

SAMENVATTING

Samenvatting

Dit proefschrift is geschreven in het kader van het COACH (Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure) onderzoek. Het COACH onderzoek is een gerandomiseerd multi-center onderzoek naar de effectiviteit van voorlichting en begeleiding bij patiënten met hartfalen. Alle hoofdstukken met uitzondering van hoofdstuk 2, zijn gebaseerd op gegevens uit dit onderzoek.

Het aantal patiënten met hartfalen neemt toe als gevolg van onder andere verbeteringen in de behandelingsmogelijkheden voor patiënten met hart- en vaatziekten, waardoor meer patiënten langer leven met een hartziekte. Daarnaast is de vergrijzing van de algemene bevolking in de Westerse wereld een factor die leidt tot een grotere prevalentie van mensen met hart- en vaatziekten en daardoor ook van patiënten met hartfalen.
Hartfalen wordt omschreven als een complex van klachten en verschijnselen ten gevolge van een tekortschietende pompfunctie van het hart. Hierdoor ontstaan symptomen als kortademigheid bij lichte inspanning of zelfs in rust, vermoeidheid, vochtretentie en oedemen. Deze symptomen hebben een grote impact op het dagelijkse leven van de patiënt. Maar ook de behandeling, de verschillende leefregels en de onzekere toekomstverwachting beïnvloeden de kwaliteit van leven van patiënten met hartfalen en kunnen leiden tot depressie of depressieve symptomen. Depressieve symptomen worden vaak gesignaleerd bij patiënten met chronische aandoeningen en komen ook voor bij patiënten met hartfalen. Onderzoek bij patiënten met hartfalen heeft laten zien dat het hebben van depressieve klachten samenhangt met een toename van het aantal heropnames en sterfte en depressie wordt daarom gezien als een belangrijk probleem.
Tot op heden is er nauwelijks onderzoek gedaan naar de relatie tussen depressieve symptomen en demografische en klinische variabelen in grote en voor de klinische praktijk representatieve groepen patiënten met hartfalen. Ook naar de relatie tussen depressieve symptomen en het aantal heropnames en sterfte is weinig onderzoek gedaan. Om heropnames en sterfte te verminderen is nationaal en internationaal onderzoek verricht naar verschillende zorginitiatieven. Echter eenduidig bewijs voor de effectiviteit (in de zin van heropnames en overlijden) van deze zorginitiatieven en in het bijzonder het geven van voorlichting en begeleiding aan patiënten met hartfalen ontbreekt nog.
In dit proefschrift zijn de volgende vier doelstellingen geformuleerd:

1. Het beschrijven van de kwaliteit van leven en depressieve symptomen van patiënten met hartfalen en het vergelijken ervan met de kwaliteit van leven en depressieve symptomen van een populatie van zelfstandig wonende ouderen.

2. Het onderzoeken van het verband tussen depressieve symptomen en demografische en klinische kenmerken bij patiënten met hartfalen.
3. Het beschrijven van de prognostische waarde van depressieve symptomen voor heropnames en overlijden bij patiënten met hartfalen.
4. Het vaststellen van het effect van zorgprogramma's voor patiënten met hartfalen op heropnames en overlijden.

In hoofdstuk 1, de algemene introductie, worden de aanleiding en een aantal centrale begrippen van dit proefschrift toegelicht. ***Hoofdstuk 2*** beschrijft een onderzoek naar het meten van kwaliteit van leven. Het betreft een onderzoek naar de relatie tussen een meetinstrument voor de algemene kwaliteit van leven met één item (Ladder of Life) en een meetinstrument voor kwaliteit van leven met meerdere ziekte-specifieke items (Minnesota Living with Heart Failure Questionnaire-MLwHFQ). Er is gebruik gemaakt van gegevens van 231 patiënten met hartfalen uit het Rijnland ziekenhuis in Leiderdorp. Het onderzoek laat zien dat de uitkomsten van beide meetinstrumenten correleren, maar dat er een grote variatie is in scores op de MLwHFQ bij zowel patiënten met een lage score op de Ladder of Life als bij patiënten met een hoge score op de Ladder of Life. De resultaten van dit onderzoek leiden tot de conclusie dat, ondanks de relatie die er tussen beide instrumenten bestaat, deze instrumenten niet uitwisselbaar zijn. Het meetinstrument met één item (Ladder of Life) geeft belangrijke informatie aan artsen en onderzoekers over hoe patiënten hun kwaliteit van leven weergeven in een globale score. Een meer gedetailleerde beschrijving van de impact van de ziekte op fysieke en mentale domeinen van kwaliteit van leven kan worden verkregen met behulp van de MLwHFQ. In het COACH onderzoek zijn zowel meetinstrumenten met één item, als meetinstrumenten met meerdere en ziekte-specifieke items meegenomen om de kwaliteit van leven van patiënten met hartfalen te beschrijven.

De kwaliteit van leven van patiënten met hartfalen wordt vaak vergeleken met die van gezonde mensen uit de samenleving. Dit lijkt een onterechte vergelijking. Immers oudere mensen hebben vaak één of meer chronische aandoeningen en hebben veelal verschillende 'life events' meegemaakt, welke hun kwaliteit van leven beïnvloed kan hebben. ***Hoofdstuk 3*** vergelijkt de kwaliteit van leven en depressieve symptomen bij patiënten met hartfalen (uit het COACH onderzoek) met de kwaliteit van leven en de prevalentie van depressieve symptomen in een groep zelfstandig wonende ouderen uit de Nederlandse samenleving. Deze groep vormt een representatieve afspiegeling van (gezonde en niet gezonde) ouderen uit de samenleving. De twee groepen, een groep van 781 COACH patiënten en een groep van 781 ouderen uit de Nederlandse samenleving zijn gematched op leeftijd en geslacht. Uit de resultaten van dit onderzoek blijkt dat ruim een derde (39%) van de patiënten

met hartfalen depressieve klachten heeft, terwijl dit bij 21% van de ouderen werd gemeten. De kwaliteit van leven op alle domeinen van de RAND-36 en op de Ladder of Life, was significant lager bij de patiënten met hartfalen in vergelijking met de ouderen zonder hartfalen. Verder geldt over het algemeen dat de kwaliteit van leven van vrouwen lager is dan de kwaliteit van leven van mannen, ongeacht de ziekte. De impact van hartfalen is het sterkst op de domeinen die de fysieke gezondheid weergeven, zoals het fysiek functioneren, rolbeperkingen ten gevolge van het fysiek functioneren en vitaliteit. De kwaliteit van leven van patiënten met hartfalen of van ouderen met meerdere chronische aandoeningen is significant lager in vergelijking met mensen zonder of met slechts één chronische aandoening. Ook komen depressieve symptomen significant vaker voor bij mensen met meerdere chronische aandoeningen. Geconcludeerd kan worden dat hartfalen negatieve gevolgen heeft voor de kwaliteit van leven. Daarnaast blijken vrouwen en ouderen met meerdere chronische aandoeningen extra kwetsbaar.

Depressieve symptomen worden vaak geconstateerd bij patiënten met hartfalen. Enerzijds komt dit door de impact van de ziekte, anderzijds kan dit ook komen door de overeenkomsten in symptomen van hartfalen en symptomen van depressie, zoals vermoeidheid, slapeloosheid, verminderde eetlust, het gevoel van nutteloos zijn en futloosheid. Er is tot nu toe weinig onderzoek gedaan naar demografische en klinische factoren die verband houden met depressieve symptomen. ***Hoofdstuk 4*** beschrijft de relatie tussen depressieve symptomen (gemeten met behulp van de Center for Epidemiologic Studies Depression Scale: de CES-D vragenlijst) en demografische en klinische factoren. Daarnaast is de relatie tussen depressieve symptomen en symptomen van hartfalen (geïnventariseerd middels een interview bij patiënten) onderzocht. Bij 41% van de 572 onderzochte patiënten met hartfalen zijn depressieve symptomen (CES-D $\geq$ 16) gemeten. Wanneer somatische symptomen, die worden uitgevraagd in de vragenlijst voor depressieve symptomen als ook in het interview naar symptomen van hartfalen (verminderde eetlust en slapeloosheid), worden verwijderd, wordt nog bij 36% van de patiënten depressieve klachten gemeten. Meer vrouwen (48%) dan mannen (36%) blijken depressieve symptomen te hebben. Er is geen verschil gevonden tussen patiënten met en zonder depressieve klachten met betrekking tot leeftijd, alleenwonend zijn of opleidingsniveau. Ook zijn er in dit onderzoek geen verschillen gevonden tussen patiënten met en zonder depressieve symptomen met betrekking tot linker ventrikel ejectie fractie, NYHA klasse, oorzaak en duur van hartfalen en het aantal andere aandoeningen. Vrouwen met hartfalen, patiënten met hartfalen en COPD, patiënten met hartfalen en klachten van slapeloosheid en verminderde eetlust hebben vaker depressieve symptomen dan patiënten met hartfalen zonder deze kenmerken.

Vanuit onderzoek in de algemene populatie is bekend dat depressieve symptomen vaker voorkomen bij vrouwen dan bij mannen en dat vrouwen en mannen verschillend omgaan met ziekte. ***Hoofdstuk 5*** beschrijft de factoren die samenhangen met depressieve symptomen bij mannen en vrouwen afzonderlijk. In een hartfalen populatie van 582 mannen en 339 vrouwen blijkt dat het voorkomen van depressieve symptomen bij zowel mannen als vrouwen samenhangt met leeftijd en de fysieke gezondheid. Ook hebben zowel vrouwen als mannen met meerdere symptomen van hartfalen vaker depressieve symptomen. Bij vrouwen blijkt dat NYHA klasse en de aanwezigheid van COPD verband houden met depressieve klachten, terwijl dit bij mannen niet het geval is.

Nadat de prevalentie van depressieve symptomen is onderzocht, evenals factoren die hiermee samenhangen, behandelt ***hoofdstuk 6*** de relatie tussen depressieve klachten, heropnames en mortaliteit. Er is gebruik gemaakt van gegevens van 958 patiënten met hartfalen uit het COACH onderzoek. In totaal geeft 39% van de patiënten depressieve symptomen (CES-D≥16) aan. Van deze groep heeft 21% (200 patiënten) ernstige depressieve symptomen (CES-D≥24). Daarnaast is 40% van de 958 patiënten binnen 18 maanden heropgenomen of overleden. In de groep patiënten met ernstige depressieve symptomen was dit 45%.
Het risico op heropname en overlijden blijkt voor patiënten met ernstige depressieve symptomen groter te zijn dan voor patiënten zonder depressieve symptomen, ongeacht hun leeftijd of geslacht. Dit risico hangt bij patiënten met hartfalen en depressieve symptomen echter wel samen met een hogere NYHA klasse en het hebben van meerdere chronische aandoeningen. Verder worden patiënten met ernstige depressieve symptomen significant vaker en langer heropgenomen vergeleken met patiënten zonder of met milde (CES-D tussen 16-24) depressieve symptomen.

Heeft een algemene interventie, die weliswaar niet specifiek is toegesneden op patiënten met depressieve symptomen, effect op heropnames en mortaliteit? ***Hoofdstuk 7*** beschrijft de uitkomsten van het COACH onderzoek. In dit onderzoek zijn twee verschillende interventies (basiszorg en intensieve zorg door een hartfalenverpleegkundige) vergeleken met zorg zoals dit in Nederland gebruikelijk is (controle bij de cardioloog). Verondersteld werd dat voorlichting en begeleiding door hartfalenverpleegkundigen effect heeft op zowel het aantal heropnames voor hartfalen als op mortaliteit gedurende 18 maanden. In totaal zijn 1023 patiënten met hartfalen uit 17 Nederlandse ziekenhuizen gerandomiseerd en hun gegevens zijn geanalyseerd. In de periode van 18 maanden is 40% van de patiënten heropgenomen voor hartfalen of overleden: 42% in de controlegroep, 41% in de groep met de

minder intensieve en 38% in de groep met de meest intensieve begeleiding. Beide vormen van voorlichting en begeleiding hebben geen significant effect op het reduceren van heropnames en mortaliteit in vergelijking met de controlegroep. Er is wel een relevante, maar niet significante reductie in sterfte gevonden. Daarnaast is er een kleine stijging in het aantal heropnames, die echter wel korter duren. Het totale aantal dagen dat patiënten opgenomen zijn geweest of overleden zijn gedurende 18 maanden, is in de controle groep 39.960. In beide interventiegroepen is dit aantal 15% lager, maar dit verschil is niet statistisch significant.

In ***hoofdstuk 8***, tenslotte, worden de resultaten van dit proefschrift besproken waarbij aanbevelingen voor de praktijk en voor verder onderzoek worden beschreven. Het proefschrift geeft meer inzicht in de kwaliteit van leven van patiënten met hartfalen. Specifieke aandacht is uitgegaan naar de prevalentie, samenhangende factoren en de prognostische waarde van depressieve symptomen bij een relatief ongeselecteerde groep patiënten met hartfalen.
De relevantie van het onderzoek voor de dagelijkse praktijk is dat depressieve symptomen bij patiënten met hartfalen worden erkend, herkend en behandeld volgens de bestaande richtlijnen. Verder is het belangrijk dat hulpverleners alert zijn op patiënten met hartfalen die een verhoogd risico hebben op depressieve symptomen, zoals vrouwen en patiënten met andere aandoeningen naast het hartfalen (bijvoorbeeld COPD). Het routinematig screenen van patiënten met hartfalen op symptomen van depressie kan bijdragen aan het op tijd herkennen en behandelen van deze symptomen. Dit proefschrift pleit daarom voor het opnemen van het onderwerp depressie in de multidisciplinaire richtlijnen voor de diagnose en behandeling van patiënten met hartfalen en voor een multidisciplinaire benadering van deze patiënten.
Voor de toekomst is het belangrijk om verder onderzoek te doen naar de complexe samenhang tussen de ziekte hartfalen, depressieve symptomen en consequenties van beide in termen van heropnames en mortaliteit.
Tenslotte is het van belang dat nader onderzoek wordt verricht naar optimale meetmethoden van depressie en depressieve symptomen in relatie tot de samenhang met symptomen van hartfalen en naar effectieve interventies specifiek gericht op de behandeling van depressieve symptomen bij patiënten met hartfalen.

DANKWOORD

Dankwoord

Met veel plezier, opluchting en een vleugje weemoed schrijf ik dit dankwoord. Plezier, omdat het mij de gelegenheid geeft om alle mensen te bedanken die hebben bijgedragen aan het tot stand komen van dit proefschrift. Opgelucht, omdat het proefschrift nu is afgerond en er weer ruimte in het hoofd en in de agenda is om andere dingen te gaan doen. Weemoed, omdat ik steeds meer besef wat een voorrecht het was om een aantal jaren volledig te kunnen werken aan zo'n mooi wetenschappelijk onderzoek.
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Hartfalenverpleegkundigen: drs. A. Koops, mevr. A. Klungel, mevr. K van Dijk, dhr. G. Westra
Cardiologen: prof. dr. D.J. van Veldhuisen, Dr. A.A. Voors
Interviewers: Mevr. G. Feringa, Mevr. A. Schwencke, Mevr. L. Grevink, Mevr. K. Bruggink

Academisch Medisch Centrum, Amsterdam
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Cardiologen/artsen: prof. dr. J.G.P. Tijssen, dr. W. Kok, dr. L.M. Konst, dr. J. van der Sloot
Interviewers: mevr. L. IJzerman, dhr. R. Zuidervaart, mevr. E. Spoelstra, mevr. S. Stultiëns

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Interviewers: mevr. J. de Natris, drs. L. Hogenhuis

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Atrium Medisch Centrum, Heerlen

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Interviewers: drs. S. Hogenhuis, drs. E. Gaasbeek, drs. C. Beumer, mevr. B. Hoen

Jeroen Bosch Ziekenhuis, Den Bosch

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Interviewers: mevr. I. Samshuizen, mevr. D. Oosterkerk

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Cardioloog: dr. F.F. Willems
Interviewers: mevr. J. de Natris, mevr. M. Hubertus, drs. L. Hogenhuis, mevr. E. Eleveld

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Cardioloog: drs. A. Derks
Interviewers: mevr. J. Bijen, mevr. I. Horstman, mevr. A. Ottenhof, mevr. W. Bakker, mevr. B. Nijhuis

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Cardioloog: dr. L. van Wijk, dr. K. de Vries
Interviewers: mevr. S. Vennik, drs. E. Prins

Tweesteden Ziekenhuis, Tilburg

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Cardioloog: dr. J. Widdershoven
Interviewers: dhr. K. Jansen, mevr. B. de Kruijf, mevr. K. de Beer

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Interviewers: mevr. J. Hendriks, mevr. A. Lotstra, dhr. K. Terlaak

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Cardioloog: drs. D.J.A. Lok
Interviewers: mevr. L. Schoterman, mevr. M. van Buijsen, mevr. M. Scholten, dhr. H. Verheij

Wilhelmina Ziekenhuis, Assen
Hartfalenverpleegkundigen: mevr. R. Aardema, mevr. J. Veninga
Cardioloog: dr. M.L. Pentinga
Interviewers: mevr. E. Tiemes, mevr. E. de Vos, mevr. N. van der Linden, mevr. E. Voois

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Hartfalenverpleegkundigen: mevr. A. Bakker, dhr. W. Veenstra, dhr J.W. van Brakel
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Interviewers: mevr. J. Kruimink, mevr. J. Pool, mevr. R. de Heus

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Hartfalenverpleegkundigen: mevr. J. Roukema, mevr. H. Glazenburg, mevr. J. Grooters
Cardioloog: dr. Ph. van der Burgh
Interviewers: mevr. T. Meijer, mevr. H. Vroom, mevr. J. Poggenklas

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Curriculum vitae

Ivonne Lesman-Leegte werd geboren op 11 april 1967 te Uithuizen. Na het behalen van haar VWO diploma op het St. Maartenscollege te Haren (1989), is zij de Hogere Beroepsopleiding voor Verpleegkundigen (HBO-V) in Groningen gaan volgen, die zij met goed gevolg heeft afgerond. De afdeling Algemene heelkunde en vaatziekten in het Universitair Medisch Centrum Groningen (UMCG, voorheen AZG), was haar eerste werkplek. Hier heeft zij van 1989 tot 1991 als verpleegkundige gewerkt. Vervolgens, geïnspireerd door dat wat zij zag op deze afdeling, wilde zij zich meer gaan bezighouden met onderzoek in de zorg. Om hiervoor de juiste opleiding te hebben, is zij in 1991 naar Maastricht verhuist en is daar gestart met de studie Verplegingswetenschap aan de Rijksuniversiteit van Limburg. Na een onderzoeksstage in Guildford (UK) op basis van het Erasmus Exange Programme en het afronden van het afstudeeronderzoek naar 'pijn bij pasgeborenen', heeft zij deze opleiding in 1994 met goed resultaat voltooid. Vervolgens heeft zij als verpleegkundige op diverse afdelingen in het UMCG gewerkt. In 1995 is zij gestart als transfusie verpleegkundige bij de afdeling Interne Geneeskunde. In deze functie heeft zij de transitie van bloedtransfusies van de verpleegafdeling naar een nog te starten Dagcentrum Interne Geneeskunde gerealiseerd. Van 1999 tot 2002 was zij werkzaam als verpleegkundig consulent astma en COPD bij de afdeling Longziekten en bij het Coördinatie Centrum Chronisch Zieken Noord Nederland. Tevens was zij projectmedewerker op het promotie onderzoek van Dr. B.M.W. Willemse naar de effecten van stoppen met roken bij patiënten met COPD. Zij heeft daar de groepscursussen 'stoppen met roken' geleid. Tevens heeft zij individuele deelnemers aan dit onderzoek begeleid bij het stoppen met roken en heeft zij onderzoek gedaan naar hun kwaliteit van leven.
Sinds 2002 is zij betrokken bij het COACH onderzoek. Dit onderzoek is gefinancierd door de Nederlandse Hartstichting en is geïnitieerd en gecoördineerd vanuit de afdeling Cardiologie van het UMCG. In de functie als onderzoeker van de COACH is dit proefschrift tot stand gekomen.

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