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Health-related quality of life, depression, sleep and breathing disorders in the elderly. With focus on those with impaired systolic function/heart failure.

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Health-related quality of life, depression, sleep and breathing disorders in the elderly. With focus on those with impaired systolic function/heart failure

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To

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Abstract

The overall aim of this thesis was to describe the prevalence of depressive symptoms, sleep disordered breathing (SDB) and sleep complaints, as well as to investigate the prognostic value of health-related quality of life (Hr-QoL) and depressive symptoms on mortality in an elderly community living population with a focus on those with impaired systolic function/heart failure (HF). Descriptive, prognostic and explorative study designs were used to examine if a single question about global perceived health (GPH) is associated with the domains of Hr-QoL as assessed by the SF-36 (**I**), as well as to evaluate whether GPH provided prognostic information concerning cardiovascular mortality (**II**). The aim was also to evaluate if depressive symptoms are associated with mortality (**III**), and to describe the prevalence of SDB and its relationship to impaired systolic function, different insomnia symptoms, as well as excessive daytime sleepiness (**IV**).

In primary care elderly patients with HF, GPH correlated to the physical and mental aspects of Hr-QoL. Patients who rated poor GPH also scored worse physical and mental Hr-QoL compared to patients with good GPH, but the mental aspect of Hr-QoL was however not significant ($p<0.07$) (**I**). Moreover, GPH also had an independent association with cardiovascular mortality during a ten-year follow-up. Compared to patients with good GPH, those who scored poor GPH had a four times increased risk for cardiovascular mortality (**II**). A total of 24% of the patients with HF suffered from depressive symptoms, not significantly different compared to 19% among those without HF. Depressive symptoms were a poor prognostic sign during the six-year follow-up and HF patients with depressive symptoms had the highest risk for cardiovascular mortality compared to HF patients without depressive symptoms (**III**). SDB is common among elderly people living in the community, almost one quarter (23%) had moderate or severe SDB. However, people with moderate impaired systolic function had a median apnea hypopnea index that was more than twice as high compared to those with normal systolic function (10.9 vs. 5.0, $p<0.001$). No obvious associations between SDB and excessive daytime sleepiness or the insomnia symptoms; difficulties maintaining sleep; non-restorative sleep; or early morning awakenings were detected. Difficulties initiating sleep were however more common in those with moderate or severe SDB (**IV).**

GPH can be used as a simple tool in clinical routine practice as an aid in identifying patients in need of additional management. SDB is a common phenomenon among elderly people and associated with impaired systolic function, but with a limited impact on subjective sleep complaints. Depressive symptoms were shown to be a poor prognostic sign and may amplify the patient's experience of suffering. Screening for depressive symptoms could therefore be an important action in the management of patients with HF.

Keywords: elderly, cardiac function, chronic heart failure, health-related quality of life, depressive symptoms, prognosis, sleep disturbances, sleep disordered breathing

List of papers

(I) Global perceived health and health-related quality of life in elderly primary care patients with symptoms of heart failure. Accepted for publication in European Journal of Cardiovascular Nursing 2008.

(II) Global perceived health and ten-year cardiovascular mortality in elderly primary care patients with a possible heart failure. European Journal of Heart Failure 2008;10:1040-1047.

(III) Depressive symptoms and six year cardiovascular mortality in elderly patients with and without heart failure. Scandinavian Cardiovascular Journal 2007;41(5):299-307.

(IV) Sleep disordered breathing in an elderly community-living population – relationship to cardiac function, insomnia symptoms and daytime sleepiness. Submitted to Sleep Medicine August 2008.

Abbreviations

ACE	Angiotensin-converting enzyme inhibitor
AHI	Apnea hypopnoea index
ARB	Angiotensin II receptor blockers
B – blockers	Beta blockers
BNP	Brain natriuretic peptide
BP	Bodily pain (SF-36)
CI	Confidence interval
CSA/CSR	Central sleep apnoea/Cheyne stokes respiration
DIS	Difficulty initiating sleep
DMS	Difficulty maintaining sleep
DSM-IV	Diagnostic statistical manual of mental disorders-IV
EDS	Excessive daytime sleepiness
EMA	Early morning awakenings
ESS	Epworth sleepiness scale
GH	General health (SF-36)
GPH	Global perceived health
HR	Hazard ratio
Hr-QoL	Health-related quality of life
HF	Chronic heart failure
LVEF	Left ventricular ejection fraction
MCS	Mental component score (SF-36)
MH	Mental health (SF-36)
MHI	Mental health index scale (SF-36)
IQR	Interquartile range
NYHA	New York heart association functional classification
ODI	Oxygen desaturation index
OR	Odds ratio
OSA	Obstructive sleep apnoea
PCO_2	Plasma carbondioxide tension
PCS	Physical component score (SF-36)
PF	Physical functioning (SF-36)
ProANP	N-terminal atrial natriuretic peptide
PSG	Polysomnography
QoL	Quality of life
RE	Role limitations due to emotional health problems (SF-36)
RP	Role limitations due to physical health problems (SF-36)
$Sa0_2$	Oxygen saturation
SDB	Sleep disordered breathing
SF-36	Short Form-36
SF	Social functioning (SF-36)
USI-HF	Uppsala Sleep Inventory-heart failure
VT	Vitality (SF-36)

Contents

Introduction

The number of patients suffering from heart failure (HF) is steadily increasing in the western world as a consequence of improved survival following myocardial infarction, improved management of HF and longer life expectancy [1,2]. The primary goals in the management of HF patients is to prevent HF, prevent progression of HF, improve survival after HF and maintain or improve quality of life (QoL) [3]. Assessment of health-related quality of life (Hr-QoL) has therefore been recognized as an important aspect in the management of HF patients [4]. However Hr-QoL instruments are believed to be time consuming and complex to use for both clinicians and patients and are therefore rarely used in routine clinical practice [5]. New instruments that allow rapid scoring and interpretation are therefore needed [6]. Such a tool could be one question about global perceived health (GPH). It is however not known whether GPH provides relevant information about Hr-QoL and prognosis in elderly patients with HF.

Sleep changes with increasing age and as a consequence of that is the prevalence of sleep disordered breathing (SDB), including obstructive sleep apnoea and central sleep apnoea Cheyne Stokes respiration and insomnia are more frequent in elderly people [7-9]. Insomnia might be caused by SDB [10] and in the elderly is also associated with a poorer rated Hr-QoL [11]. In patients with HF, SDB has been recognized as being a major problem and some studies report SDB as being associated with insomnia [12], decreased Hr-QoL [13] and higher mortality rates [14]. Another condition more frequent among the elderly [15] as well as in patients with HF [16] is depression. Among patients with HF, depression has been found to cause decreased Hr-QoL [17] as well as being a poor prognostic sign [18]. Today the mean age for community dwelling elderly HF patients is at least 75 years [2,19]. Most studies evaluating the prevalence of SDB and its association with subjective sleep complaints such as insomnia or excessive daytime sleepiness (EDS), as well as depression and its associations to mortality, have included HF patients with a much lower mean age (60-70 years). Little is therefore known about SDB and depression in elderly HF patients. To offer effective management of elderly HF patients, healthcare professionals should have knowledge about simplified tools to assess Hr-QoL, to understand the relationship between SDB, insomnia and EDS as well as how depression impacts on mortality.

Background

Heart Failure

Definition, etiolology and epidemiology of chronic heart failure

HF is a complex syndrome and many different definitions exist [2], but one common definition describes HF as: "*A pathophysiological state in which an abnormality of cardiac functioning is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues*" [20].

Ischemic heart diseases (IHD) and hypertension are the major causes of developing HF [21,22]. Although the pathophysiological pathways may be several, there seems to be a convergent point where a structural remodelling of the myocardium has started, which leads to a pump dysfunction, or HF [23]. The dominating symptoms and signs of HF are dyspnoea, peripheral oedema and fatigue. These are however not unique for HF [2,24]. To establish the diagnosis of HF the following criteria must be fulfilled: symptoms and/or signs associated with HF together with an abnormal cardiac function, mostly assessed by the use of echocardiography [2]. Increased plasma concentrations of brain natriuretic peptides (BNP) and its precursor N-terminal fragment (NT-proBNP) have been found to reflect the cardiac dysfunction and therefore to act as an aid/a tool in the diagnosis of HF [25-27]. No definitive cut-off value has been recognized, but normal plasma concentrations of BNP or NT-proBNP in an undiagnosed patient makes HF unlikely to be the cause of the symptoms [2]. The severity of HF is mostly evaluated by the use of the New York Heart Association functional classification (NYHA) (Table 1) [2].

The prevalence of HF rises with age from 3-20 cases/1000 in the general population to >100/1000 in those aged ≥ 65 years [28]. Estimates suggest that about 4.7 million patients in the USA, and at least 150.000-200.000 or approximately 2% of the general population in Sweden, experience HF [2,29,30]. The number of hospitalizations due to a primary diagnosis of HF rose in Sweden from about 30.000 in 1987 to approximately 35.000 in 1996 [31] and in 1999 the costs for HF care were approximately 2% of the healthcare budget [32]. More recent figures estimate the annual costs for patients with HF in primary care to range between 5.0-6.7 billion SEK, 47% of these costs were due to hospital care [33]. For the patients, HF carries a worse prognosis than many common malignancies [34] and the five year survival after diagnosis was in the Framingham study 25% for men and 38 % for women respectively [1].

Table 1. Description of the New York Heart Association functional classification (NYHA) [2]

NYHA class I	No limitations, ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations
II	Slight limitation of physical activity, comfortable at rest but ordinary activities result in fatigue, dyspnoea or palpitations
III	Marked limitation of physical activity comfortable at rest but less than ordinary activities results in fatigue, dyspnoea or palpitations
IV	Unable to carry out any physical activity without discomfort, symptoms of heart failure are present even at rest with increased discomfort with any physical activity

Management of chronic heart failure

Pharmacological therapy is based on the use of angiotensin-converting enzyme inhibitors (ACE-I) and/or angiotensin II receptor blockers (ARB), Beta-blockers (B-blockers) and diuretics. ACE-I is the first line pharmacological treatment in patients with symptomatic as well as asymptomatic left ventricular dysfunction and has showed beneficial effects for survival [2]. In NYHA functional class II-IV patients, the complement of B-blockers has been found to improve survival [2]. Diuretics are essentials in the symptomatic treatment of HF when fluid overload is present as pulmonary congestion or peripheral oedema [2].

Non-pharmacological management is based on education and counselling to promote patients' self-care behaviours needed to improve or maintain health. Important topics for education for patients with HF are HF pathophysiology, monitoring of symptoms, daily weighing, pharmacological treatment, prognosis, advice about necessary life style changes such as dietary changes, fluid restrictions, as well as exercise recommendations [2,23]. Non-pharmacological management led by nurses in co-operation with doctors has been found reduce hospital admissions, as well as to improve survival rates [35] .

Health-related quality of life

Definitions of health-related quality of life

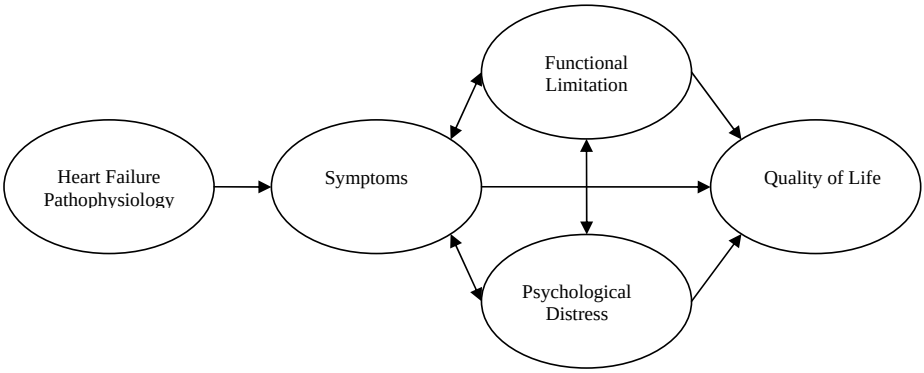
According to Zahn [36] the concept QoL has its roots in the ancient philosopher Aristotle's description of happiness. Aristotle described happiness as an activity of the soul and that a happy man also lives a good life. Qol has achieved increased attention as an important outcome in medicine [37]. One reason for this is due to a growing number of people with chronic diseases in whom freedom of disease is an impossible goal. In these patients the goal therefore must be to help them to live as well as possible, i.e. to achieve good QoL [38].

Today no consensus on how to define QoL exists, instead, these definitions vary in relation where they are used [37,39]. A simple taxonomy divides QoL into global, component and focused definitions. Global definitions can be generalized to describe the person's degree of satisfaction, well-being or happiness. In contrast, component definitions break QoL into different dimensions such as health, privacy, freedom or emotional well-being. Focused definitions are those which refer to only one or a small number of components of QoL. The most common type is the definition that refers only to the components of health, such as Hr-QoL [37].

The concept Hr-QoL originates from World Health's Organisations definition: *" health is a state of complete, physical, mental, and social well-being and not merely the absence of disease or infirmity"* [40]. Achat et al. [41] describe that the basic dimensions of Hr-QoL are functional status, well-being and general health. These dimensions are essential for a person to cope with the demands in daily life and fulfil needs and desires. According to Wilson & Cleary [42] most conceptualizations of Hr-QoL include the dimensions of physical functioning, social functioning, role functioning, mental health and general health. Wilson & Cleary [42] describe in their model that Hr-QoL is an interaction between biological and physiological factors, symptoms, functional status, general health perceptions and overall QoL. Alterations in biological and physiological factors, e.g. cells and organ systems, result in perceptions of physical and emotional symptoms, which means that focus shifts to the organism as a whole. These symptoms have an impact on the person's physical, social and psychological functional status. The next level in the model is general health perception which in turn influences the last factor in the model; the overall QoL which is a general measure of the person's well-being, happiness or life satisfaction [42]. All relationships in this model are also affected by the characteristics of the individual and environment. A test of the model in a group of HF patients found that age, symptom status, general health perceptions were the variables that explained most variance (29%) in overall QoL [43]. In that study the overall QoL was conceptualised as Hr-QoL.

Inspired by Wilson & Cleary [42], Rector [44] developed an Hr-QoL model in relation to HF (Figure 1). This model describes Hr-QoL as an interaction between HF pathophysiology, such as impaired ejection fraction or plasma concentrations of BNP, HF symptoms (dyspnoea, oedema and fatigue), functional limitation (NYHA functional classification), psychological distress (anxiousness, worry, depression) and QoL. In HF patients QoL is not a direct measure of the impaired cardiac function, but to a higher extent explained by the patients' perceptions of symptom impact, functional ability as well as their psychological reactions to the situation, or that psychological distress influences the patients' perceptions of their functional limitations and symptom experience [44]. Rector et al. [45] tested some of the relationships between these domains and QoL. HF pathophysiology, which included echocardiographic data of cardiac function and BNP, explained 17% of the variance in symptoms but only 7% in QoL. Symptoms and functional limitation (NYHA class) explained 41% of the variance in QoL. In this study the Hr-QoL instrument Minnesota Living with Heart Failure questionnaire measured the perceived QoL [45].

Figure 1. Hr-QoL model in relation to heart failure developed by Rector [44]. Adapted from: A conceptual model of quality of life in relation to heart failure. J Card Fail 2005; 11:173-176.



Measurement of health-related quality of life

The measurement of Hr-QoL can be made by the means of, generic instruments, disease-specific instruments or a battery approach [46,47]. Generic instruments are broader measures that offer the possibility to compare the scores between HF and other diseases, whereas disease specific instruments are designed to measure a specific disease's impact on Hr-QoL. The battery approach

means that multiple domain-specific instruments are used to measure the different Hr-QoL domains. One disadvantage with a battery approach is the fact that there are various opinions about what an Hr-QoL domain is and how to measure the domain [47]. In patients with HF today at least 30 different Hr-QoL instruments have been used and the most commonly used ones are the generic Short Form-36 (SF-36) and the disease-specific Minnesota Living with Heart Failure [47,48].

Assessment of Hr-QoL has been shown to obtain important prognostic information concerning mortality [49,50]. Yet, Hr-QoL instruments are rarely used in the clinical evaluation of the patient due the reason that they are too lengthy and time consuming [5]. One study found that patients with HF needed about 15 minutes to answer such instruments and that 27% also needed assistance [51]. Another study reported that 43% out of 624 HF patients did not answer the Hr-QoL questionnaires. The most common reason for not participating was weakness due to age or disease [52], indicating that Hr-QoL instruments can be demanding for elderly patients with HF. Another aspect is that most Hr-QoL instruments are developed for research and that the scores most often are presented as means. Such results are not easy to use in clinical routines, since they do not have any obvious meaning or suggest when a problem should be considered [5,6]. One suggestion is to convert the scores into meaningful responses such as severe, mild, or good [6].

Developing instruments that are easily administered and that produce clinical meaningful results have therefore been highlighted as an important aspect of future health status research [6]. A simple and easier way to measure Hr-QoL could be to use a single item that measures global perceived health (GPH). This item has been suggested to provide a patient's global perception of physical and psychosocial health [53,54]. In patients diagnosed with coronary artery diseases, GPH has been found to correlate with the physical, social and mental aspects of Hr-QoL, as measured by the SF-36 [54]. GPH has also been shown to provide prognostic information in epidemiological studies [53] as well in two studies in patients with HF [55,56]. These studies were however performed on younger patients (mean age 60-65 years) who were in clinical trials [55,56] and such populations may not be seen to be representative of HF patients in the community.

Health-related quality of life in patients with chronic heart failure

HF has a major impact on the patients' life situation and Hr-QoL [4,57]. The seriousness may also be underlined by the fact that HF patients rate poorer Hr-QoL compared to patients with other chronic diseases such as chronic pulmonary disease, arthritis and myocardial infarction [58]. Limitations in physical capacity such as walking and climbing stairs disrupts the ability to perform daily tasks such as shopping, travelling or taking part in family responsibilities or social activities [59-61]. HF

patients also report thoughts about loss of control of one's life, feelings of powerlessness [62], and a high proportion seem to suffer from anxiety and/or symptoms of depression [59,63].

HF symptoms, decreased activity status, as well as sleeping problems are some factors associated with worse scoring of Hr-QoL [61,64,65]. On the other hand internal resources such as high self-esteem and optimism [66,67] as well as external resources such as support from family and healthcare - professionals have been found to have a positive impact on Hr-QoL [61,62]. Higher age of the patient has been reported to be associated with a more positive scoring of Hr-QoL [61,63] whereas women seem to score Hr-QoL worse, compared to men [68,69].

Depression

Definition of depression.

According to the American Psychiatric Association Diagnostic Statistical Manual of Mental Disorders-IV (DSM-IV), depression is defined by the presence of a specific group of affective, cognitive, psychomotor and somatic symptoms (Table 2) [10]. The core symptoms of depression are the two affective symptoms; a depressed, sad mood and loss of interest or pleasure in nearly all activities (i.e. anhedonia). To have a diagnosis of depression different combinations of these symptoms must have been present for at least two weeks [10].

Table 2. Depression symptoms according to the American Psychiatric Association Diagnostic Statistical Manual of Mental Disorders-IV (DSM-IV) [10].

Affective symptoms (Core symptoms)
1. Depressed, sad mood most of the day. 2. Markedly diminished interest or pleasure in all or almost all activities most of the day, nearly every day.
Psychomotor, cognitive and somatic symptoms
1. Weight loss or weight gain, or decrease or increase in appetite. 2. Insomnia or hypersomnia. 3. Psychomotor agitation/retardation. 4. Fatigue or loss of energy. 5. Feelings of worthlessness or inappropriate guilt. 6. Diminished ability to think or concentrate or ambivalence. 7. Thoughts of death or suicidal ideation.

Major depression, minor depression, dysthymia, adjustment disorder, mood disorder due to a general medical condition are different types of depression diagnoses. Major depression means that the patients suffer from at least one of the core symptoms and at least four of the cognitive, psychomotor or somatic symptoms (i.e. at least a total of five symptoms). The symptomatology in minor depression in many cases is the same as in major depression, but involves a maximum of four symptoms, one of which must be a core symptom [10]. Dysthymia requires fewer symptoms than major depression (at least two) but depressed sad, mood should be present for at least two years. Adjustment disorder should be used if a major depression occurs in response to an identifiable psychological stressor. Mood disorder due to a general medical condition means that the disturbance should be a physiological consequence of the specific medical condition. This diagnosis means there must be evidence that the specific medical condition physiologically is the

cause of the depressive disorder [10,70]. Another type of depression, that is not included in the DSM-IV, is sub-threshold, or subsyndromal depression [71,72]. This type is defined by at least two or more depressive symptoms, present most of the time for at least two weeks, in persons not meeting criteria for minor depression, major depression or dysthymia [71]. The most commonly reported symptoms in patients affected by sub-syndromal depression are insomnia, fatigue, thoughts of death and trouble in concentrating [71]. Judd et al. [73] suggested that sub-syndromal depression could be an aspect of the clinical course of depression, in which some patients experienced sub-syndromal depression as the onset of a minor or major depression and in others being symptoms of a resolving episode.

Diagnosis and assessment of depression

It has been suggested dividing the measurement of depression into categorical and dimensional assessments. Categorical assessments are made by structured interviews performed by trained healthcare - professionals and decide whether the symptom profile corresponds to a diagnosis of depression. One disadvantage is that the length of the interviews has been reported to last for an average of 90 minutes [74]. Dimensional assessments are primarily based on self-reports which rank the symptom profile on a continuum of depression severity [70,75,76]. Self-reports can not be used as diagnostic tools, as these instruments use cut-off scores that distinguish between subjects with and without a presumable depressive disorder [77,78]. Dimensional instruments are today frequently used as a help to identify depression in primary care [78].

A review with the aim of describing the measurement of depression in patients with HF found that both categorical and dimensional instruments were used (Table 3). The Beck Depression Inventory was the most frequently used instrument and was included in eight of the 34 reviewed studies [79].

Table 3. Instruments used to measure depression in patients with HF [79].

Categorical instruments	**Dimensional instruments**
PRIME-MD DIS SCID CIDI	BDI CES-D HDRS GDS SDS SCL-20 HAD MO-CQ MOS-D

Categorical instruments: CIDI – Composite International Diagnostic Interview, **DIS** – Diagnostic Interview Schedule, **PRIME-MD** – Primary Evaluation of Mental Disorder; **SCID** – Structured Clinical Interview for DSM-IV.

Dimensional instruments: BDI – Beck Depression Inventory, **CES-D** – Centre for Epidemiological Studies Depression scale, **GDS** – Geriatric Depression Scale, **HAD** – Hospital Anxiety Depression Scale, **HDRS** – Hamilton Depression Rating Scale, **MO-CQ** – Maudsley Obsessive-Compulsive Questionnaire, **MOS-D** – Medical Outcomes Study-Depression, **SCL-20** – Symptom Checklist 20 Depression Scale, **SDS** – Zeung Self Depression Scale.

Depression in the general population

When using the DSM-IV criteria of depression a study reported that the total prevalence of depressive disorders among adults aged 18-64 years in Europe was approximately 8% (10% in women and 6% in men) [80]. Of these 6.6% had major depression, 1% dysthymia and 0.3% adjustment disorder. Higher rates of depression, 22.6%, were reported in a study that also screened for minor and sub-syndromal depression. In this study 14 % were found to have had one depressive symptom (8.7%), sub-syndromal depression (3.9%) or minor depression (1.5%). Major depression and dysthymia occurred in 2.3% respectively. In additional 3.9%, sub-syndromal depression occurred with a mental and/or substance disorder [73]. Depression is common among the elderly, Stordal et al. [81] showed that the prevalence of depression, in both men and women, increased by age from 4% of those aged 20-29 years to 14% and 17% of those aged 60-69 years and 70-79 years respectively. In those aged 80-89 years depression was found in 23% of the men and 18% of the women. The higher rate of depression in the elderly may be explained by factors that are common in this age group, such as poor physical health and sleep disturbances which also are associated with depression [82,83].

Depression in patients with chronic heart failure

In a recent meta-analysis of studies performed on patients with HF the total prevalence of depression was estimated as 22%, with a higher rate in women compared to men (33% vs. 26%) [84]. The prevalence varies in relation to the type of assessment [79]. In the meta-analysis the prevalence measured with dimensional instruments was estimated to be 34% whereas the rate was 19% in studies that have used categorical instruments [84]. The high prevalence of depression in patients with HF could depend on false positive ratings, especially when dimensional instruments are used [85]. This is because depression and HF to some extent share the same symptom profile, i.e. fatigue, sleep problems, weight changes [76,79]. To avoid this problem when measuring depression in patients with HF, one approach could be to exclude these symptoms [86]. Two studies in patients with HF however could not detect any major difference in the prevalence rate of depression depending on an inclusion or exclusion of the symptoms loss of appetite or fatigue/sleeping difficulties [16,87]. Similar experiences were found in a study including primary care patients suffering from different chronic diseases (IHD, diabetes and chronic pulmonary disease) and could not detect any major differences regarding the symptoms fatigue, weight/appetite and sleep disturbance between those with or without depression (major depression, dysthymia and sub-syndromal depression) [88]. In that study it was discussed that the high rates of depression in patients with chronic diseases should be

taken seriously and an exclusive approach could increase the risk of missing patients with depression [86].

One prospective study including 245 non-depressed HF patients reported that 21% developed depression within 12 months [89]. Living alone, the economic burden associated with costs of medical care, alcohol abuse and poor rated health were independent risk factors for the development of depression, and importantly, the incidence of depression rose from 7.9% in those without any risk factor to 69.2% in those with three of the four risk factors [89]. HF patients who complained of poor sleep run a threefold risk of suffering from depression [16] and a high correlation between SDB and depression has been reported [12]. Other factors associated with depression in HF patients can be age below 60-65 years, poor NYHA functional class, social conflicts and negative attitudes towards the loss of autonomy [90].

Depression in prospective studies is associated with higher levels of fatigue and breathlessness, poorer functional performance as measured by the 6-minute walk test, as well as a decreased Hr-QoL [91,92]. Table 4 shows studies (n=15) that have examined the effect of depression on patients with HF with mortality as one of the outcomes. Of these 15 studies, eight found depression to be independently associated with mortality [18,93-99]. But in the study by Faller et al. [97] significant results were found only in women. Among the seven studies that did not find depression associated with mortality [87,100-105] four found depression independently associated with the outcomes mortality/cardiac transplantation[102], mortality/functional decline [103], or mortality/hospitalizations [104,105]. Outpatients were used in five studies [18,93,96,102,104], and seven studies included inpatients. One study included both in and out patients [97] and the other studies used data from medical records or patients included in a clinical trial [87,94,95,98-101,103,105]. Three studies included patients with an age above 70 years [87,100,103].

*Table 4. Studies (n=15) that have examined the impact of depression on patients with HF with mortality as one of the outcomes. A hazard ratio (HR) **in bold** means that a significant result was found.*

Author	n, setting, age and gender	Instrument	Follow up	Risk for mortality
Freedland [87] 1991	60 inpatients, >70 years and 43% males	DIS	12 months	At follow-up, 50% of the depressed patients had died, not significantly different to 29% in the non-depressed group.
Koenig [100] 1998	107 inpatients, age range 60-89 years (55% >70 years) and 48% males	DIS CES-D	46 weeks	At follow-up 29% of the depressed patients had died, not significantly different compared to 20% amongst the non-depressed patients.
Murberg [93] 1999	119 outpatients, mean age 66 years and 71% males	SDS	24 months	**HR 1.9, p=0.002**, after adjustments for subjective health, ProANP, age and gender.

Table 4 continued

Author	n, setting, age and gender	Instrument	Follow up	Risk for mortality
Jiang [101] 2001	357 inpatients, mean age 64 years and 60% males	DIS BDI	3 and 12 months	Major depression 12 months HR 1.44, p= 0.03. Not significant after adjustments for age, NYHAl class, LVEF and etiology. BDI 3 months HR 2.3, p=0.04, adjustments unknown.
Vaccarino [103] 2001	391 inpatients, >50 years and 51% males. <65 years, n=101 65-75 years, n=106 >75 years, n=184	GDS	6 months	Mortality/ functional decline, **HR 1.82, p=0.004**. Adjusted for a wide range of different covariates.
Faris [94] 2002	396 medical records, mean age 53 years and 74% males	Medical records	48 months	**HR 3.0, p=0.004**, adjusted for demographics, medical history, NYHA class and clinical severity.
Jiang [95] 2004	291 inpatients, mean age 64 years and 64% males	BDI	12 months	**HR 1.045, p=0.003**, adjusted for state of anxiety, age, LVEF, NYHA class and etiology.
Sullivan [102] 2004	142 outpatients, mean age 54 years, and 75% males	PRIME-MD HAM-D	12 months	Mortality/cardiac transplantation **HR 2.41, p=0.009,** adjusted for age, NYHA, disease severity and serum sodium.
Murberg [96] 2004	119 outpatients, mean age 66 years, and 71 % males	SDS	72 months	**HR 1.05, p=0.016** for one unit increase in depressive symptoms. Adjusted for age, neuroticism and ProANP.
Junger [18] 2005	209 outpatients, mean age 54 years and 86 % males	HAD	36 months	**HR 1.08, p=0.02,** adjusted for NYHA functional class, LVEF and peak VO_2.
Faller [97] 2007	231 in and outpatients, mean age 64 years and 70% males	PHQ-9	986 days	**HR 4.5, p=0.02** for women, but not significant for men (HR 2.1, p=0.08). Adjusted for age, NYHA class, LVEF and etiology.
Friedman [99] 2006	153 patients included in a clinical trial, mean age 61 years, 77% males	BDI	25 months	**HR 2.4, p=0.02**. Adjusted for treatment group, atrial fibrillation, LVEF and social support.
Sherwood [104] 2007	204 outpatients, 57 years and 68% males	BDI	36 months	Mortality/cardiovascular hospitalizations **HR 1.06, p<0.001**, adjusted for age, etiology, LVEF, NT-ProBNP and antidepressants.
Jiang [98] 2007	1006 inpatients, 68 years and 62 % males	BDI	971 days	**HR 1.40, p=0.003**.Adjusted for age, LVEF, etiology, NYHA, diabetes and marital status.
Parissis [105] 2007	155 inpatients, 65 years and 83% males	BDI SDS	6 months	Mortality/HF hospitalizations **HR 1.1, p=0.02** for SDS. SDS≥40 points+ BNP≥290 pg/ml compared to SDS<40 points+ BNP≥290 pg/ml provided additive prognostic information.

Note: BDI – Beck Depression Inventory; BNP – Brain natriuretic peptide; DIS – Diagnostic Interview Schedule; GDS – Geriatric Depression Scale; HAD – Hospital Anxiety Depression Scale; HAM-D – Hamilton Depression Rating Scale; HR – Hazard ratio; LVEF – Left ventricular ejection fraction; NT-proBNP – N terminal fragment brain natriuretic peptide; NYHA – New York Heart Association functional classification; PRIME-MD – Primary Evaluation of Mental Disorder; PHQ-9 – Patients Health Questionnaire Depression Module; ProANP – N-terminal atrial natriuretic peptide; SDS – Zeung Self Depression Scale.

Sleep

Definition of normal sleep

Sleep can, according to a simple description, be seen as a reversible behavioural state of perceptual disengagement from unresponsiveness to the environment [106]. The sufficient length of sleep is debated, but an average of 7-8 hours sleep seems to be enough for adult people [107]. Alapin et al. [108] compared the total self-reported sleep time between groups of old (mean age 73 years) and young (mean age 20 years) good and poor sleepers. The total reported amount of sleep time among the young good sleepers was 7.2 hours whereas the old good sleepers reported a total sleep time of 6.8 hours. Among the poor sleepers, younger ones reported 6.1 hours total sleep time compared to 5 hours among the older ones [108].

Subjective measurement of sleep

Self-assessment of sleep can be done with questionnaires and/or sleep diaries. Questionnaires are often performed retroperspectively and include items about perceived sleep quality, sleep latency, sleep duration and habitual sleep disturbances [109,110]. A disadvantage with questionnaires is that subjects often tend to amplify their worst experiences [109]. Another problem is that many of them are poorly validated and/or unpublished and unique for each sleep centre [111,112]. The Pittsburgh sleep quality index (PSQI) is an example of a frequently used questionnaire and discussed as being a well validated sleep questionnaire [112]. PSQI includes 19 items and was primarily developed for psychiatric patients, but has today been used in various populations [112]. In sleep diaries the patient fills in his/her sleep patterns and quality as well as presleep activities during one or two weeks. Sleep diaries are user-friendly and valid tools to measure sleep disturbances (e.g., insomnia). They can however be time consuming and patients' natural sleep may be disturbed by concentrating on providing exact information on clock times and other activities [109,111].

Definition and prevalence of insomnia

Insomnia can be described as a perception by the patient that their sleep is insufficient or inadequate [113]. According to DSM-IV, insomnia is divided into difficulty in initiating sleep (DIS), difficulty in maintaining sleep (DMS), and non-restorative sleep (NRS). To be diagnosed as having insomnia, the disturbance must have been present for at least one month and have caused suffering and/or decreased functioning in social, occupational, or other important areas of functioning [10]. Insomnia can be caused by an underlying mental or somatic disorder, SDB, or abuse. In the absence of these factors, it is referred to as primary insomnia. In addition to the DSM-IV definition

of insomnia, early morning awakenings (EMA) are included in many studies as a symptom of insomnia [114].

Insomnia is the most reported sleep disturbance in the general population [115], in a survey including people older than 18 years 21 %, 16 % and 11% respectively complained of DIS, DMS and NRS for at least three times a week the last month or more [116]. In a Swedish study in people aged 65-79 years a total of 31% reported complaints of DIS. DMS was found in 43% whereas EMA occurred in 44% [9]. A high prevalence of insomnia is not necessarily predicted by age itself. Studies indicate that insomnia is associated to comorbidities common in the elderly, such as depression and somatic health problems [117,118].

Definition, measurement and prevalence of excessive daytime sleepiness

EDS is a major symptom of a sleep disorder that can be described as the propensity of falling asleep during wakefulness in situations of diminished attention [119,120]. A uniform definition of EDS is lacking [120]. Other descriptions of EDS such as drowsiness, hypersomnia or somnolence are sometimes used [121]. It is also not clarified whether fatigue which can be described as weariness, weakness or loss of energy, should or would be a part of EDS [120,122].

Objective measurement of EDS can be done with the Multiple Sleep Latency Sleep Test or the Maintenance of Wakefulness Test. The former measures the subject's speed of falling asleep in a highly soporific situation i.e. lying supine in a quiet dark room. In contrast the latter assesses the subject's ability to stay awake while sitting in a dark room [123-125]. The Stanford Sleepiness Scale and Epworth Sleepiness Scale (ESS) are two well-known rating scales for self-evaluation of EDS. The former rates the subject's level of sleepiness for the moment, while the ESS asks people to indicate their probability of falling asleep under different situations in daily life [123-125].

The prevalence varies in relation to definitions and methods of measurement, but most studies report rates between 4% and 21% [120]. In two studies in people above 65 years screened with ESS, 12% and 13% of males and 6% and 8% of females scored themselves as suffering from EDS [126,127]. Some gender differences exist, but factors commonly associated with EDS in the elderly are signs of SDB (e.g., snoring, snorting and gasping), limited capacity to perform activities of daily living and mental health problems such as depression [126,127].

Objective measurement of sleep disordered breathing

Objective measurement of SDB can be performed with four types of monitors in a variety of settings, such as a sleep laboratory, a hospital or in the patient's home. Type 1, standard

polysomnography (PSG) in a sleep laboratory includes measurement of electroencephalogram, electro-oculogram and electromyogram, electrocardiogram, heart rate, airflow, oxygen saturation ($Sa0_2$), thoracic and abdominal movements and body position. PSG is regarded as the gold standard to which other monitors are compared. Type 2 means a less comprehensive PSG that can be performed outside a sleep laboratory. Data based on a minimum of seven channels must allow scoring of sleep stages. Type 3 means a modified portable sleep apnoea monitor (polygraph) which can be used either in a sleep laboratory or outside it. Data incorporates a minimum of four channels including ventilation, respiratory movements, heart rate and $Sa0_2$. Type 4 means a simplified monitor that measures one single parameter, such as airflow or $Sa0_2$. This type is however not recommended for the investigation of SDB [128,129].

Due to increasing referrals of patients in need of an SDB examination, it has been suggested to use type 3 monitors in the patient's home [130,131]. Simple home-based sleep studies might have several advantages such as that patients may sleep better, they can regulate their own sleep times and have access to their home comforts. One major disadvantage with unattended home-based studies is a higher risk of data failure [131].

Definitions of obstructive sleep apnoea and central sleep apnoea

Obstructive sleep apnoea (OSA) is characterised by a cessation in airflow (apnoea) or reduced airflow (hypopnoea) for at least 10 seconds because of complete or partial upper airway obstruction during sleep accompanied with maintained, increased or paradoxical respiratory effort in a response to generate airflow (Figure 2). For the scoring of a hypopnoea, a more than 50% reduction in airflow together with at least 3 % fall in $Sa0_2$ or an arousal are required [128]. To establish the diagnosis and severity of OSA the number of apnoeas and hypopnoeas per hours of sleep are scored into an index, the apnoea-hypopnoea index (AHI) [128]. Today there are no universally accepted AHI thresholds for OSA [132], but an AHI ≥ 5 , ≥ 15 and >30 have been suggested to reflect mild, moderate or severe OSA [128].

Central sleep apnoea (CSA) in association with Cheyne-Stokes respiration (CSR) is a form of periodic breathing in which central apnoeic/hypopnoeic episodes for at least 10 seconds alternate regularly with hyperventilation that is characterised by a regular waxing-waning breathing pattern in tidal volume. In contrast to OSA, CSA/CSR involves reduced or no respiratory efforts during the apnoeic/hypopnoeic episode [128,133] (Figure 3). To have a diagnosis of CSA/CSR, HF or a neurological disease must be present [128].

Figure 2. Raw data from Study IV of a five minute epoch describing the respiratory pattern in obstructive sleep apnoea. The figure describes cessations in nasal airflow (1) together with continued abdominal and thorax respiratory movements (2). Note the deep fluctuations in $Sa0_2$ *(3) during the breathing pauses and the rapid increase in pulse (4) at the termination of the breathing pauses. During these 5 minutes there are a total of 17 breaths.*

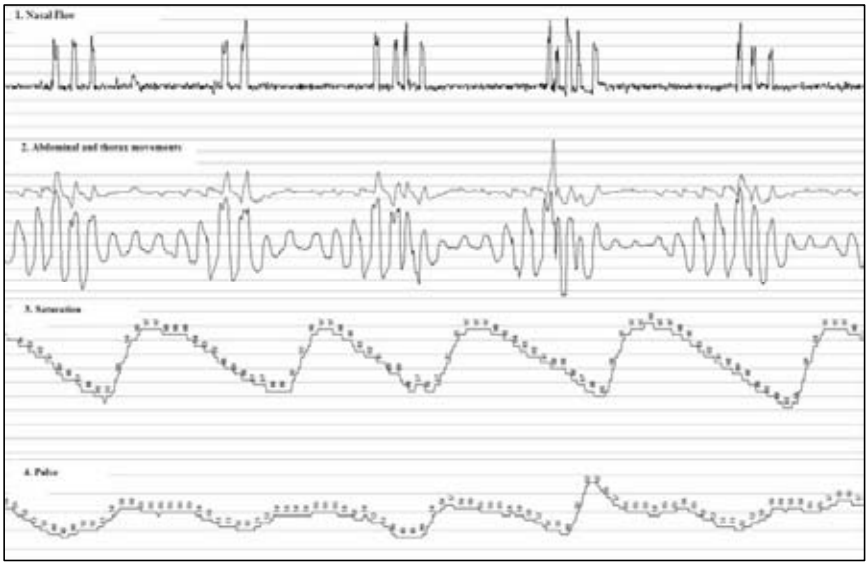
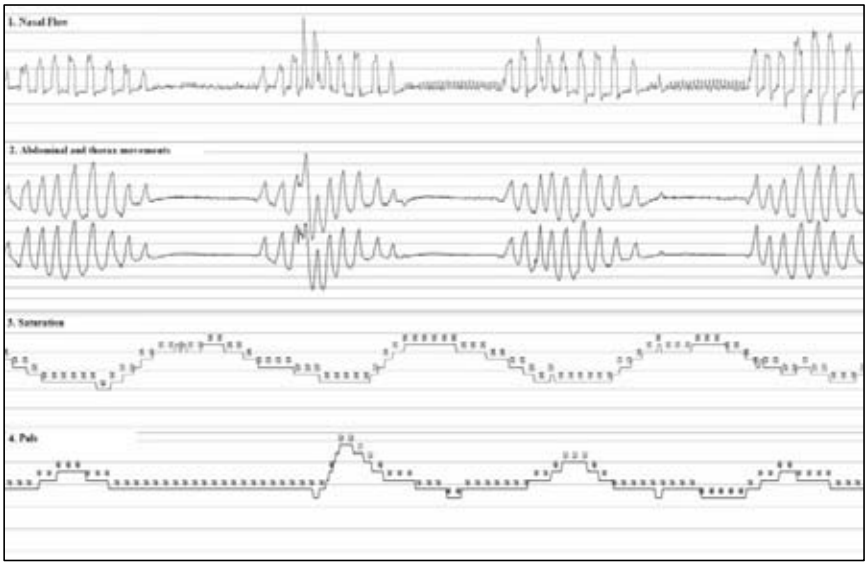


Figure 3. Raw data from Study IV of a five minute epoch describing the regular waxing-waning respiratory pattern that is characteristic for central apnoea/Cheyne-Stokes respiration. The figure describes cessations in nasal flow (1) and absence of respiratory movements during the breathing pauses (2). Note the fluctuations in $Sa0_2$ *(3) and pulse (4).*



Prevalence of sleep disordered breathing in the general population

Among middle-aged men and women it has been reported that 9% and 4% have OSA defined as an AHI≥15 [134]. The prevalence increases with age and OSA (AHI≥15) have been found in 24% and 16% of men and women aged 60-70 years [135]. It has been reported that the highest AHI levels and deepest decreases in $Sa0_2$ during the apnoeas and/or hypopnoeas become less severe as age increases [136]. This indicates that OSA may be more severe in younger persons and that the clinical impact of OSA in the elderly therefore may be weaker [136].

Less is known about the prevalence of CSA/CSR in the general population[128], but CSA/CSR seems to be less common in women [137]. A study performed in men only, reported that the prevalence rose from 0% in those 20-44 years to 12% in those aged 65-100 years [136].

Prevalence of sleep disordered breathing in patients with chronic heart failure

SDB is a common sign in patients with HF. Table 5 presents studies (n=12) that have examined the prevalence of SDB in patients with HF. To define the presence of SDB an AHI≥15 was the most utilised cut-off and was used in eight studies [132,138-144]. In these studies the prevalence of SDB ranged between 17%- 61%. An AHI≥10 was used in four studies and in these the prevalence ranged between 31%-72% [132,143,145,146]. CSA/CSR seems to be more common than OSA in patients with HF. Using the cut-off AHI≥15, the prevalence of CSA/CSR ranges between 29%-38%, whereas the prevalence of OSA ranges between 12%-32% [132,138,139,141]. Most studies (n=7) were performed in patients recruited from cardiology departments or units [138,139,141,142,144,147,148]. Three studies examined outpatients only [140,143,146], whereas another study examined both inpatients and outpatients [145]. One study examined HF patients referred to a sleep laboratory [132]. Only one study included patients with a mean age above 70 years [148].

Pathophysiology and effects of sleep disordered breathing in chronic heart failure

OSA causes mechanical, haemodynamic and neurohormonal changes that contribute to stress for the heart [149,150]. Development of a negative intrathoracic pressure induced by inspiratory efforts against the obstructed airway during apnoeas/hypopnoeas leads to increased afterload and reduced cardiac output. Elevated blood pressure and heart rate can be seen as a result of an increased sympathetic activity caused by hypoxia, hypercapnia, as well as arousals due to apnoeas/hypopnoeas. OSA has been discussed as being associated with hypertension [151], left ventricular hypertrophy [152], as well as to be a risk factor for the development of cardiovascular morbidity and mortality [150,153]. In a 10-year prospective study including OSA patients without HF, those with severe OSA (AHI>30) had an increased risk for cardiovascular mortality as compared to

matched healthy individuals [154]. In HF, patients with predominantly OSA have also been shown to have a reduced survival rate [155]. The pathophysiology of CSA/CSR in patients with HF is complex and unclear [133,156], but hyperventilation and subsequent reduction in carbon dioxide tension (PCO_2) seems to be central for the occurrence of CSA/CSR [153]. Pulmonary congestion, as a response to increased left ventricular filling pressures, activates lung receptors and stimulates to hyperventilation, resulting in a reduction of PCO_2 below the threshold required for ventilation and an apnoea/hypopnoea is initiated. During the apnoea/hypopnoea PCO_2 rises over the apnoea threshold which triggers hyperventilation and thereby a reduction in PCO_2 occurs [133,153]. Despite pathophysiological differences, CSA/CSR exerts similar sympathetic activation as in OSA [133]. The presence of CSA/CSR may therefore affect the progression of HF and impair prognosis [157]. Some studies have found that CSA/CSR in patients with HF is associated with higher rates of mortality [14,156,158,159] while others have not[160,161].

Table 5. Studies (n=12) examining the prevalence of sleep disordered breathing (SDB) in patients with chronic heart failure (HF).

Author, year	**n,setting, age and gender**	**Overnight measurement**	**SDB criteria**	**Findings**
Javaheri [147] 1995	42 (LVEF<45%) patients recruited from cardiology and medical clinics. Mean age 63 years and 100% males.	Sleep laboratory. PSG.	AHI≥20. Hypopnoeas included, $Sa0_2$ ≥4%.	45% had SDB. More than 50% of the respiratory events were classified as CSA/CSR.
Javaheri [144] 1998	81 (LVEF<45%) patients recruited from cardiology and medical clinics. Mean age 63 years and 100% males.	Sleep laboratory. PSG.	AHI≥15. Hypopnoeas included, $Sa0_2$ ≥4%. CSA/CSR group classified according to an OSA <10/h. OSA group classified as OSA>15.	51% had SDB. CSA/CSR in 40%. OSA in 11%.
Sin [132] 1999	450 HF patients referred to a sleep laboratory by a cardiologist. Mean age 57 years, 85% males and 60% in NYHA class II.	Sleep laboratory. PSG.	AHI≥10, ≥15 and ≥20. Hypopnoeas classified as CSA or OSA. CSA/CSR if >50% of the events were central. OSA if >50% of the events were obstructive.	According to AHI≥ 10, ≥15 and ≥20 SDB in 72%, 61% and 53%. CSA/CSR in 33%, 29% and 25%. OSA in 38%, 32% and 27% .
Lanfranchi [142] 2003	47 (LVEF<40%) patients recruited from a cardiology clinic. Mean age 54 years and 90% males.	Place not described. Polygraph.	AHI≥15. Hypopnoeas included, $Sa0_2$ ≥4%.	55% had SDB.
Mared [148] 2004	191 inpatients, mean age 73 years, 68 % males and 60% in NYHA class III-IV.	Cardiology clinic. Polygraph.	CSA/CSR>10% of recorded time in bed. CSA-CSR respiration described as gradual waxing and waning of respiration followed by CSA or hypopnoea. OSA classified as CSA/CSR<10%.	CSA/CSR were found in 66%. Of these 31% had CSA/CSR>50% of the recorded time.

Table 5 continued

Author, year	n,setting, age and gender	Overnight measurement	SDB criteria	Findings
Quintana-Gallego [143] 2004	75 (LVEF<45%) outpatients, mean age 56 years, 65% males and 86% in NYHA class I-II.	Sleep laboratory PSG. Home-based polygraph.	AHI≥5, ≥10, ≥15. Hypopnoeas classified as OSA or CSA, including $Sa0_2$ ≥4%. OSA diagnosed if mixed and obstructive events represented>29% of all events. CSA/CSR diagnosed if >70% of the events were central.	AHI≥5, ≥10 and ≥15 and PSG; SDB in 53%, 39% and 25%. AHI ≥10, CSA/CSR in 82% and OSA in 18%. Polygraph SDB in 44%, 31% and 17%.
Ferrier [146] 2005	53 (LVEF<45%) outpatients mean age 60 years, 77% males and 75% in NYHA class I-II.	Sleep laboratory PSG.	AHI≥10. Hypopnoeas included $Sa0_2$ ≥3%. CSA group classified according to CSA>50%. OSA group classified according to OSA>50%.	68% had SDB. CSA/CSR in 15%. OSA in 53%.
Javaheri [141] 2006	100 (LVEF<45%) patients recruited from primary and cardiology clinics.	Sleep laboratory PSG.	AHI≥15. Hypopnoeas classified as OSA or CSA. Hypopnoeas included $Sa0_2$≥ 4%. CSA group classified according to CSA>50% and OAHI <10/h. OSA group classified as OAHI>15.	49% had SDB. CSA/CSR in 37%. OSA in 12%.
Schulz [145] 2007	203 (LVEF<40%) in and outpatients, 75% males, mean age 65 years, NYHA class II-III.	In hospital or home-based polygraph. A total of 82% were registered at hospital.	AHI≥10. Hypopnoeas classified as OSA or CSA. OSA if AHI>10 and CSA<50 of the total AHI. CSA if OSA AHI<10 and CSA AHI>50% of total AHI.	71% had SDB. CSA/CSR in 28% OSA in 43%.
Oldenburg [139] 2007	700 (LVEF<40%) inpatients, mean age 64 years, 80% males, NYHA class II-IV.	In hospital polygraph.	AHI ≥5, ≥15. Hypopnoeas included $Sa0_2$ ≥ 4%	SDB (AHI ≥5) in 76% SDB. CSA/CSR in 40% and OSA in 36%. SDB (AHI≥15) in 51%. CSA/CSR in 32% and OSA in 19%.
Vazir [138] 2007	55 (LVEF<45%), patients recruited from cardiology clinics, 100% males, mean age 61 years, NYHA class II.	Sleep laboratory PSG.	AHI≥5, ≥15,>30 Hypopnoeas classified as OSA or CSA, including $Sa0_2$ ≥ 4%. CSA and OSA classified if apnoeas and hypopnoeas >50%.	AHI≥5, ≥15, >30 SDB in 80%, 53% and 22%. Cut-off AHI ≥15, CSA/CSR in 38% and OSA in 15%.
Rao [140] 2006	84 (LVEF<40%) outpatients, mean age 69 years, 86% males, NYHA class I-IV.	At home Polygraph	AHI≥15 Hypopnoeas were not differentiated as OSA or CSA. Hypopnoeas included $Sa0_2$ ≥4%	24% had SDB.

Note: AHI – Apnoea hypopnoea index; CSA – Central sleep apnoea; CSA/CSR – Central sleep apnoea-Cheyne-stokes respiration; LVEF – Left ventricular ejection fraction; HF – Heart failure; NYHA – New York Heart Association functional classification; OSA – Obstructive sleep apnoea; SDB – Sleep disordered breathing; PSG – Polysomnography

Insomnia, excessive daytime sleepiness and sleep disordered breathing in patients with heart failure

A HF patient's sleep can be affected by problems that occur in daily life, worries and negative thoughts related to the disease itself, as well as of dyspnoea, coughing, dysrhythmia and nocturia [162]. About one quarter report being awake 1-3 hours per night [65] and higher percentages of activity after sleep onset are found compared to patients without HF [163]. Almost 60% of the HF patients report trouble with sleeping, or not getting enough of sleep at least 3-4 times a week [164,165]. In a study by Broström et al. [65] major complaints of DMS were the most commonly reported insomnia type, reported in 23% of the men and 20% of the women. The prevalence of self-rated EDS is high and rates range between 21% [65] to 44 % [163]. The relationship between SDB, insomnia and EDS, in patients with HF is however sparsely studied and inconclusive. One study reported that HF patients with SDB rated poorer subjective sleep quality [12]. More subjectively scored EDS have been found in HF patients with OSA compared to patients with CSA/CSR and [145] and others have found those with CSA/CSR to have more EDS [13,166]. In another study SDB was not associated with subjectively scored EDS, despite objective evidence of EDS [167]. In other studies no associations between SDB and patients who subjectively scored EDS were found [140,146].

Aims of the thesis

The overall aim of this thesis is to describe the prevalence of depressive symptoms, SDB and sleep complaints, as well as to investigate the prognostic value of Hr-QoL and depression on mortality in an elderly community living population with the focus on those with impaired systolic function/heart failure.

The specific aims are:

- To examine whether a single question about GPH is correlated to the domains of Hr-QoL as assessed by the SF-36 and whether the scores in these domains differed from the different scores of the GPH in relation to LVEF.
- To examine whether GPH can provide prognostic information concerning cardiovascular mortality over ten-year follow-up in elderly patients in primary health care with possible HF.
- To evaluate whether depressive symptoms in elderly primary care patients with HF in the community are associated with increased mortality.
- To describe the prevalence of SDB and its relationship to impaired systolic function in an elderly community living population.
- To describe the relationship between SDB and the different insomnia symptoms as well as EDS in an elderly community living population.

Material and Methods

Population and investigations

Population

All subjects in this study were elderly persons who lived in a rural community with 10 300 inhabitants in the southeast of Sweden. All participants were included and examined between 1995-1996 (population I) or 2003-2005 (population II). Figure 4 describes the inclusion of the participants and the different examination forms.

Data from population I were used in Papers I, II and III. Characteristics of the 510 patients are described in Table 6. All patients were chosen from a cohort of 1168 patients between 65 and 82 years of age who attended a primary care centre because of symptoms and/or signs associated with HF (dyspnoea, fatigue and/or peripheral oedema). All patients, in whom HF could not be ruled out by scrutinizing patient documentation and finding other obvious explanatory diagnoses such as pneumonia or malignant diseases among others, were invited to participate. Out of 548 patients who received an invitation, 510 agreed to participate (participation rate 93%). Reasons for not participating were transport problems, severe illness or mental insufficiency [24].

Data from population II were used in Paper IV and data were collected during the years 2003-2005. All participants in population II were primarily included in a study that took place in the years 1998-2000. In that study all inhabitants between 65-82 years were invited for a clinical and echocardiographic examination. A total of 1130 individuals were contacted and of those 876 agreed to participate (participation rate 78%). Between the years 2003 to 2005 this cohort was contacted again and invited to another clinical and echocardiographic examination. Totally 675 subjects agreed to participate. Reasons for not participating were death, had moved to nursing homes or left the area, or not showing up. A total of 346 (participation rate 51%) subjects also accepted the invitation to have their breathing pattern during sleep recorded. Basic characteristics of those included in the sleep study are presented in Table 7.

Figure 4. Describing the inclusion of study populations I and II. The figure also describes the different examination forms.

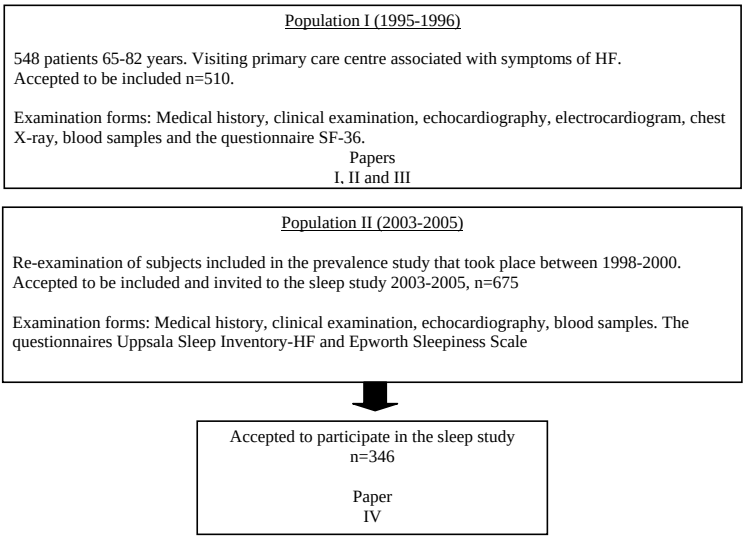


Table 6. Basic characteristics of study population I (n=510).

Variable	**Number**
Male/Female, n (%)	266 (52)/244 (48)
Age, SD	73±6
NYHA	
I, n (%)	224 (44)
II, n (%)	218 (43)
III, n (%)	68 (13)
LVEF	
≥50%, n (%)	363 (71)
40%-49%, n (%)	61 (12)
<40%, n (%)	63 (12)
LVEF not evaluated, n (%)	24 (5)
Systolic blood pressure, mean SD	158±16
Diastolic blood pressure, mean SD	86±8
Diabetes, n (%)	106 (21)
Ischaemic heart disease, n (%)	157 (31)
Hypertension,n (%)	453 (89)
ACE-I, n (%)	168 (33)
B-blockers, n (%)	203 (40)
Diuretics, n (%)	231 (42)
Digitalis, n (%)	55 (11)

Note: ACE-I – Angiotensin converting-inhibitors; B-blockers – Beta-blockers; LVEF – Left ventricular ejection fraction; NYHA – New York Heart Association functional classification; SD – Standard deviation.

Table 7. Basic characteristics of the subjects included in the sleep study (n=346).

Variable	Number
Male/Female, n (%)	171 (49)/175 (51)
Age, mean SD	78±3
NYHA I, n (%) II, n (%) III, n (%)	 189 (54) 103 (30) 54 (16)
LVEF ≥50%, n (%) 40%-49%, n (%) <40%, n (%)	 291 (84) 33 (10) 22 (6)
Systolic blood pressure, mean SD Diastolic blood pressure, mean SD	148±19 74±9
Diabetes, n (%) Ischaemic heart disease, n (%) Hypertension, n %) Respiratory disease, n (%) TIA/stroke, n (%)	82 (24) 90 (26) 250 (72) 60 (17) 33 (9)
ACE-I/ARB, n (%) B-blockers, n (%) Diuretics, n (%) Digitalis, n (%)	93 (27) 131 (38) 120 (35) 18 (5)

Note: ACE-I/ARB – Angiotensin converting-inhibitors/Angiotensin receptor-blockade; B-blockers –Beta-blockers; LVEF – Left ventricular ejection fraction; NYHA – New York Heart Association functional classification; SD – Standard deviation; TIA/stroke – Tran´s- ischaemic attack/stroke.

Clinical examination and comorbidities

All patients (populations I and II) were examined by an experienced cardiologist, who took a new patient history and performed a clinical examination. The examination included electrocardiogram, blood sampling and measurement of blood pressure, length and weight. All participants also underwent standard physical assessment of functional status, i.e. New York Heart Association Functional Classification. Doppler echocardiographic examinations were used to determine left ventricular ejection fraction (LVEF). In this thesis LVEF≥ 50% corresponded to normal systolic function, LVEF 40-49% corresponded to mildly impaired systolic function and LVEF<40% corresponded to a moderately impaired systolic function.

Diabetes mellitus was defined as ongoing treatment for diabetes or a fasting blood glucose concentration ≥ 7 mmol/L. Hypertension was defined if the patient had a previous diagnosis, or had a blood pressure of more than 165/95 mm/hg (Paper I) or 140/90mm Hg (Papers II, III and IV). Participants with a history of angina pectoris, or myocardial infarction, or coronary angioplasty, or coronary bypass surgery. Respiratory disease was established if the participant had a diagnosis, or was undergoing treatment for chronic pulmonary disease or asthma. TIA/stroke was defined if the participants had a diagnosis of TIA, or stroke.

Health-related quality of life and global perceived health

Hr-QoL was measured with the generic instrument SF-36. The 36 item instrument includes eight domains of Hr-QoL: physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional health problems (RE) and mental health (MH). These domains form two higher order components: physical component score (PCS) and mental component score (MCS) [168]. The scores are transformed into values of 0-100, with a higher score indicating a better Hr-QoL [169]. SF-36 is a well established and a frequently used instrument and has been found to have good reliability and validity [168-170].

The first item in SF-36 concerning current health status is; "In general, would you say your health is…", was used to measure GPH[169] . In answering the item patients rank their health as excellent, very good, good, fair or poor. In this thesis a patient reporting "excellent or very good" GPH was amalgamated to "good GPH" in Paper I and "very good GPH" in Paper II. Those scoring "good GPH" were in Paper I labelled "moderate GPH" and in Paper II "good GPH". Those reporting "fair or poor GPH" were amalgamated to "poor GPH" in both Papers I and II. This item has been used as a help to evaluate the criterion validity of the SF-36 [171], as well as being used as a measure of general health [56] and health perceptions [43] in patients with HF.

Depressive symptoms

The Mental Health Index-Scale (MHI) taken from the SF-36 was used to measure depressive symptoms. The MHI consists of five items and the scores can range from 0 (the worst) to 100 (best mental health) [169]. A cut-off score <60 points indicates a possible diagnosis of depression [172-174]. The MHI has been tested in a normal German population aged 18-65 years [172], elderly Swedish women 70-84 years of age [173] and functionally impaired elderly (>65 years) patients [174]. Validation to different diagnostic depression tools shows the sensitivities and specificities for the cut-off of <60 points, to range between79%-83% and 73%-84% respectively [172-174].

Sleep questionnaire

The Swedish sleep questionnaire Uppsala Sleep Inventory (USI) has previously been used in several studies to measure sleep complaints [9,175]. The original version consists of 80 items about demographic data, sleep habits and the insomnia symptoms DIS, DMS, NRS and EMA [176]. In this thesis a shortened version called USI-HF was used. USI-HF includes 27 items and was developed by Broström et al. [65] in order to reduce the burden for the respondents and to be adapted to patients

with HF. To test the construct validity of the USI-HF, a factor analysis was performed which found five dimensions: sleep complaints, physical and emotional arousals, daytime symptoms, sleep need and sleep disruption [65]. The items about, DIS, DMS, NRS and EMA are answered on a five point Likert type scale: no problems (1), small problems (2), some problems (3), great problems (4) and very great problems (5). In this thesis, scoring some problems or more indicated the presence of DIS, DMS, NRS or EMA.

Excessive daytime sleepiness

The Epworth Sleepiness Scale (ESS) was used to measure the self-reported daytime sleepiness [177]. ESS consists of eight items that describe different common daily situations in which the subjects are asked to rate the likeliness to doze off or fall asleep. The items are rated on a scale of 0-3 (0=would never doze off, 1=slight chance of dozing, 2=moderate chance of dozing and 3=high chance of dozing) and are summarised into a score between 0-24 points [177]. A cut off value of ≥10 indicates EDS [178]. ESS has been found to have good validity as well as reliability [177,179]. The instrument has been found to correlate with the Multiple Latency Sleep Test ($r=-.51$, $p<0.01$) as well as being able to discriminate between healthy controls and patients with OSA [177].

Sleep-breathing measurement

Screening for SDB was performed unattended for one night in the participants' home using the Embletta Portable Diagnostic System (Flaga Medical, Reykjavik, Iceland). The Embletta is a type three polygraph, designed to record respiratory parameters in ambulatory settings and suggested to act as a cost-effective and acceptable tool in the screening for SDB [180]. The Embletta has also been used in studies in patients with HF [139,166]

The recordings include nasal air flow pressure measured with a nasal cannula. The subject's posture and physical motions are detected by a body positioned sensor. Abdominal and thoracic movements are recorded with a respiratory inductive plethysmograph that generates a measure of the chest/abdomen circumference during ventilation. Oxygen saturation ($Sa0_2$) and pulse is measured by light transmission with a flex sensor placed on the subject's finger.

Apnoea was defined as a cessation of nasal air flow for at least 10 s. A more than 50% reduction in airflow and/or respiratory movements for at least 10 s accompanied by a ≥4% fall in $Sa0_2$ was defined as a hypopnoea. An apnoea with maintained, paradoxical or increased thoracic/abdominal respiratory movements was characterised as OSA, while apnoeas with highly

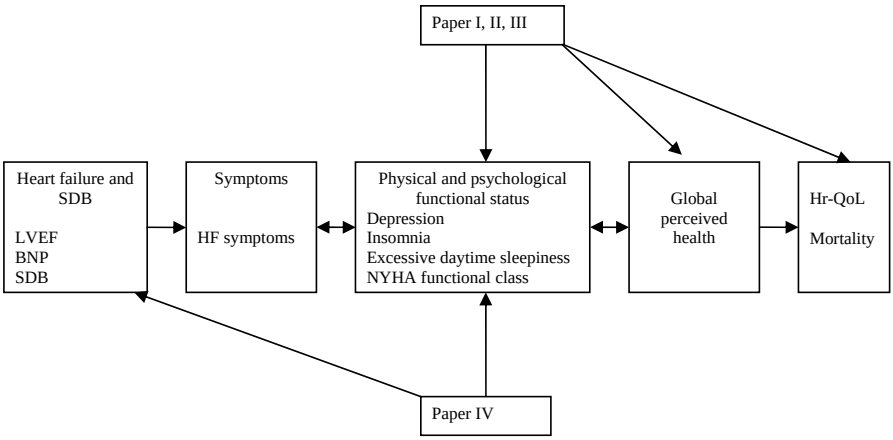
reduced or absent respiratory effort were defined as CSA/CSR [128]. The total number of apnoeas and hypopnoeas were summed and divided by the hours of total sleep time to the AHI.
All patients who had come to the clinical and echocardiographic examination received an invitation letter about the sleep study and a stamped envelope. Those who accepted the invitation were contacted by telephone and were given careful information about the procedure. In the evening, before the study, the main researcher (PJ) came and attached the device on the participants. Start and stop of the sleep registration were adapted to the participants' sleep habits. The participants also received a questionnaire asking them to estimate the time for going to bed, lights out, falling asleep and time for waking up. The device was removed the following morning, and at this visit, weight, blood pressure as well as information about pharmacological treatment was collected.

As the Embletta does not record sleep, onset and end of the study period was determined with the combination of the breathing pattern, posture, movements and information about the subject's self-estimated sleep onset and morning awakening. All recordings were scored by the main researcher (PJ).

Study design

Figure 5 below describes the overall design of the four studies in relation to the different areas of Hr-QoL. The model is inspired by the Hr-QoL model described by, Wilson & Cleary [42]and Rector [44].

Figure 5. Describing the overall design of the studies in relation to a Hr-QoL model inspired by Wilson & Cleary [42]and Rector[44],



In the HF model of Rector [44], LVEF and BNP were suggested as acting as biological variables and representing HF pathophysiology. The symptom variable includes dyspnoea, oedema and fatigue. Functional limitation was described by Rector [44] by the NYHA functional class, whereas depression, worries and anxiousness were considered as being psychological distress. In contrast Wilson & Cleary [42] divide functional limitation into physical, social, role and psychological function, as the variables SDB, insomnia or EDS, have not been used in these models. In this thesis, SDB is regarded as a biological variable whereas insomnia and EDS are seen as functional variables. General health perception was not included in Rector's model [44], but according to Wilson & Cleary [42] general health perception represents an important variable as it includes an integration of all health concepts. We therefore choose to let GPH represent this variable. The outcome in the models described by Wilson & Cleary [42] and Rector [44] is overall QoL, this outcome can be regarded as a broader concept than Hr-QoL [37]. However Rector et al. [45] as well as Heo et al. [43] both used the disease specific Hr-QoL instrument Minnesota Living with Heart Failure to be a

measure of overall QoL. In this thesis the generic instrument SF-36 was chosen to represent an overall measure of Hr-QoL. Since mortality besides Hr-QoL is another important outcome in the management of patients with HF [3], mortality was added into this model.

Paper I

Paper I used a cross-sectional descriptive design aimed to examine whether a single question about GPH correlated to the domains of Hr-QoL as assessed by the SF-36 and whether the scores in these domains differed from the different scores of the GPH in relation to LVEF. Out of the 510 patients with symptoms associated with HF, 428 (84%) could be analysed with regard to their responses to the SF-36 questionnaire, of these 16 were excluded due to lack of Doppler echocardiographic data of their LVEF. Thus the final study population consisted of 412 patients.

Paper II

Paper II used a prospective design aimed to examine if GPH could provide prognostic information concerning cardiovascular mortality over a 10-year follow-up of elderly patients with possible HF in primary healthcare. Cardiovascular mortality was defined as deaths caused by heart failure and/or fatal arrhythmias, sudden death, ischemic heart disease or cerebrovascular death. Information about cardiovascular mortality was obtained from the National Board of Health and Welfare, Stockholm, Sweden. A total of 464 persons (91%) had responded to the question concerning GPH, 16 of these patients were excluded due to lack of data concerning their LVEF. Thus the final study population consisted of 448 patients.

Paper III

A cross-sectional descriptive and prognostic study design (population I) that was used to evaluate the prevalence of depressive symptoms and their impact on cardiovascular mortality in elderly patients with symptoms associated with HF. Cardiovascular mortality was defined as in Paper II. A total of 453 patients had responded to the items in the MHI in such a manner that they could be analysed, of these 16 were excluded since their LVEF not had been evaluated. Thus the final study population consisted of 437 patients.

Paper IV

Paper IV used a cross-sectional descriptive design to examine if SDB is a sign of cardiac function or age as well as its association with insomnia and EDS. To answer such questions a sleep study was performed in elderly community living people who also had their systolic function examined. This gave us a possibility to describe and compare the prevalence of SDB in those with and without impaired systolic function/HF. Of the total 675 participants included, a total of 346 individuals accepted to participate in the sleep study. The only difference found between those participating in the sleep study and those who did not, was more history of respiratory disease (asthma or chronic obstructive pulmonary disease) (17% vs. 12%, p=0.04) in the sleep study participants. Of the 346 (participation rate 51%) sleep recordings, 15 were lost due to technical failure. Thus the final study population in Paper IV consisted of 331 persons. Sleep recording was performed over a median of 12 days (interquartile range (IQR) 12) after the clinical and echocardiographic examination.

Ethical aspects

All studies in this thesis have been planned and conducted in accordance with the declaration of Helsinki and the study protocol was approved by the Ethics Committee at the Faculty of Health Sciences, University of Linköping. All patients included in the study received both verbal and written information before accepting participation. They were also informed that their participation was voluntary and that they could withdraw at any time and that the information they provided would be treated confidentially.

Statistical processing

The statistical analyses were performed with SPSS software 13.0 or 16.0 (Statistical Package for the Social Sciences, SPSS Inc). Statistical methods are described in Table 8. Descriptive statistics are presented as the arithmetic means and standard deviations (I, II, III IV) or median and IQR (IV) for parametric data and numbers and percentages for non-parametric data (I, II). Missing values on the SF-36 were replaced with the average score across completed items in the same scale, if the respondent had answered at least 50% of the items in that scale (I, III) [181].

For comparison between group differences, a BNP values analysis was done after [10] logarithmic transformations to normality (I, II). Analysis of covariance was used to adjust for gender differences (II). Differences between three groups or more were tested using analysis of variance (II, IV) or Kruskal-Wallis (IV) and post-hoc analysis using Bonferoni was applied (I).

To explore if GPH was an independent predictor of the physical as well as mental aspects of Hr-QoL, a multiple regression analysis was performed (II). A backward logistic regression analysis was used to examine if left ventricular systolic function independently was associated to SDB. Variables having an association of $p<0.15$ were used as covariates (IV). Survival analysis was done using Kaplan-Meier survival curve analysis (I, III) and log – rank comparisons were carried out to examine differences in survival between the different GPH groups (II). Cox-proportional hazard regression analysis was performed to explore if GPH (II) and depressive symptoms (II) were independent predictors of mortality. Variables that had a univariate association to mortality of $p<0.15$ were used as covariates in the prognostic models (II, III).

Table 8. Statistical methods used in the different papers

Paper	**Statistical methods**
(I) Global perceived health and health-related quality of life in elderly primary care patients with symptoms of heart failure.	Chi^2-tests Student's t-test Pearson correlation Analysis of variance Bonferroni correction Multiple regression analysis
(II) Global perceived health and ten years cardiovascular mortality in elderly primary care patients with possible heart failure	Chi^2-tests Student's t-test Univariate logistic regression analysis Kaplan-Meier survival curves Log – rank comparisons Cox proportional hazard regression analysis
(III) Depressive symptoms and six year cardiovascular mortality in elderly patients with and without heart failure.	Chi^2-tests Student's t-test Kaplan-Meier survival curves Cox proportional hazard regression analysis
(IV) Sleep disordered breathing in an elderly community living population – relationship to cardiac function, subjective sleep complaints and daytime sleepiness.	Chi^2-tests Student's t-test Mann-Whitney U-test Spearman and Pearson correlations Analysis of variance Kruskal-Wallis Logistic regression analysis

Results - Review of the papers

Global perceived health and health-related quality of life in elderly primary care patients with symptoms of heart failure (Paper I)

On the five-graded scale of GPH, no differences were found between patients with LVEF≥50% or LVEF<40%. Combining "fair" and "poor" GPH into one category ("poor GPH"), showed that a higher percentage of the patients with LVEF<40% scored a poor GPH (54% vs. 37%, p=0.045, χ^2 =6.2).

In patients with LVEF≥50%, GPH was significantly correlated to all domains and the two composite scores of the SF-36 (Table 9). The correlation ranged from 0.33 (RE) to 0.64 (VT). For patients with LVEF<40%, GPH correlated to all domains with the exception of MH (r= 0.27, p=0.06). The lowest and highest correlations were found in the PF (0.29) and VT (0.59) domains, respectively. Multiple regression analyses using PCS and MCS as dependent variables showed that GPH compared to age, gender, NYHA functional classification, diabetes, IHD and hypertension were the strongest predictors of Hr-QoL.

Table 9. Correlations between domains and summary scores of the SF-36 and global perceived health (GPH) in patients with LVEF≥50% or LVEF<40%. N.B. ,because GPH is included in the GH domain, GH is excluded from this analysis.

SF-36 domains	LVEF≥50%	p	LVEF<40%	p
PF	0.57	<0.001	0.29	0.04
RP	0.46	<0.001	0.40	0.004
BP	0.46	<0.001	0.52	<0.001
VT	0.64	<0.001	0.59	<0.001
SF	0.39	<0.001	0.44	0.001
RE	0.33	<0.001	0.40	0.004
MH	0.43	<0.001	0.27	0.06
PCS	0.62	<0.001	0.52	<0.001
MCS	0.36	<0.001	0.42	0.002

Note: PF — Physical functioning; RP — Role limitations due to physical health problems; BP — Bodily pain; VT — Vitality; SF — Social functioning; RE — Role limitations due to emotional health problems; MH — Mental health; PCS — Physical component score; MCS — Mental component score; LVEF – Left ventricular ejection fraction

Patients with LVEF≥50% scoring a poor GPH (n=114) had significantly (p<0.001) worse scores in all domains and in the two summary scores of the SF-36, compared to those with good (n=54) or moderate GPH (n=141). Those with moderate GPH rated lower scores in the domains PF (p=0.002), BP (p=0.004), GH (p<0.001), VT (p<0.001) and the summary score PCS (p<0.001), compared to those with good GPH. In patients with LVEF<40%, those with poor GPH (n=27), had lower scores in PF, RP, BP, GH, VT, SF and PCS, compared to those with good GPH (n=9).

Compared to those with moderate GPH(n=14), differences were found in BP, GH, VT, SF and PCS respectively (Table 10).

Table 10. Describing the different SF-36 domains and summary scores in patients with LVEF<40% in relation to good, moderate or poor GPH.

	Good GPH	**Moderate GPH**	**p[a]**	**Poor GPH**	**p[b]**	**p[c]**
PF	71.7±29.5	54.9±24.2	0.4	54±26	0.05	1.0
RP	72.2±42.3	51.2±42.1	0.7	31.5±35.8	0.03	0.4
BP	88.1±17.0	69.5±26	0.2	49.9±25	<0.001	0.05
GH*	80.6±13.9	64.1±13.2	0.02	37.9±13.1	<0.001	<0.001
VT	79.4±21.5	61.8±14.2	0.1	43.5±20.9	<0.001	0.02
SF	93±16.7	86.6±23.7	1.0	68.5±20.3	0.01	0.03
RE	88.9±33.3	76.2±37.9	1.0	50.6±45.6	0.06	0.2
MH	84±23.7	74.8±15.1	0.8	72.9±19	0.4	1.0
PCS	46.5±12.4	37.8±9.2	0.1	30.1±8.6	<0.001	0.05
MCS	54.7±6.8	51.5±7.6	1.0	45.3±12.3	0.07	0.2

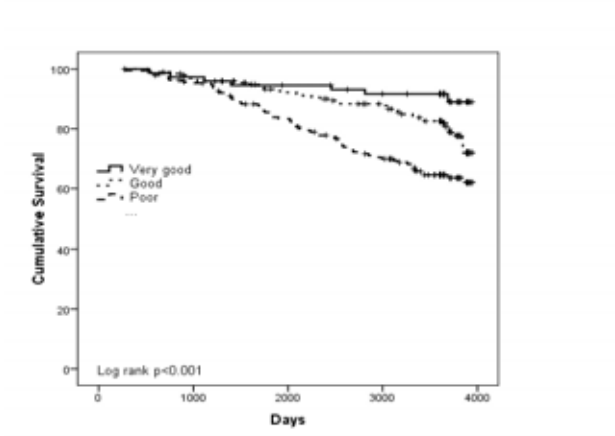
Note: PF — Physical functioning; RP — Role limitations due to physical health problems; BP — Bodily pain; GH— general health; GPH – Global perceived health; VT — Vitality; SF — Social functioning; RE — Role limitations due to emotional health problems; LVEF – Left ventricular ejection fraction; MH — Mental health; PCS —Physical component score; MCS — Mental component score.
p^a Significant good GPH compared to moderate GPH
p^b Significant good GPH compared to poor GPH
p^c Significant moderate GPH compared to poor GPH
** GPH is included in the GH domain*
All p-values adjusted for muliple comparisons with Bonferroni

Global perceived health and ten-year cardiovascular mortality in elderly primary care patients with possible heart failure (Paper II).

During the ten-year follow-up period, 167 patients (37%) suffered all-causes mortality and 108 patients (24%) suffered cardiovascular mortality (n=448).

Kaplan-Meier analysis and log rank comparisons showed a significant ($p<0.001$) association between poor GPH and cardiovascular mortality (Figure 6). Those who at baseline reported good GPH did not have significantly more cardiovascular mortality ($p=0.06$, $\chi^2=3.5$) compared to patients reporting very good GPH. Those reporting poor GPH had significantly more cardiovascular mortality ($p=0.001$, $\chi^2=11.8$) compared to those reporting good GPH. The possibility that poor GPH is only a reflection of disease severity cannot be ruled out in these analyses. Therefore we analyzed whether poor GPH was an independent predictor of cardiovascular mortality.

Figure 6. .Kaplan-Meier survival curves for ten-year all-causes mortality by range of global perceived health (GPH)). The p-value (p<0.001) is true for the association between poor GPH and cardiovascular mortality.



Cox proportional hazard regression analysis, including male gender, age, NYHA class, diabetes, LVEF and quartiles of BNP as covariates, revealed both good and poor GPH to be independent predictors of ten-year cardiovascular mortality (Table 11). In a subsequent analysis, the patient group with poor GPH was divided into fair and poor GPH. The analysis, that included the same covariates as in Table 11, revealed more than a seven-fold (HR 7.4 CI 95% 2.3-23.5) increase in the risk of cardiovascular mortality among those with poor GPH, whereas those reporting fair GPH were at four times the risk of cardiovascular mortality (HR 4.1 CI 95% 2.3-9.3).

Table 11. Cox proportional regression analysis of variables influencing ten-year cardiovascular mortality. Analysis based on those where blood samples of BNP had been obtained (n=438).

	Hazard ratio (CI 95 %)	**p**
Very good GPH	Reference group	-
Good GPH	3.4 (1.4-7.8)	0.005
Poor GPH	4.1(1.8-9.4)	0.001
Male	1.9 (1.3-2.9)	0.002
Age <70 years	Reference goup	-
Age 70-75 years	2.9 (1.5-5.8)	0.002
Age >75 years	3.6 (1.9-7.1)	<0.001
NYHA III	2.2 (1.2-4.3)	0.014
Diabetes	1.8 (1.1-2.7)	0.01
LVEF<40%	2.5 (1.5-4.1)	<0.001
BNP quartiles (q)		
q1= 0-7.2	Reference group	-
q2= 7.3-14.3	3.6 (1.6-8.0)	0.001
q3= 14.4-27.8	2.3 (1.0-5.4)	0.048
q4=>27.8	4.4 (2.0-9.7)	<0.001

Note; BNP – Brain natriuretic peptide; GPH – Global perceived health; LVEF – Left ventricular ejection fraction; NYHA-New York Heart Association functional classification

Depressive symptoms and six-year cardiovascular mortality in elderly patients with and without heart failure (Paper III).

Totally 20% (n=85) of the 437 patients screened had depressive symptoms according to the MHI scale (<60 points). In those with HF (LVEF<40%) 24% (n=13) had depressive symptoms, not significantly different to the 19% (n=72) found in those without HF (LVEF≥40%).

After six years, there was a significant difference (p=0.0001) in cardiovascular mortality in patients with and without depressive symptoms (Figure 7). A total of 24% (n=20) of those with depressive symptoms had, compared to 8% (n=31) of the patients without depressive symptoms, suffered cardiovascular mortality. To examine if depressive symptoms independently increased the risk for cardiovascular mortality Cox proportional hazard regression analysis was used. In this analysis male gender, age, NYHA functional classification III, LVEF, diabetes, ^{10}log plasma concentrations of BNP, haemoglobin, sodium and creatinine were used as covariates. In the adjusted model (Table 12), depressive symptoms were found to independently increase the risk for cardiovascular mortality threefold. .

Figure 7. Kaplan Meier analysis of cardiovascular mortality for six years in elderly patients (n=437) with symptoms and signs associated with heart failure with and without depressive symptoms.

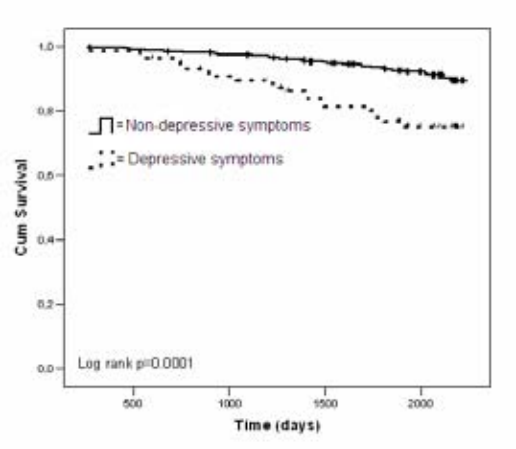


Table 12. Adjusted Cox proportional hazard regression analysis of variables influencing cardiovascular mortality during a follow-up period of almost six years.

	Hazard ratio (CI 95%)	**p**
Depressive symptoms	3.0 (1.6-5.5)	0.0001
Male gender	2.1 (1.1-4.0)	0.018
Age, per year	1.1 (1.0-1.13)	0.045
NYHA III	2.5 (1.3-5.0)	0.008
LVEF<40%	2.3 (1.1-4.6)	0.03
BNP (^{10}log)	3.0 (1.4-6.7)	0.006

Note; BNP – Brain natriuretic peptide; NYHA – New York Heart Association functional classification; LVEF – Left ventricular ejection fraction.

In a second analysis of cardiovascular mortality, patients with normal systolic (LVEF≥50%) and normal left ventricular diastolic function (n=229) with and without depressive symptoms were compared to patients with HF (LVEF<40%) (n=54) with and without depressive symptoms. According to the Kaplan-Meier analysis those with HF and depressive symptoms had the poorest survival rate compared to all groups (p=0.0001) (Figure 8). Patients with HF and depressive symptoms had, after adjustments, a more than fifteen times increased risk for cardiovascular mortality compared to patients with normal systolic and diastolic function without depressive symptoms (Table 13). Within the group of patients with HF, those with depressive symptoms ran a risk for cardiovascular mortality more than four times higher (HR 4.5 CI 95% 1.6-12.3, p=0.004) as compared to HF patients without depressive symptoms.

Figure 8. Kaplan Meier analysis of cardiovascular mortality for almost six years in patients categorized in four groups: LVEF<40%+depressive symptoms (HF+DS, n=12), LVEF<40%+non-depressive symptoms (HF+non-DS, n=41), LVEF≥ 50% and normal left ventricular diastolic function with and without depressive symptom (NF+DS, n=39, and NF+non-DS, n=190).

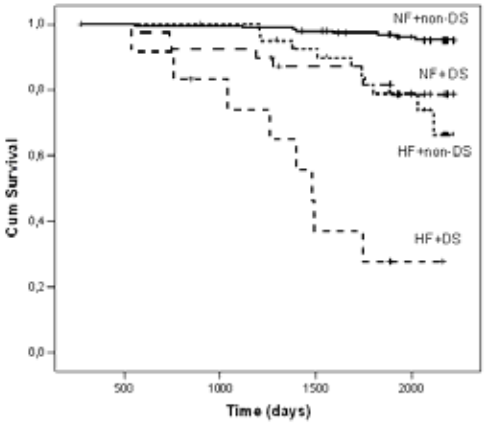


Table13. Cox proportional hazard regression analysis of elderly patients with LVEF<40% (HF) or LVEF≥ 50% and normal left ventricular diastolic function (NF) with or without depressive symptoms (DS or non-DS) concerning cardiovascular mortality during a follow-up period of six years.

	Hazard ratio (CI 95%)	**p**
NF+non-DS, (n=190)	Reference group	
HF+DS, (n=12)	15.7 (4.8-52.2)	0.0001
HF+non-DS, (n=41)	2.9 (1.0-8.4)	0.049
NF+DS, (n=39)	5.0 (1.7-14.8)	0.03
Age, per year	1.1 (1.0-1.2)	0.044
Male gender	2.2 (1.0-5.0)	0.049
NYHA class III	2.0 (0.85-4.6)	0.11
BNP (^{10}log)	3.5 (1.3-9.5)	0.013

Note;BNP – Brain natriuretic peptide; DS – Depressive symptoms;LVEF – Left ventricular ejection fraction; NF – Normal left ventricular ejection fraction and diastolic function; non-DS – non-depressive symptoms, NYHA – New York Heart Association functional classification.

Sleep disordered breathing in an elderly community living population – relationship to cardiac function, subjective sleep complaints and daytime sleepiness (Paper IV)

In the total populations screened (n=331), AHI ranged between 0 and 69 (median 6.1, IQR 12.4). A total of 32% had mild SDB, whereas moderate or severe SDB occurred in 16% and 7% of the subjects, respectively. Those with moderate impaired systolic function 36% had moderate or severe SDB. Significant associations between impaired systolic function and almost all SDB variables were found (Table 14). The median AHI was significantly ($p<0.001$) more than twice as high in the groups with mild (AHI 11.7) and moderate impaired systolic function (AHI 10.9) respectively, compared to those with normal systolic function (AHI 5.0). No differences were detected between those with mild or moderate impaired systolic function.

Table 14. Sleep study characteristics in relation to left ventricular ejection fraction LVEF categorized as normal (LVEF≥50%), mild impaired (LVEF 49-40%) or moderate impaired systolic function (LVEF<40%).

Characteristics and sleep study variables.	**LVEF≥50%**	**LVEF 49-40%**	**LVEF<40%**		
	(n=276)	(n=33)	(n=22)	p^1	p^2
OSA, (AHI≥5, 15), % (n)	36 (100)/14 (39)	46 (15)/18 (6)	36 (8)/ 18 (4)	0.58/0.74	0.48/0.44
CSA, (AHI≥5, 15), % (n)	12 (34)/5 (15)	27 (9)/21 (7)	50 (11)/18 (4)	<0.001/<0.001	<0.001/<0.001
AHI, md (IQR)	5.0 (10)	11.7 (17.2)	10.9 (17.2)	<0.001	<0.001
AI, md (IQR)	1.4 (4.8)	5.3 (16.8)	5.2 (14)	<0.001	<0.001
HI, md (IQR)	2.6 (5.3)	5.9 (5.8)	3.7 (9.6)	0.02	0.005
OAI, md (IQR)	0.6 (2.6)	2.3 (5.6)	0.85 (5.3)	0.02	0.007
CAI, md (IQR)	0.2 (0.8)	1.1 (4)	1.9 (3.4)	<0.001	<0.001
MixI, md (IQR)	0 (0.2)	0.2 (1.3)	0.2 (0.6)	<0.001	<0.001
ODI, md (IQR)	4.6 (9)	9 (19.2)	9.8 (14.9)	<0.001	<0.001
Min $Sa0_2$, mean (SD)	84.2 (5.1)	83.4 (4.3)	82.8 (4.5)	0.75	0.05
Mean $Sa0_2$, (SD)	94.4 (1.8)	94.2 (1.7)	94.3 (1.7)	0.14	0.64

Note: AHI – Apnoea-hypopnoea index; AI – Apnoea index; CAI – Central apnoea index; CSA – Central sleep apnoea; HI – Hypopnoea index; IQR – interquartile range; LVEF – Left ventricular ejection fraction; MixI – Mixed apnoea index; OAI – Obstructive apnoea index; OSA – Obstructive sleep apnoea; ODI – Oxygen desaturation index; $Sa0_2$ – Oxygen saturation; SD – standard deviation.
p^1 P-value for comparison of several groups with Chi-square or Kruskal-Wallis test.
P^2 P-value for the correlation between the different variables and the LVEF groups.

To examine if impaired systolic function independently was associated with SDB, backward logistic regression analysis was used. Besides the measures of systolic function, age, male gender, body mass index, IHD, TIA/stroke was also entered in the regression models. Independent predictors of SDB, as indicated by an AHI≥10, were mild impaired systolic function (Odds ratio (OR) 3.0, p=0.005) and moderate impaired systolic function (OR 2.7, p=0.03) and BMI (OR 1.1, p=0.03). Independent predictors of an AHI≥15 were: mild impaired systolic function (OR 2.6,

p=0.02) and TIA/stroke (OR 2.8, p=0.01), while moderate impaired systolic function (OR=2.4) only had a borderline significance (p=0.08).

OSA according to AHI≥5 and AHI ≥15 was not associated with different levels of LVEF (Table 15). However, regardless of AHI cut-off level, CSA was significantly more common in study participants with mild or moderate impaired systolic function than in those with normal systolic function (Table 13). No significant difference was found between those with mild or moderate systolic function.

Few significant associations between SDB and insomnia symptoms or EDS were revealed in the analyses (Table 15). However, DIS correlated significantly (p<0.04) with the severity of SDB. But DIS did not differ significantly between the different SDB severity groups. However, DIS was significantly more common in those with AHI≥15 compared to those with AHI<15 (p=0.024).

Table 15. Insomnia symptoms and excessive daytime sleepiness across the severity of sleep disordered breathing (SDB).

	AHI					
Characteristics	<5 **No SDB** (n=148, 45%)	5-14.9 **Mild SDB** (n=107, 32%)	15-29.9 **Moderate SDB** (n=53, 16%)	≥30 **Severe SDB** (n=23, 7%)	p^1	p^2
Insomnia symptoms:						
DIS, % (n)	36 (53)	38 (41)	51 (27)	52 (12)	0.15	0.04
DMS, % (n)	65 (96)	63 (67)	66 (35)	61 (14)	0.95	0.84
NRS, % (n)	36 (54)	41 (44)	49 (26)	52 (12)	0.27	0.06
EMA, % (n)	43 (63)	36 (38)	38 (20)	44 (10)	0.68	0.50
Excessive daytime sleepiness:						
ESS, mean (SD)	6.5 (3.8)	6.6 (3.8)	6.8 (3.5)	6.7 (4.1)	0.81	0.57
EDS, % (n)	18 (27)	21 (22)	24 (13)	22 (5)	0.80	0.36

Note: AHI – Apnoea-hypopnoea index; DIS – Difficulties initiating sleep; DMS – Difficulties maintaining sleep; EDS – Excessive daytime sleepiness; ESS – Epworth sleepiness scale; EMA – Early morning awakening; NRS – Non-restorative sleep; SD – Standard deviation; SDB – Sleep disordered breathing.
p^1 P-value for comparison of several groups with Chi-square or Kruskal-Wallis test.
p^2 P-value for the correlation between the different variables and SDB groups

Discussion

Result issues

Clinical perspectives on health-related quality of life

In the assessment of patients' health much attention has been paid to objective quantifiable information such as laboratory or clinical tests [5]. It is therefore also important to collect information regarding the individual's personal values concerning the impact of the disease, such as the patients' perception of their Hr-QoL. Assessment of HF patients Hr-QoL has been found to be one of the main objectives in nursing research [47]. Complexity in relation to the number of items and time of responding has however led to instruments measuring Hr-QoL rarely being used in clinical practice. Moreover, Hr-QoL scores are often presented as means and such scores do not indicate when a problem should be considered [5,6,182]. In this thesis (I and II) one question concerning GPH was used as a simple method to assess Hr-QoL. Moreover, the response alternatives in GPH can be said to offer a clinical meaning. Paper I evaluated if a single question about GPH could be used as a simplified and an interpretable way of measuring Hr-QoL. The results suggest that GPH could be used as an Hr-QoL measure, as it correlated to the physical, social and mental components of Hr-QoL. However in patients with impaired systolic function the MH scale was not significant, one reason for this could be due to the limited sample of patients. Patients who scored as having poor GPH also rated worse Hr-QoL than those scoring good GPH. These findings are consistent with other studies that have included patients with different chronic diseases, which also report that Hr-QoL scores decline when the rating of GPH moves from excellent to poor [54,183]. Another important question is the relevance of Hr-QoL instruments in clinical practice? [5,6]. Paper I showed GPH to be associated to cardiovascular mortality during a ten-year follow-up. After adjustments for risk factors such as gender, NYHA functional class, LVEF and plasma values of BNP, GPH remained as a predictor of cardiovascular mortality (II). The highest risk was found for those who scored poor GPH. These findings are in accordance with another study performed on patients without HF [184]. In that study patients who scored poor GPH also had the greatest risk of mortality. A relationship between between different types of single item questions about Hr-QoL and mortality in patients with HF are reported [55,56,185], however none of these studies included elderly patients in a primary care setting or classified their answers into a clinically useful response, such as good or poor.

Given its global nature, GPH should be seen as a simple screening tool to identify patients in need of improved management. Thus, GPH does not suggest in which areas of Hr-QoL that the patient needs help. Therefore GPH could be seen as the first step in measuring Hr-QoL [183]. Patients

scoring poor GPH could in a second step then have their Hr-QoL more carefully evaluated. In such secondary evaluation more focused disease-specific Hr-QoL instruments could be used.

Prevalence of depressive symptoms

Depressive symptoms were found in 20% of the total population screened (n=437) (III). Our finding is comparable to the 17% of those aged 70-79 years in the study by Stordal et al. [81] that was found with a dimensional instrument. In a recent meta-analysis about depression in patients with HF the overall prevalence was estimated to 22% [84]. In our study 24 % of those with HF had depressive symptoms (III). The prevalence of depression may vary in relation to the measurement method [79]. In Paper III a dimensional instrument was used. Studies in outpatients with HF using the same measurement approach report the prevalence to be 22% [63] and 25% [186] respectively. Depression rates seem to be higher in younger patients with HF [85]. On the other hand compared to the mean age of 73 years in our study (III), the mean age in the studies of HF outpatients was approximately 50 years [63,186]. There are few studies that have examined the prevalence of depression in elderly outpatients with HF. Turvey et al. [187] reported in a community survey of people older than 70 years that 11% of the participants with self-reported HF suffered from depression, according to a categorical instrument. However data from the meta-analysis showed that the overall prevalence using dimensional instruments was almost twice as high compared to the prevalence measured with categorical instruments (34% vs. 19%). A categorical instrument was not used in Paper III, but our prevalence is more than twice as high as Turvey's. One explanation can be due to symptom overlap between HF and depressive symptoms and that dimensional instruments to a higher extent compared to categorical instruments include patients who are falsely depressed [85]. A recent study compared the depression symptom profile in patients with depression with and without HF [188]. This study could not detect any differences in the somatic symptoms between the groups. Another explanation for higher prevalence rates when using dimensional instruments, may be that these detect people with depressive disorders that go beneath the threshold for a diagnosis of depression, such as sub-syndromal depression. Explaining problems with appetite, sleep or fatigue only as a sign of HF, may instead increase the risk that patients who suffer from depression go undetected.

Paper III showed a higher prevalence of depressive symptoms in those with HF compared to those without HF, however the difference was not significant (24% vs. 19%, p=0.35). There are few studies that have examined if depression is more common among patients with HF compared to other populations. Turvey et al. [187] examined an elderly community population and found that

11% of those with self-reported HF met the criteria for syndromal depression. This was significantly higher compared to 4.8% among people with other heart conditions and 3.2% among those with no heart conditions. As depression in the elderly is associated with factors such as the presence of chronic diseases and poor physical health [189], this could explain the lack of difference regarding depressive symptoms in Paper III. Despite the fact that all the included patients suffered from symptoms associated with HF, such symptoms are not always specific for HF, but could be indicative of other chronic diseases. The question as to whether depressive symptoms are more prevalent among those with HF compared to other patients groups or the normal population of the same age warrants further investigations.

Outcomes of depressive symptoms

To reach the goals established in the guidelines, restored or improved Hr-QoL and increased duration of life, this thesis suggests that to identify depressive symptoms in patients with HF must be regarded as an important healthcare action. Paper III showed that depressive symptoms had an independent relationship to cardiovascular mortality in elderly patients with symptoms associated with HF. The highest risk for cardiovascular mortality was found for those with moderate impaired systolic function and depressive symptoms (III). Others have also found depressive symptoms to be a prognostic marker in patients with HF [18,93-99], however none of these have studied patients older than 70 years. The importance of depressive symptoms may be further underlined by the fact that depressive symptoms can be seen as a factor that has a great influence on Hr-QoL. Strong associations between depressive symptoms and Hr-QoL in patients with HF have been described in other studies[190,191]. In the study by Muller-Tasch et al. [191] depressive symptoms had the greatest impact on Hr-QoL scores when compared to sociodemographic variables and HF severity. In a world health survey including patients with different types of chronic diseases, the lowest Hr-QoL scores were found in those with depression alone, or depression with more than one chronic disease [192].

As there is an overlap between depressive symptoms and symptoms of HF, it could be suspected that depressive symptoms are only a reflection of the severity of HF, explaining its negative impact on prognosis. Our prognostic analysis included an adjustment for both plasma values of BNP and LVEF (III) and thereby to some extent the severity of the impairment of cardiac function. Depressive symptoms may be seen as a factor that adds a further burden on the severity of disease. It has been suggested that depressive symptoms are associated with an increased sympathetic and neuroendocrine activation, which can speed the severity of the failing heart [193,194]. In patients with HF, depressive symptoms have been found to have an independent relationship,

after adjustments for BNP and comorbidities, to an increasing number of somatic symptoms [17]. The same experience was found in an prospective study where baseline depressive symptoms after six months' follow-up were associated with worse ratings on a HF symptom scale [91]. Moreover, higher rates of mortality/HF hospitalizations are reported among HF patients with depressive symptoms and plasma levels of BNP ≥290 pg/ml compared to a group of non-depressed patients with BNP ≥290 pg/ml [105]. Another burden could be that depressive symptoms may amplify the patients' perception of how HF impacts on their health and abilities to cope with the disease in a more negative manner. Several studies in patients with HF have found an association between depressive symptoms and poor self-efficacy [195], negative attitudes of impairment [196], use of negative coping styles [197] and more problems to follow medical regimen [198]. Thus the association between depressive symptoms and poor outcomes might be seen as a result of a complex relationship between physiological and behavioural factors, which also may trigger each other.

Prevalence of sleep disordered breathing in relation to impaired systolic function/heart failure

SDB has been reported as being a frequent phenomenon among patients with HF and studies show the prevalence of moderate or severe SDB to range between 17% to 61%[132,138-143]. In this thesis 36% of those with moderate impaired systolic function had moderate/severe SDB (IV). Most studies concerning HF and SDB have only included patients recruited from hospitals and who are younger than 70 years and these studies report the prevalence of moderate/severe SDB (AHI≥15) to range between 49% to 55% [138,139,141,142]. Two studies have investigated outpatients and in these 17%-25% of the patients were found to have moderate/severe SDB, [140,143] respectively. These results are lower compared to our 36% (IV). Rao et al. [140] discussed that they, to some extent, may have underestimated the prevalence since their recording method did not allow them to discriminate apnoeas from hypopnoeas. In the other study the mean age of the population was only 56 years [143], because the prevalence of SDB seems to increase by age a direct comparison with our data therefore could be problematic to perform.

SDB seems to be a more prevalent phenomenon in patients recruited in hospitals. One reason for this may be related to a higher presence of CSA/CSR. HF patients with CSA/CSR have been found to have poorer LVEF, higher plasma levels of BNP and more hospital admissions compared to those without CSA/CSR [139,166,199]. Thus, CSA/CSR may reflect the severity of HF and is therefore probably more common in unstable or hospitalised patients. In our study 18% of those with moderate impaired systolic function had CSA/CSR (IV). In another study including HF outpatients a rate of CSA/CSR was reported in 15% [146]. These rates are lower compared to studies

performed on HF patients recruited from hospital clinics, which report the rates of CSA/CSR in those with moderate/severe SDB to range between 32% and 38% respectively [132,138,139,141]. Although the prevalence of SDB in HF patients is high, it also is prevalent among the elderly in general. In our study 23% of the total population had moderate/severe SDB, a rate comparable to another study including elderly community living people [8]. One critical question that may therefore be asked is: Is SDB in patients with HF a sign of age or of the disease? An independent association between HF and SDB has been reported, but this study included participants with a mean age of about 64 years and the presence of HF was noted by self-reports [200]. Our study, which used echocardiography in elderly participants who were screened for SDB, showed that SDB was associated with impaired systolic function (IV). In Paper IV those with moderate impaired systolic function had an AHI twice as high compared to those with normal systolic function and moreover, in Paper IV it was shown that moderate impaired systolic function was independently associated with SDB (AHI≥10) (IV).

Sleep disordered breathing in relation to insomnia and excessive daytime sleepiness

Paper IV showed few associations to subjectively rated complaints of insomnia or EDS. Suggestions have been made that SDB in the elderly is age dependent and a less severe condition [136]. Higher AHI levels and deeper nocturnal oxygen desaturations, among younger compared to elderly people, have been reported [136] . In our study only 7% had severe SDB (AHI>30), which may explain why we could not detect any evident associations between SDB, insomnia or EDS. A recent study including OSA patients above and below 65 years recruited from a sleep laboratory found that the AHI correlated with EDS in those below 65 years, whereas it did not in those above 65 years. Moreover compared to a normal group of the same age OSA patients below 65 years rated poorer Hr-QoL in all scales of the SF-36 except for the GH scale [201]. In contrast those above 65 years, compared to a normal group of their age, only scored worse in the physical scales (PF and RP). There were no differences in the AHI or the number of cases with an AHI>30 in those below or above 65 years. Another aspect may be that the effect of SDB in the elderly may be diminished by the presence of other diseases or poor health. In those below 65 years the presence of EDS and BMI were the variables with the greatest influence on Hr-QoL Whereas the comorbidity index and greater nocturnal oxygen desaturations were the variables with the largest influence on Hr-QoL in the older persons [201]. In OSA patients recruited at sleep clinics as many as 50% report insomnia [202], however such high rates may be biased since more people with sleep problems may be more likely to come to a sleep clinic, thus suffering more from insomnia. The association between SDB and insomnia or EDS is poorly investigated in elderly non-sleep-clinic

populations. But our result regarding a poor association between SDB and insomnia (IV) is to some extent in accordance with another recent study that reported more insomnia in elderly community residents of a mean age of 72 years without SDB [203]. However, in that study insomnia only was measured as a composite score. In Paper IV, insomnia was analyzed with regard to the different symptoms, DIS, DMS, EMA and NRS. The results showed that DIS was more common in those with moderate or severe SDB compared to those with no or mild SDB. This result is problematic to explain since sleepiness normally can be seen as the cardinal symptom of SDB, resulting in those with moderate or severe SDB should logically not have any problems to fall asleep. One explanation for this could be that those with moderate or severe SDB actually were sleepier and therefore took more naps during daytime, which may generate problems with DIS. However this is probably not a plausible explanation because SDB was not associated to NRS or EDS (IV). In Paper IV both impaired systolic function and TIA/stroke were however associated with SDB. Patients with HF report that problems in daily life related to the impact of the disease, worries and negative thoughts can disrupt their sleep [162]. One could therefore speculate that DIS could be a sign of a disease, such as HF, more than being a sign of SDB. Because of a limited sample of HF patients, we could not specifically analyze the effects of SDB on subjective sleep complaints in those with moderately impaired systolic function (IV). The result in Paper (IV) however indicates that SDB in elderly people seems to have a limited impact on subjective health complaints, such as insomnia or EDS. The question as to whether SDB should be screened in elderly people with HF is today still unclear and the impact of different severity levels of SDB needs to be further studied.

Methodological issues

Population I consisted of participants who had visited a primary care centre due to symptoms or signs that could be attributed to HF and of these 12% had LVEF<40%. In population II only 6% had LVEF<40%. The limited number of participants with HF and moderately impaired systolic function is a limitation of this thesis. Another important aspect is the fact that the participants in population II earlier had been examined by an experienced cardiologist, both clinically as well as with Doppler echocardiography. Our population may therefore, from a cardiovascular perspective, be seen as very well examined and well treated compared to other elderly community populations. This could explain the low number of subjects with LVEF<40% in population II, as well as justifying the question if they are representative for an elderly community population. Our rate of 6.0% is comparable to the 6.8 % with LVEF<43% found in a Swedish community population

study including people aged 75 years [204]. A majority of the studies concerning HF, depressive symptoms, Hr-QoL and SDB generally include hospitalised patients who are 60-70 years of age. The mean age in HF patients who live in the community is today about 75 years. It is therefore questionable if the results in these reports can be converted to an aged community population. One advantage with this thesis is that the included participants are of the same age as HF patients in the community. Another advantage with our study design is that it allowed us to compare individuals with SDB with participants of the same age, with and without a normal systolic function investigated by Doppler echocardiography. To our knowledge no studies have used such methodology.

The instruments SF-36 and ESS are well-established instruments. Chronbach alphas for the different domains of the SF-36 in this thesis were 0.90 (PF), 0.87 (RP), 0.88 (BP), 0.78 (GH), 0.79 (VT), 0.66 (SF), 0.85 (RE) and 0.78 (MH). For ESS the Chronbach alpha in this thesis was 0.73. The USI-HF has been used in earlier studies, but needs further testing concerning validity and reliability.

In the prospective studies (II, III) depressive symptoms and GPH were only measured at baseline. Depressive symptoms as well as perceptions of health may vary over time, which limits our analyses because we cannot explore how changes in these parameters may have impacted on our outcome of interest. In this respect our methodology is not rare; most studies have used the same design in patients with HF when examining the impact of depressive symptoms on mortality (Table 4). Another limitation is that no sociological variables, such as social support, were used. Our participants had to answer many different multi-item questionnaires concerning sleep, depression, EDS and Hr-QoL. As they were old an additional questionnaire regarding social support may have been perceived as being a burden to some of our participants.

A cross-sectional design was used in Paper IV. Causal relationships between SDB and systolic function can therefore not be established. A study designed to establish such causality would have been too costly and burdensome and was therefore not the method of choice.
The evaluation of SDB was recorded unattended for one night in the participant's home with a limited polygraphic device (Embletta). Polygraphic devices have been found to be valid as well as a less costly method compared to PSG and today are a common method in the screening of SDB in patients with HF [139,140,142,145,148]. Homebased studies have also been discussed to cause less burden on the participants since they probably sleep better in their normal environment [131,180]. More time spent in a supine position in a laboratory compared to home studies has been reported and home-based studies may in a better way reflect the participant's burden of SDB [205]. Furthermore, the recruited population lived approximately 30-60 minutes travelling distance by car from our

hospital and many of them had probably refused to participate if they had to travel to the hospital to perform the sleep study. Another crucial question is if the AHI after one night of recording is representative for participants' nocturnal breathing patterns. A study performed on patients with OSA studying during four consecutive nights reported both high correlations (.91) and no significant differences in the AHI between nights [206]. On the other hand there were individual alterations showing that AHI in some people may vary especially when applying the classifications mild, moderate or severe SDB. The same study design has been performed in patients with HF. This study reported a high correlation (.94) for the AHI across the four nights. Forty two per cent of the participants who were classified as OSA or CSA/CSR on the initial night shifted their diagnoses the following nights [207]. More than one night of recording may have been a better choice, but this was not possible due to economical reasons as well as our not knowing if our participants would have accepted such a design.

Clinical Implications

Our study shows that clinical routine practice could use the question about GPH as a simple tool to assess Hr-QoL. The association between GPH and future prognosis also shows that patients' own opinion of their state of health contains important information, which could help healthcare - professionals to identify patients in need of more individualized management.

Our study shows that to relieve suffering and increase duration of life, screening and caring for depression must be seen as an important healthcare activities in the management of patients with HF. Educational programmes offering healthcare - professionals information about different strategies on how to detect and treat depression must therefore be developed.

Our study shows SDB is a frequent phenomenon among elderly people, but its effects on insomnia and daytime sleepiness are however limited.

Conclusions

- In clinical practice the single item about GPH can be used as a simple tool to assess Hr-QoL
- Those scoring poor GPH generally have worse Hr-QoL in all domains of the SF-36 compared to patients with good or very good GPH.
- Scoring poor GPH increased the risk for cardiovascular mortality fourfold during a follow-up period of ten-years.
- In elderly primary care patients with HF, 24% have depressive symptoms.
- Depressive symptoms increased the risk of cardiovascular mortality threefold, during a follow-up period of six-years.
- Those with HF and depressive symptoms had a 4.5 times increased risk for cardiovascular mortality compared to HF patients without depressive symptoms.
- Moderate or severe SDB (AHI≥15) occurred in 23 % of the population screened.
- In those with moderate impaired function (LVEF<40%) 36% had an AHI≥15. Median AHI index was more than twice as high in those with impaired systolic function compared to those with normal systolic function (LVEF≥50%) (10.9 vs. 5.0, $p<0.001$).
- SDB had no obvious relationship to subjective complaints of insomnia or EDS.

Future research

GPH has been shown to provide an overall description of the patients' Hr-QoL as well as their prognosis. But more studies are needed to evaluate the prognostic ability of GPH. Moreover perceptions of health may change over time therefore such prospective studies should also include serial measurements of GPH.

Depressive symptoms are common and have a negative impact on HF patients' Hr-QoL and survival. More studies that examine simple and effective methods to detect depression in patients with HF are therefore needed. One method that suggestively could be tested is the use of a comprehensive two item depression tool on patients who score poor GPH. Very few studies have examined the management of HF patients who suffer from depression or depressive symptoms. Today there is a need for randomised controlled trials that examine the effectiveness of antidepressant treatments as well as of non-pharmacological methods, such as stress management, cognitive behavioural therapy or exercises, in HF patients who suffers of depression.

A majority of the studies regarding the impact of SDB have been performed on younger patients recruited at hospitals. Most HF patients are however old and living in community and less is known about the impact of SDB in such populations. To improve the management of elderly HF patients, it is therefore of the highest importance to perform studies that examine the impact of SDB on subjective health complaints, such as Hr-QoL, depression as well as mortality.

This thesis only examined some correlations between SDB, insomnia and EDS, but we suggest performing studies that elucidate the associations between SDB, depressive symptoms, insomnia, EDS, HF symptoms and their effects on GPH or Hr-QoL. Such studies could be a help for healthcare professionals to understand which of these factors that are the most important determinants of HF patients, GPH or Hr-QoL.

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