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Behind the Screen

–Internet-Based Cognitive Behavioural Therapy
to Treat Depressive Symptoms in Persons with
Heart Failure

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To my family
Lina, Moa and Wilmer

The care of the body can never be separated from the care of the soul.
Florence Nightingale

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ABSTRACT

Introduction

The prevalence of depressive symptoms in persons with heart failure is higher than in age- and gender-matched populations not suffering from heart failure. Heart failure in itself is associated with an unpredictable trajectory of symptoms, a poor prognosis, high mortality and morbidity, and low health-related quality of life (HrQoL). With the addition of depressive symptoms to heart failure the negative health effects increase further. Though the negative consequences of depressive symptoms in heart failure are well known, there is a knowledge gap about the course of depressive symptoms in heart failure and about how to effectively manage these symptoms. Pharmacological treatment with serotonin reuptake inhibitors has not been able to demonstrate efficacy in persons with heart failure. In a few studies, cognitive behavioural therapy (CBT) delivered face-to-face, has demonstrated effects on depressive symptoms in persons with heart failure. However, currently there are barriers in delivering face-to-face CBT as there is a lack of therapists with the required training. As a solution to this, the use of Internet-based CBT (ICBT) has been proposed. ICBT has been shown to be effective in treatment of mild and moderate depression but has not been evaluated in persons with heart failure.

Aim

The overall aim of this thesis was to describe depressive symptoms over time and to develop and evaluate an ICBT intervention to treat depressive symptoms in persons with heart failure.

Design and Methods

The studies in this thesis employ both quantitative (Studies I, II and III) and qualitative (Studies II and IV) research methods. The sample in Study I (n=611) were recruited in the Netherlands. The participants (n=7) in Study II were recruited via advertisements in Swedish newspapers. Studies III and IV used the same cohort of participants (Study III n=50, Study IV n=13). These participants were recruited via an invitation letter sent to all persons who had made contact with healthcare services in relation to heart failure during the previous year, at the clinics of cardiology or medicine in four hospitals in southeast Sweden.

Study I had a quantitative longitudinal design. Data on depressive symptoms was collected at baseline (discharge from hospital) and after 18 months. Data on mortality and hospitalisation was collected at 18 and 36 months after discharge from hospital. Study II employed three different

patterns of design, as follows: I) The development and context adaptation of the ICBT program was based on research, literature and clinical experience and performed within a multi-professional team. II) The feasibility of the program from the perspective of limited efficacy and function was investigated with a quantitative pre-post design. III) Participants' experience of the ICBT program was investigated with a qualitative content analysis. Data on depressive symptoms was collected pre and post intervention. The time used for support and feedback was logged during the intervention, and qualitative interviews were performed with the participants after the end of the intervention. Study III was designed as a randomised controlled trial. A nine-week ICBT program adapted to persons with heart failure and depressive symptoms was tested against an online moderated discussion forum. Data on depressive symptoms, HrQoL and cardiac anxiety was collected at baseline (before the intervention started) and after the end of the intervention (approximately 10 weeks after the start of the intervention). Study IV had a qualitative design to explore and describe participants' experiences of ICBT. The participants were recruited from within the sample in Study III and all had experience of ICBT. Data collection occurred after the ICBT program ended and was carried out using qualitative interviews by telephone.

Results

The mean age of the samples used in this thesis varied between 62 and 69 years of age. Concerning the symptom severity of heart failure, most persons reported New York Heart Association (NYHA) class II (40-57%) followed by NYHA class III (36-41%). Ischaemic heart disease was the most common comorbidity (36-43%). The vast majority had pharmacological treatment for their heart failure. Six percent of the persons in Study I used pharmacological antidepressants. In Studies II and III, the corresponding numbers were 43% and 18% respectively.

Among persons hospitalised due to heart failure symptoms, 38% reported depressive symptoms. After 18 months, 26% reported depressive symptoms. Four different courses of depressive symptoms were identified: 1) Non-depressed 2) Remitted depressive symptoms. 3) Ongoing depressive symptoms. 4) New depressive symptoms. The highest risk for readmission to hospital and mortality was found among persons in the groups with ongoing and new depressive symptoms.

A nine-week ICBT program consisting of seven modules including homework assignments on depressive symptoms for persons with heart failure was developed and tested. The RCT study (Study III) showed no significant difference in depressive symptoms between ICBT and a moderated discussion forum. Within-group analysis of depressive symptoms demonstrated a significant decrease of depressive symptoms in the ICBT group but not in the discussion forum group.

The participants' experience of ICBT was described in one theme: ICBT- an effective, but also challenging tool for self-management of health problems. This theme was constructed based on six categories: Something other than usual healthcare; Relevance and recognition; Flexible, understandable and safe; Technical problems; Improvements by live contact; Managing my life better.

Conclusion

After discharge from hospital, depressive symptoms decrease spontaneously among a large proportion of persons with heart failure, though depressive symptoms are still common in persons with heart failure that are community dwelling. Depressive symptoms in persons with heart failure are associated with increased risk of death and hospitalisation. The highest risks are found among persons with long-term ongoing depressive symptoms and those developing depressive symptoms while not hospitalised.

ICBT for depressive symptoms in heart failure is feasible. An intervention with a nine-week guided self-help program with emphasis on behavioural activation and problem-solving skills appears to contribute to a decrease in depressive symptoms and improvement of HrQoL.

When ICBT is delivered to persons with heart failure and depressive symptoms the participants requests that the ICBT is contextually adapted to health problems related to both heart failure and depressive symptoms. ICBT is experienced as a useful tool for self-care and something other than usual healthcare. ICBT also requires active participation by the persons receiving the intervention, something that was sometimes experienced as challenging.

Keywords

Cognitive behavioural therapy, Depression, Heart failure, Internet-based cognitive behavioural therapy, Patients' experiences, Self-care, Telehealth

ABBREVIATIONS

CAQ	Cardiac Anxiety Questionnaire
CBT	Cognitive Behavioural Therapy
CES-D	Center for Epidemiological Studies – Depression Rating Scale
COACH	Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure
DSM	Diagnostic and Statistical Manual of Mental Disorder
ECT	Electroconvulsive Therapy
ESC	European Society of Cardiology
HrQoL	Health-related Quality of Life
ICBT	Internet-based Cognitive Behavioural Therapy
ICD	International Statistical Classification of Diseases and Related Health Problems
ICT	Information and Communication Technologies
LVEF	Left Ventricular Ejection Fraction
MADRS-S	Montgomery Åsberg Depression Rating Scale- Self-rating
MINI	Mini International Neuropsychiatric Interview
MLHF	Minnesota Living with Heart Failure questionnaire
NYHA	New York Heart Association
PHQ-9	Patient Health Questionnaire 9
QoL	Quality of Life
SSRI	Selective Serotonin Reuptake Inhibitors
TCA	Tricyclic Antidepressants
TMS	Transcranial Magnetic Stimulation
WHO	World Health Organisation

LIST OF PAPERS

- I. Johansson P, Lesman-Leegte I, Lundgren J, Hillege H L, Hoes A, Sanderman R, van Veldhuisen D J, Jaarsma T, (2013). *Time-course of depressive symptoms in patients with heart failure*. Journal of Psychosomatic Research 74 (3), 238-243.
- II. Lundgren J, Andersson G, Dahlström Ö, Jaarsma T, Kärner Köhler A, Johansson P, (2015). *Internet-based cognitive behavior therapy for patients with heart failure and depressive symptoms: A proof of concept study*. Patient Education and Counseling 98 (8), 935-942.
- III. Lundgren J, Dahlström Ö, Andersson G, Jaarsma T, Kärner Köhler A, Johansson P, (2016). *The Effect of Guided Web-Based Cognitive Behavioral Therapy on Patients With Depressive Symptoms and Heart Failure: A Pilot Randomized Controlled Trial*. Journal of Medical Internet Research 18 (8), e194.
- IV. Lundgren J, Johansson P, Jaarsma T, Andersson G, Kärner Köhler A, (2017) *Effective but challenging – Patients' experiences of Internet-based cognitive behavioural therapy on heart failure and depression*. Submitted manuscript.

INTRODUCTION

Heart Failure

Heart failure is a syndrome that can occur because of a number of cardiac causes. Most common are myocardial abnormalities as a consequence of Ischaemic heart disease or due to untreated hypertension over time. Other causes, which can lead to heart failure, are for example abnormalities in heart valves and different types of arrhythmias. In people, suffering from heart failure it is common that there is more than one myocardial abnormality present [1]. Heart failure is a complex health problem to manage, often with multiple underlying cardiac causes and comorbid with other chronic somatic diseases such as diabetes and chronic obstructive pulmonary disease [2, 3]. This complexity is also mirrored in definitions of heart failure, especially when it comes to differentiating subtypes of heart failure. The European Society of Cardiology (ESC) defines heart failure as:

a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress. (Ponikowski et al., 2016 page 2136)

Furthermore, heart failure is divided into different types. In contemporary literature, this classification is based on measures of left ventricular ejection fraction (LVEF). In the ESC's guidelines there are three such types defined: Heart failure with reduced ejection fraction (LVEF <40%); with mid-range ejection fraction (LVEF 40-49%) and with preserved ejection fraction (LVEF ≥50%) [1]. In clinical diagnosis manuals such as the international classification of diseases and related health problems -10 (ICD-10) [4] and NANDA International [5], the classification of different types of heart failure is not always based on the ejection fraction but rather on symptoms and/or different types of cardiac dysfunction. Examples of this type of classification are diastolic heart failure and systolic heart failure. 'Diastolic heart failure' refers to causes of the heart failure due to impaired left ventricular filling or suction capacity (i.e. cardiac dysfunction that appears during diastole) and is sometimes used interchangeably with the term 'heart failure with preserved ejection fraction'. Likewise, the term 'systolic heart failure' is sometimes still used interchangeably with 'heart failure with reduced ejection fraction' as the cause of the heart failure is due to cardiac dysfunction during systole. However, as it is common that persons with heart failure with reduced ejection fraction also have diastolic dysfunction and that persons with preserved ejection fraction may have subtle changes in systolic function it is recommended to classify heart failure according to the ejection fraction [1, 6]. Regardless of the exact

definition and classification used, heart failure is associated with serious consequences for the suffering persons. In this thesis, heart failure is based on the description in the overall definition provided in the ESC guidelines [1].

Epidemiology of Heart Failure

Just as the definition of heart failure varies between studies, so does the prevalence. Approximately 1-2% of the adult population in high-income countries suffers from heart failure, increasing to more than 10% in people over 70 years of age [1]. In Sweden the estimated prevalence is 2.2% [3]. In a European perspective the mean age for persons with heart failure varies but is reported to be between 66 [7] and 79 years of age [2]. In Sweden, the mean age is 80 ± 12 years and 74 ± 13 years for women and men respectively [3]. Heart failure is more common among men compared to women, with an exception for persons that have never been admitted to hospital for their heart failure and for those of the highest age [2, 3, 7]. Mortality rates vary considerably depending on whether the person has been recently hospitalised for heart failure or not. Persons managed as ambulatory patients have a one-year mortality rate of 7-13%. Persons recently hospitalised due to heart failure have a one-year mortality rate of 17-24% [2, 7] and the five-year survival rate in Sweden is 48% [3]. To compare, heart failure has higher mortality rates than common forms of cancer, such as prostatic cancer and breast cancer [8]. Persons with heart failure demonstrate an unpredictable health trajectory with one-year readmission to hospital rates reported to be between 31% [2] and 44% [7] and visits to hospital emergency departments being common (53% during a one-year period) [2]. For the northern European countries, Denmark, Norway and Sweden, the one-year hospitalisation rate is approximately 50% for persons recently hospitalised and 38% for persons managed as ambulatory patients [7]. The prevalence in middle- and low-income countries is less well studied. However, also in middle- and low-income countries heart failure contributes substantially to the healthcare burden [9].

Symptoms of Heart Failure

As mentioned in the ESC's definition of heart failure, a number of symptoms are associated with it. Typical symptoms are: breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance, fatigue, and ankle swelling. [1] The most common symptoms, reported by at least 35% of different investigated samples are: dyspnoea, fatigue, sleeping problems, pain, and psychological symptoms such as worries and feeling sad [10-12]. Alpert et al. 2017 [12] found that between seven and 19 different symptoms were common in persons with heart failure.

One way of classifying the severity of heart failure symptoms, or more exactly how the symptoms affect the person's physical function, is to use the New York Heart Association (NYHA) classification (table 1).

Table 1. Physical function classification of heart failure according to the New York Heart Association

NYHA class	Symptom description
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations or dyspnoea.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitations or dyspnoea.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitations or dyspnoea.
IV	Unable to carry out any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

NYHA – New York Heart Association

As seen in table 1 the NYHA classification ranges from no symptoms in the everyday life to symptoms at almost any given time and situation [13]. The NYHA functional classification is dynamic and persons may move between the classes as function (and symptom severity) improves and worsens [13, 14]. Thus, the presence of symptoms, their severity and their burden may vary considerably among persons with heart failure.

Symptom Burden in Heart Failure

The burden of symptoms in heart failure is often comparable with that in advanced cancer [15] and other serious diseases [12]. Persons with heart failure report that difficulties sleeping, other pain, lack of energy, feeling drowsy, and dyspnoea are the most severe symptoms experienced. It is also common for persons with heart failure to experience psychological symptoms on at least a moderately severe level. The symptoms creating most distress are dyspnoea, lack of energy, difficulties sleeping, worrying, and pain. Feeling sad and difficulties concentrating are experienced as at least quite distressing among approximately 34-44% of the heart failure population [10, 11].

Treatment of Heart Failure

Contemporary treatment of heart failure rarely offers a cure. Instead, the treatment aims to prevent development and/or worsening of heart failure, preserve cardiac function, improve clinical status, and control symptoms. Pharmacological treatment, including angiotensinogen converting enzyme inhibitors and beta-receptor blockers, is a cornerstone in the treatment of heart failure with reduced LVEF. Depending on the occurrence of symptoms and the severity of cardiac dysfunction, other pharmacological agents and devices for cardiac resynchronisation and/or defibrillation are added to the treatment. Diuretics are used to relieve symptoms of congestion. In heart failure with resistant symptoms, a left ventricular

assistive device and/or heart transplantation may be considered. For heart failure with preserved LVEF, no treatment has been shown to reduce morbidity or mortality. Therefore, treatment must focus on underlying comorbidities and symptom alleviation [1].

Alongside pharmacological treatment, there is strong evidence that aerobic exercise and the use of multidisciplinary care management are beneficial for persons with heart failure [16, 17]. Included as key components in multidisciplinary care are shared decision-making and patient involvement in symptom monitoring and the use of flexible diuretic regimes [1]. Thus, self-care is an important aspect of treatment of heart failure [18].

Living with Heart Failure

Heart failure is a serious and chronic disease. It comes with an unpredictable trajectory, a gloomy prognosis, and a high symptom burden. Heart failure also raises demands on the affected person's ability to perform self-care. From that perspective, it is not surprising that heart failure also has a significant impact on the affected person's life and health-related quality of life (HrQoL).

Living with heart failure often means a low HrQoL [11]. Persons with heart failure have lower HrQoL compared to persons with other cardiac diseases and medical illnesses [19]. Furthermore, heart failure has a serious impact on daily life [20], and HrQoL becomes worse as the heart failure progresses and physical function decreases [19, 21]. Müller-Tasch et al. 2007 [22] showed in a cross-sectional study that depressive symptoms were the main contributing factor to low HrQoL in persons with heart failure. Women and younger persons (age <55 years) are reported to have lower HrQoL compared to men and persons of higher age. Insomnia is also reported to negatively affect HrQoL in persons with heart failure [23]. Other factors such as perceived social support and comorbidities [24] and individual characteristics such as optimism, self-esteem and coping ability [23] also affect HrQoL in persons with heart failure.

Self-care is a demanding but important aspect of living with heart failure. For example, persons with heart failure often wait for days before seeking healthcare when symptoms worsen [25]. In a meta-synthesis looking at barriers and facilitators for self-care in heart failure Siabani et al. [26] found that atypical and puzzling symptoms, the complexity of self-care, insufficient knowledge, comorbidity burden, cognitive decline, and depression and anxiety hindered self-care. Furthermore, in another meta-analysis by Sedlar et al. [27] depression was the only factor significantly negatively associated with self-care behaviour in heart failure.

Qualitative studies have found that living with heart failure implies many challenges and burdens in the daily life. Adjustment of the practical management of life essentials, such as cooking and cleaning, are made due

to the heart failure. Daily tasks require more time or may not be possible without help from others. Living with heart failure also implies recurrent thoughts about life that can be both comfortable and filled with worries, sadness and fear [20, 28]. Experiencing intense negative emotions, loss of roles and social isolation is common when living with heart failure. Uncertainty regarding the future, and powerlessness are commonly described among persons living with heart failure. Adjusting life to heart failure is described as necessary to be able to go on with life. However, this adjustment is sometimes both hard and painful [29].

In essence, living with heart failure is about managing the physical, psychological and social impacts of a progressive and life-threatening disease, in which many symptoms (e.g. dyspnoea, fatigue, and depressive symptoms) are common and perceived as severe or causing distress. At the same time, the affected person must also adhere to and actively participate in a complex treatment and try to have a meaningful role in everyday life.

Depression

Depression can generally be described as an emotional state where the one affected experiences feelings of sadness and despair and/or an inability to feel enjoyment or happiness. In many situations, other feelings such as indecisiveness, fatigue and impaired ability to make decisions are included in the experience of depression. Depression is a common phenomenon in humans since most people are likely to be affected by depression-like episodes for short periods during life, e.g. in connection to the loss of loved ones or divorce. [30, 31]

The Role of Emotions in Depressive State

To understand what depression is there is a need to understand the roles of emotions in a persons life. Emotions are psychological states and behavioural outcomes that direct and/or reinforce behaviours. Experiencing emotions such as sadness, loneliness and, anxiety can be seen as a normal part of human life [32]. Emotions play an important role in regulating and activating behaviours through the intricate interaction between them and motives, emotional and behavioural responses from others and the environment. Gilbert [32] argues that emotions can be divided into three patterns:

- i) Threat-focused emotions, used to stimulate protective and/or safety-seeking behaviours.
- ii) Resource-focused emotions, corresponding to wanting, pursuing and achieving things.
- iii) Non-wanting and/or affiliative-focused emotions, corresponding to kindness, and feelings of safety and being soothed.

When an emotional reaction to a situation or event in life is beneficial for the person i.e. emotions contribute to avoiding harm, having sufficient resources or feeling connected to a social context, it can be said that the emotion and the emotional reaction are normal. In other situations, the reaction can be non-beneficial or harmful. In depression for example, the threat-focused pattern is elevated, meaning that the depressed person feels anxious, trapped, and angry in situations where these emotions are non-beneficial. At the same time, the resource- and affiliative- focused patterns are toned down, leading to a loss of drive and energy, an inability to experience joyful feelings, and feelings of loneliness and loss of connectedness.

Depressed Mood, a Normal Reaction and a Disorder

What are normal and what are abnormal emotions and emotional responses? That is a question scientists have long asked and still struggle with. However, three aspects are of interest when assessing if emotions should be considered normal or abnormal [33]:

- i) Frequency: if a person feels sad every hour of the day, or every day for a long period that is probably not a normal frequency of the emotion.
- ii) Functionality: to experience anxiety every time one leaves the home is not functional and may cause maladaptive behaviour. In contrast, experiencing anxiety at the prospect of having to go through a rough neighbourhood may be highly functional as it may cause an adaptive behaviour in the situation.
- iii) Distress: the experience of emotions is subjective. For example, some persons appreciate loneliness and may actively seek situations where they can experience it. Others may not be able to stand the thought of being lonely even for short periods.

Depression, a Phenomenon with Numerous Plausible Causes

From a biological and physiological perspective, there are a number of different mechanisms that are involved in the development and maintenance of depression.

- Genetic factors explain between 30-40% of the susceptibility to depression. However, there is no solid evidence for specific genes that cause depression.
- Stress hormones and cytokines seem to be involved in the pathophysiology of depression. However, their roles are not yet fully understood. Activation of the inflammatory response system can lead to depression-like symptoms (i.e. sickness behaviour) and this can in some cases be an instigator of depression. In other cases, elevated levels of cortisol may act as a mediator between depression and other diseases such as coronary heart disease.
- Monoamines such as serotonin, norepinephrine and dopamine affect and regulate mood and emotions. The exact role of monoamines in depression is not yet fully understood. Serotonin is the most extensively studied neurotransmitter in depression, and reduced central serotonergic functioning, including lack of some types of serotonin receptors, appears to create depressive symptoms in some people. However, the fact that not all persons with depression respond to treatment targeting the monoamine system suggests that the dysfunction in the monoaminergic system related to depression is likely to be an effect of other more primary abnormalities or dysfunctions in the brain.

Hasler 2010 [34]

Given the many coexisting theories and different research findings demonstrating associations between different neurobiological processes and depression it is unlikely that there is a single explanation of the pathophysiology of depression [34]. It is more likely that a number of different factors or a combination of factors, such as biological, psychological, and social factors, all giving rise to similar symptoms, explain the phenomenon we today describe as depression.

Diagnosis of Depression

The phenomenon of depression can appear both vague and broad. In the context of healthcare and healthcare research, it is often the variation of depression as a disorder or the presences of symptoms with a negative impact on health that is of interest. To standardise the definition of depression and the diagnosis of depression within the healthcare context, different systems of diagnostic criteria are used.

Internationally, the two most common systems are the ICD-10 and the *Diagnosis and Statistical Manual of Mental Disorder* (currently the fifth revision is being used) (DSM-5). The diagnostic criteria for 'major depressive disorder' and 'depressive episode' as the main diagnosis of depression is called in DSM-5 and ICD-10 share great similarities, although there are minor differences in the wording and structure of the criteria between the two systems [35, 36]. In this thesis, the DSM criteria have been used. According to DSM, major depressive disorder is present if, during most of the last 14 days, the person has suffered from:

- i) at least one of the two core symptoms, depressed mood and/or anhedonia (Figure 1, box A),
and
- ii) at least four other symptoms, such as feeling guilt or worthlessness, sleep disturbance, concentration problems, and/or change in psychomotor activity (Figure 1, box B).

Of interest for this thesis is also the fourth revision of DSM (DSM-IV) as this was the version of DSM in use at the start of the studies included in this thesis. The diagnostic criteria for major depressive disorder do not differ between DSM-IV and DSM-5 except that symptoms no longer have to be persistent for more than two months if they occur during bereavement in DSM-5 [37, 38].

The use of standardised diagnostic criteria in research is important as it facilitates a clear definition of what health problem and what symptoms to refer to when using concepts such as depression and depressive symptoms. Measurements of depression can be separated into categorical and dimensional assessments. Categorical assessments (e.g. Mini international Neuropsychiatric Interview (MINI)) are used to decide whether the specific symptom profile corresponds to the diagnosis of depression. The main disadvantage with categorical assessments, from a research perspective, is that they generally require trained healthcare professionals, and require more time compared to dimensional assessments. Dimensional assessments (e.g. the Patient Health Questionnaire 9 (PHQ-9) and the Montgomery Åsberg Depression Rating Scale (MADRS)) are primarily based on self-reports, ranking the specific symptoms profile on a continuum of depression severity. Thus, dimensional assessment cannot be (singlehandedly) used to set the diagnosis of depression. Instead, it provides a distinction between persons with and without a presumed depressive disorder based on cut-off scores [39]. In this thesis, with the exception of Study I, depression and depressive symptoms are based on the criteria and symptoms described in DSM-IV see figure 1.

Figure 1: Diagnostic criteria for Major Depressive Disorder according to DSM-IV.

Depressive Symptoms

The presence of a combination of emotional, cognitive and somatic symptoms constitutes the basis for the diagnosis of depression. These symptoms are often more than a quantification of the amount of sadness, guilt, or lack of happiness. Many persons that have personal experience of depression describe the depression as being in another world where one is alienated from the way others (non-depressed people) experience the world and feelings [31].

Emotional Symptoms

Depressed mood and loss of interest or pleasure in activities (i.e. anhedonia) are the two most specific symptoms of depression. Depressed mood is characterised by experiencing life and events in life in a negative way, often accompanied by feelings of not being able to interact with other people [31]. Anhedonia is characterised by the inability to experience pleasure from activities that the person usually finds enjoyable. Anhedonia may also result in the affected person appearing to not care about events in life. [30]

Other emotional symptoms of depression are suicidal ideations, and experiences of worthlessness and guilt. Even though not all persons suffering from depression have suicidal ideations, depression is one of the most common causes of suicide [30]. Regarding worthlessness and guilt, the qualitative difference in how these feelings are experienced in depression makes these experiences appear incomprehensible or inappropriate in the eyes of a non-depressed person [31].

Cognitive Symptoms

A change in psychomotor activity can manifest through slow speech and movement being markedly slower than normal for the affected person. Less common, but possible, is agitation of psychomotor activity [40]. The cognitive symptoms may also contribute to the experience of not being connected to the world of others [31]. Agitation as a depressive symptom is however questioned by some research in depression [41].

Persons affected by depression often describe problems with concentration. However, there is often a difference between self-perceived cognitive functioning among persons with depression and the level of cognitive function that can be observed by tests and measurement. This may in part be explained by the overuse of negative schema among persons with depression [40].

Somatic Symptoms

Weight changes, both increased and decreased, disturbed sleep, and loss of energy are all associated with depression [30]. Despite the heterogeneity of depressive symptom profiles (based on the DSM 5 criteria, 16,400 different profiles are at least theoretically possible), weight problems, insomnia and energy loss are common symptoms frequently reported by many persons with depression [42].

Challenges in Diagnosing Depression

The vast majority of these symptoms are not specific to depression but can occur in connection to many other health problems and diseases. This makes it somewhat complicated to set the diagnosis of depression. As long as the diagnosis criteria are purely based on symptoms, there will always be a subjective assessment as to whether or not a person should be diagnosed as depressed. Another challenge, especially in research, is that setting the diagnosis of depression requires skilled professionals to assess each person presenting or experiencing depressive symptoms. One way that is commonly used in research is to assess the level of depressive symptoms through different instruments. From a strict scientific perspective, assessing the presence and level of depressive symptoms cannot be said to be the equivalent of setting the diagnosis of depression. This is because instruments always will be a simplification of the full

clinical assessment needed to set a diagnosis. However, if such assessment instruments are well constructed and used correctly, they will give an indication of the level of depressive symptoms, and, with a reasonable probability, will distinguish persons likely to fulfil the diagnostic criteria for depression from those that do not [39].

Prevalence and Epidemiology of Depression

There is no universal definition of what depression is. Thus, depending on the definition of depression, the prevalence and other epidemiological data will vary between studies. Of interest in this thesis are types of depression that have a negative impact on health, i.e. significant levels of depressive symptoms that probably correspond to a diagnosis of depression, or depression defined as a mental health disorder.

The World Health Organisation (WHO) estimates that 4.4% of the world population suffers from depression and have ranked depression as the single greatest cause of disability in the world and the main contributor to suicide [43]. The lifetime and 12-month prevalence of depression defined as a significant health problem or disorder vary considerably between different countries but appear to be higher in high-income countries compared to low- and middle-income countries. The lifetime prevalence is reported to be in the range of 0.8-1.0% to 16.9-19.0% and the midpoint value for 12-month prevalence is approximately 5-6% [44]. Using dimensional screening values Johansson et al. 2013 [45] reported a prevalence of 10.8% in the adult (age 18-70) Swedish population. Applying a diagnostic algorithm aligned to the DSM-IV criteria resulted in 5.2% of the population being likely to have the diagnosis of major depressive disorder [45].

Major depressive disorder and depressive symptoms (regardless of whether the diagnostic criteria for depressive disorder are fulfilled or not) have a significant association with a large number of chronic physical illnesses (e.g. asthma, cancer, cardiovascular disease and, diabetes) making the prevalence of depression higher in persons suffering from these illnesses [44].

Depression and Heart Failure

Prevalence of Depressive Symptoms in the Heart Failure Population

Most studies on depression in persons with heart failure have used questionnaires (i.e. dimensional instruments) in the assessment of depression. Implicating that the term 'depressive symptoms' is more accurate than using the clinical diagnosis of major depressive disorder.

Depressive symptoms in people with heart failure are common and a number of studies have demonstrated that the prevalence of depressive symptoms is higher compared to the general population. In a meta-analysis, Rutledge et al. 2006 [46] found that a conservatively estimated prevalence of depressive symptoms in people with heart failure was approximately 20% (approximately four to five times higher than in the general population cf. Kessler and Bromet, 2013 [44]). When a more liberal measure of depression was applied, the prevalence rose to approximately 36% [46].

There are also more recent studies reporting a high prevalence of depression and/or depressive symptoms in people with heart failure. Konrad et al. 2016 [47] showed that 28.9% of the persons with heart failure treated in primary care were diagnosed with depression within the five-year study period. The corresponding number in the matched control group (primary care patients without heart failure) was 18.2%. In a study of a mixed sample of in- and outpatients with heart failure, 42.1% were found to have depressive symptoms and 14.4% were classified as having moderate to severe depression [48]. In a meta-analysis by Sokoreli et al. 2016 [49] the 26 included studies about depression reported prevalence numbers ranging from 10-79%, with the majority reporting numbers between 20 and 30%. As reported above, the prevalence of depressive symptoms ranges from 14.4-79%. Based on meta-analysis and studies applying conservative criteria for depressive symptoms an estimate of approximately 20% appears reasonable. Thus, heart failure increases the risk of having depressive symptoms compared to other common somatic illnesses such as cancer, stroke and diabetes [47].

The fact that the prevalence of depression and/or depressive symptoms in persons with heart failure varies, may in part be explained by different methods of assessment. When dimensional methods are used, the reported prevalence is generally higher compared to studies using categorical methods (solely or in combination with questionnaires). In addition, other factors also appear to influence the prevalence of depression in persons with heart failure. Higher NYHA classification [46] lower age, and being female are factors found to be associated with depression/depressive symptoms [50].

Fulop et al. 2003 [51] have studied the trajectory of depressive symptoms in persons with heart failure and found a small decrease in the proportions of persons with depressive symptoms over time. At discharge from hospital, 36% of the participants were assessed as depressed compared with 33 and 26% after four weeks and six months respectively. There was also a significantly higher number of medical encounters (e.g. visits to physicians) but not re-hospitalisation among those still depressed after six months.

Although the prevalence of depressive symptoms in heart failure is rather well described, less is known about the trajectory of depressive symptoms, i.e. how symptoms develop and change over time and whether the increased risks associated with depressive symptoms are correlated to any specific trajectory.

Outcomes of Depressive Symptoms in Heart Failure

The combination of heart failure and depressive symptoms has been shown to have serious consequences for the life and health of the persons affected. As seen in table 2, depressive symptoms come with a significantly increased risk of mortality in most studies and subgroups [46, 49, 52-54]. However, minor depression may be excepted from this as indicated by the subgroup analysis by Fan et al. 2014 [52]. Regarding re-hospitalisation, the hazard ratio is reported to be between 1.08 and 1.51 [48, 55]. Depressive symptoms in heart failure also contribute to a high use of healthcare resources and thus increased healthcare costs [46, 56].

Table 2. Hazard ratios for mortality and morbidity in persons with heart failure and depressive symptoms compared with persons without depressive symptoms

Study	Variable	Hazard Ratio	95% CI
Rutledge et al. 2006 [46]	All-cause mortality	2.10	1.71-2.58
Fan et al. 2014 [52]	All-cause mortality	1.51	1.19-1.91
Sokoreli et al. 2016 [49]	All-cause mortality	1.40	1.22-1.60
Fan et al. 2014 [52]	All-cause mortality in persons with major depression ^a	1.98	1.23-3.19
Fan et al. 2014 [52]	All-cause mortality in persons with minor depression ^a	1.04	0.75-1.45
Adelborg et al. 2016 [53]	All-cause mortality	1.03	1.01-1.06
Gathright et al. 2017 [54]	All-cause mortality	1.20	1.10-1.31
Jani et al. 2016 [48]	Re-hospitalisation	1.42	1.13-1.80
Freedland et al. 2016 [55]	Re-hospitalisation	1.08	1.03-1.13
Freedland et al. 2016 [55]	Re-hospitalisation in persons with major depression ^b	1.51	1.15-1.97

^a Results from subgroup analysis where the sample was divided into persons with and without major depressive disorder. ^b Only persons with major depressive disorder were included in this analysis by Freedland et al. 2016 [55]. CI – Confidence Interval

Low HrQoL is a common consequence of depressive symptoms in persons with heart failure [22, 45, 57, 58]. Persons with depressive symptoms and heart failure have worse HrQoL compared to those with heart failure only [59]. Persons living with heart failure and depressive symptoms report that financial stressors, poor health and negative thinking contribute to depressive symptoms and lower quality of life. Living with depressive symptoms and heart failure also means experiencing hopelessness, despair and impaired social relationships [60].

In a qualitative study, depressive symptoms have been identified as a barrier to self-care [26]. In their systematic review, Sedlar et al. 2017 [27] found that depression was the only factor to be consistently and significantly associated with self-care behaviour, and Kessing et al. 2016 [61] reported similar results in their meta-analysis. Depressive symptoms can impede self-care as they contribute to less physical activity and also negatively affect adherence to medication prescriptions [61] and prolong delay in seeking healthcare when heart failure symptoms worsen [62, 63]. Thus, depressive symptoms in persons with heart failure may partly explain the increase in morbidity and mortality seen in this group.

Symptom Overlap in Heart Failure and Depression

Some symptoms are common in both depression and heart failure, such as fatigue [12, 64]. Other symptoms are more common in one condition compared to the other but can occur in both, such as weight change, which is more common in heart failure than in depression. Symptoms may also occur or be described in such a way that they are misinterpreted [65]. For example dyspnoea may mask a change in activity or be used as an explanation for why a person has started to be slow in speech or movement. The context and situation in which a symptom starts to occur may also affect how that symptom is interpreted and what health problem it is associated with [65]. If a person with heart failure experiences a worsening of her/his heart failure and is in need of extensive help from healthcare personnel and family, thoughts about being useless and being a burden for others may be fully understandable. Yet if those thoughts persist over time, and the person cannot adapt to the new situation, they can also be a maladaptive response and part of a depression. Figure 2 illustrates shared symptoms and overlapping symptoms between heart failure and depression

Figure 2: Overlapping and shared symptoms of heart failure and depression. The figure is constructed based on the synthesis of published literature (cf. Ponikowski et al. 2016 [1], Zambroski et al. 2005 [10], Blinderman et al. 2008 [11], Alpert et al. 2017 [12], Herlofson et al. 2016 [30], Ratcliffe 2015 [31], Fried and Nesse 2015 [42], Demyttenaere et al. 2005 [64], Joynt et al. 2004 [65])

Shared and overlapping symptoms potentially complicate assessment and diagnosis of depressive symptoms and depression in persons with heart failure [66]. Rutledge et al. 2006 [46] found a 25% lower prevalence in studies based on clinical interviews compared with studies based on only self-assessment instruments. Similarly, Johansson et al. 2013 [45] reports an approximately 50% decrease in the prevalence of depression when applying a diagnostic criteria-based algorithm compared to a well-established cut-off score for a moderate level of depressive symptoms. In a clinical context there are studies indicating that depression and depressive symptoms are under-diagnosed [67]. Adding on a disease with overlapping

symptoms, such as heart failure may further contribute to depressive symptoms being undetected [68]. Some studies show that healthcare personnel managing heart failure are not comfortable with addressing the topic of depression in heart failure. This is because the healthcare personnel perceive themselves as not having the required skills to recognise depressive symptoms and think that the treatment of depressive symptoms is not effective, and patients do not want such treatment [69].

Despite the theoretical overlap of somatic symptoms between heart failure and depression, Holzapfel et al. 2008 [70] found that the features discriminating between depression in persons with and without heart failure was found in the cognitive/emotional symptoms.

There are risks associated with both over and under detection of depressive symptoms in heart failure. A high sensitivity to depressive symptoms may lead to an increased burden on the healthcare system and to persons being subjected to treatments that have no health benefits for them but may cause side effects.

On the other hand, depression should not be considered as a normal reaction to heart failure [66] and the differences in symptomatology in depression between persons with and without heart failure appear to be associated with cognitive/emotional symptoms and not somatic symptoms [70]. Furthermore, it is well known that depressive symptoms are associated with profound negative health effects (cf. Rutledge et al. 2006 [46], Sokoreli et al. 2016 [49], Adelborg et al. 2016 [53]). Thus, it appears that the choice between over and under detecting depressive symptoms is a simple one. If depressive symptoms are undetected due to symptom overlap, this comes with a high risk of negative health effects. A highly sensitive initial screening can on the other hand be balanced by thorough evaluation of borderline cases.

Treatment of Depression in Heart Failure

Treatment of depression can generally be divided into three different categories. I) Pharmacological treatment using different pharmacological substances. II) Physiological neuromodulation treatments e.g. Electroconvulsive Therapy (ECT) and Transcranial Magnetic Stimulation (TMS). III) Psychotherapeutic treatment employing different psychotherapies. [71, 72].

Generally, pharmacological treatment of depression can be done with Selective Serotonin Reuptake Inhibitors (SSRIs), TriCyclic Antidepressants (TCAs) and other agents such as mirtazapine, mianserin and venlafaxine. Today, the SSRI is the most used agent. Both SSRIs and TCAs mainly work by different pathways to increase the level of serotonin in the synaptic cleft. TCAs also have an effect on the norepinephrine system and have an anticholinergic effect [73]. TCAs should be avoided in persons

with heart failure due to their cardio-toxic effects [1]. On the other hand, SSRIs appear safe in treatment of depression in persons with heart failure [74]. However, in two randomised controlled trials, the antidepressant effect of SSRIs on depression in heart failure was not demonstrated to be better than placebo [74, 75]. With regard to other antidepressant agents (e.g. mirtazapine, mianserin and venlafaxine), they have not been thoroughly evaluated in heart failure. But venlafaxine has shown a tendency to increase blood pressure [57] and may therefore be inappropriate in heart failure.

Different types of physiological stimulation of the brain, such as ECT and TMS, have shown an antidepressant effect. Though ECT can be used with caution in persons with heart failure [76], it is a highly specialised psychiatric intervention [30] to be used in severe cases of depression [77]. TMS may provide new treatment choices in the future [78], but there are still knowledge gaps related to TMS in depressed persons with or without heart failure.

Pharmacological treatment of depression in heart failure constitutes a complex and challenging task as many antidepressant substances interact with pharmacological substances used in the treatment of heart failure and have cardiovascular side effects [57]. Moreover, the effect of SSRIs on depression in heart failure has not been sufficiently demonstrated. Suggesting that psychotherapeutic treatment forms may be important for alleviating depression in heart failure.

Today there are a number of different forms of psychotherapies, of which some have demonstrated effectiveness in the treatment of depression. In contemporary treatment of depression, psychotherapies are important parts of the treatment arsenal with cognitive behavioural therapy (CBT) and interpersonal therapy proposed as first line treatments in mild and moderate depression [71]. There are some studies investigating CBT on depression in persons with coexisting chronic diseases. Even though the evidence is limited, most of these studies show promising results [79].

Psychotherapy offers an advantage in that it does not have any somatic side effects. However, there is still a risk of negative effects related to psychotherapy [80]. Unlike pharmacological treatment of depression, there is no increased risk of pharmacological interaction associated with psychotherapy - a risk found especially for persons that are already having complex multi-substance treatment, such as persons with heart failure [81]. Persons with cardiovascular disease and depression also express a preference for different forms of talking therapies over pharmacological treatment [82, 83]. As CBT for depression demonstrates similar effects to pharmacotherapy [84], and other forms of psychotherapies have only rarely demonstrated better effects [85], CBT appears to be an attractive approach to the treatment of depressive symptoms in heart failure.

Cognitive Behavioural Therapy

The Origin and Development of Cognitive Behavioural Therapy

The development of behaviourism during the first half of the 20th century led to behavioural therapy. During the mid-20th century, cognitive psychology developed, leading to an increased use of cognitive therapy during the 1960s and 70s. During the 80s and 90s, cognitive and behavioural therapeutic components merged into what today is known as second wave CBT. Recently, the development of CBT has continued the incorporation of concepts such as acceptance and mindfulness. Today, CBT is often used as an umbrella term for all psychotherapies using a mix of cognitive- and behavioural-based components [86].

CBT is also influenced by social learning theory and developmental psychology. Cognitive theory concepts; as basic assumptions, activation of schedules and automatic thoughts explains why functional or adaptive reactions sometimes become dysfunctional and maladaptive. According to the cognitive theory, concepts such as selective abstraction, overgeneralisation, magnification/reduction, emotionalising and personalisation are factors that contribute to maintaining dysfunctional assumptions. Behavioural theory contributes the concept of behaviour seen as all activities that an organism performs in relation to its context i.e. not merely what we do but also what and how we think. Behaviour theory explains how the human learns and thereby shows how the specific behaviour is formed, maintained, altered, or extinguished through different types of conditioning [87-89].

Given this blending of components and concepts from different areas of behavioural science, CBT takes different forms depending on what it is used for. For example, exposure techniques are important components in the treatment of phobias. On the other hand, the concept of behavioural activation is central in the treatment of depression. The communality holding CBT together is some basic assumptions regarding the connections between thoughts, behaviours and emotions, and that the components used should involve the patient's participation and have been shown to be effective.

CBT in Depression

CBT in depression can be divided into two main orientations: CBT with focus on behaviour and CBT with focus on cognition [90]. The behavioural perspective focusses on the observable (overt) behaviour. The development of depression is explained with low levels of positively reinforced adaptive behaviours, and high levels of negative reinforcement and punishment (i.e. painful events leading to termination of a behaviour). One important assumption is that by changing the behaviour this will lead to a change in emotions and thoughts (cognitions). [90]

The cognitive-based orientation is largely based on Aron T. Beck's work. According to the theory of Beck, depressive problems arise from dysfunctional thoughts, emotions and behaviours which can be activated as a response to stressful life events [87, 91-93]. The development of depression is explained by a triad consisting of negative views about oneself, the world and, the future. Another important part of Beck's theory of depression is negative self-schemas (with a self-schema being a stable set of memories, beliefs and experiences creating basic assumptions about oneself). Furthermore, cognitive distortions are common in depression. For example, persons with depression tend to focus on negative aspects of events, overgeneralise and exaggerate their role in negative events, and have difficulties seeing their role in positive events. Beck's theory of depression also stresses that depression develops because of previous experiences. For example, a negative self-schema may have been established during childhood but become activated in connection to a negative life event later in life [92, 93].

The application of this CBT theory [87, 92, 93] to a hypothetical example in persons with heart failure and depressive symptoms is illustrated in figure 3 and in the following example:

Heart failure causes impairment in physical capacity (a negative and stressful event in life). The person focuses much of the attention on this loss (cognitive distortion). The person starts to form a belief about the loss as a sign of weakness and that the person is a burden to others (automatic thought /activation of negative self-schema). This belief about being a burden leads to maladaptive behaviours as the person starts to withdraw from social activities (presumably with the intent of decreasing the burden for others). There is now a risk that the maladaptive behaviour will reinforce the distorted thoughts leading to more intense beliefs about being a burden, and/or will contribute to the development of other negative beliefs in a process that can be described as a negative spiral of more depressive symptoms and depressive symptoms becoming more severe.

The goal of using CBT in depression is to break this process by helping the depressed persons to change the way they think and behave. This can be done by using different CBT techniques or components. [90]

Figure 3. A CBT model describing how heart failure leads to development of depression.

CBT Components for Treatment of Depression

Depending on the theoretical foundation for CBT in depression, the components included in the therapy may vary. Behavioural-focused CBT often only employs components that focus on changing behaviours (such as behavioural activation). Cognitively-focused CBT tends to employ components that address behaviours and cognitions. Examples of cognitively focused components are cognitive restructuring and recognition of automatic thoughts [90]. Below there follows a description of components commonly used in CBT for depression. Depending on individual differences between patients and therapists, other components may also be used.

Psycho-Education

Though not specific to CBT in depression, psycho-education is considered important in CBT. The purpose of psycho-education is for the person suffering from a health problem to gain sufficient knowledge about the health problem, how it affects her/him and, what treatment/therapy there is that can improve the health of the person. Another important aspect of psycho-education is to learn how the CBT is meant to work. Furthermore, psycho-education also contributes to a common understanding regarding the health problem and CBT between the person receiving CBT and the therapist. [94]

Behavioural Activation

Behavioural activation is a CBT component used to change (overt) behaviours. In depression, the aim of this component is primarily to increase behaviours associated with positive emotions, and decrease behaviours with negative consequences. Another important aspect of behavioural activation in depression is to identify factors that increase the probability of a positive outcome of a behaviour. Behavioural activation is often performed by first mapping behaviours and assessing if they are associated with positive or negative emotions. Then an activity plan is made that includes an increase of behaviours associated with positive emotions, and sometimes, techniques to reduce the number of behaviours with negative consequences are implemented. [90]

Problem-Solving

Problem-solving skills (sometimes also described as problem-solving therapy) is a component that focuses on learning effective techniques for solving problems in a way that is beneficial for the health. People with depressive symptoms tend to feel overwhelmed by problems and have problems managing them in a constructive way, leading to either inactivity or avoiding behaviours. Problem-solving skills provide the person with a structured and simple way to identify problems, formulate possible solutions, assess and choose one solution, and finally, test and evaluate the chosen solution. [94]

Registration of Automatic Thoughts and Cognitive Reconstruction

Especially within cognitively-focused CBT (also known as cognitive therapy) the root of depression is attributed to cognitive distortions. Thus, changing the way the depressed person thinks is seen as important for maintaining an improvement in depressive symptoms. This process is carried out stepwise. First (negative) automatic thoughts are registered, often by the person her/himself. Then alternative and more functional ways of thinking are presented in a collaboration between the therapist and

the person with depression. If needed, the new/alternative way of thinking can be tested in behavioural experiments, often performed as homework by the person with depression between therapy sessions. Later in the therapy, when the person with depression has started to feel better, the work with self-schemas is approached. This work is similar to the work with automatic thoughts, and aims to provide a more balanced view of different phenomena in the person's life. [90]

Ways of Providing CBT

CBT is often provided through a traditional face-to-face approach. The therapist and the persons receiving treatment meet on a weekly basis over a period of 10-20 weeks. During the end of the treatment period, sessions are sometimes less frequent. It is also common to schedule booster sessions after the end of the treatment [90]. Face-to-face CBT have been found to be at least as effective as other forms of psychotherapy in depression and have demonstrated similar effectiveness to pharmacological treatment in mild and moderate depression. However face-to-face CBT is resource-demanding compared to pharmacological treatment of depression, and there is a lack of CBT therapists in relation to the demand for CBT among persons with depression [95].

Today, there is a treatment gap regarding CBT for depression (i.e. there are fewer persons receiving CBT compared to the number of people in real need of the treatment) [96, 97]. To counter this treatment gap other ways to provide CBT have been suggested [95]. One such form of CBT is Internet-based CBT (ICBT).

Internet-Based Cognitive Behavioural Therapy

ICBT (also referred to as computer based-, web-based- or Internet delivered- CBT among other variations) is a form of CBT in which the treatment is provided at a distance. From a broader perspective, ICBT is a form of telehealth intervention as it provides healthcare to a person by a care provider situated in a location remote from the care receiver [98]. There is a variation in ICBT for depression but a rough division can describe two main types of ICBT:

I) Generic, self-guided ICBT programs with no direct feedback or support from a therapist or care provider, for example MoodGym and Deprexis [99].

II) Guided or supported ICBT programs. The amount and form of support and feedback in guided ICBT programs varies between programs but the most common form is to provide individualised written feedback on homework assignments, guiding the participants to progress in the program and provide individualised answers to questions. Other forms of support and feedback may include telephone follow-ups and live chats [100].

ICBT programs for depression typically consist of a number of modules in which the persons with depression are requested to read texts about depression and CBT components known to have effects on depression. There are also homework assignments or exercises in connection with each module, designed so that the participants can learn about and try to implement the different CBT components, e.g. behavioural activation or problem-solving, in their everyday life. In guided ICBT programs the participants typically receive feedback on their work after completing each module [101]. The length of ICBT programs varies but most programs are similar in length as that of face-to-face CBT, and eight- to ten-week programs are common in the treatment of depression [102].

In ICBT, the time used by the healthcare provider or therapist is considerably shorter compared to face-to-face CBT. Usually 10-20 minutes per treated person, per week is needed for feedback in ICBT [103-105]. This can be compared to face-to-face CBT where the session is usually 40-60 minutes [90]. The time-saving aspect makes it possible to deliver ICBT to more people with the same number of therapists. Another important aspect making ICBT attractive in respect of reducing the treatment/demand gap is that it appears that persons with little or no formal training in CBT can provide feedback without reducing the effect of the treatment [106, 107]. ICBT can also be delivered within a primary care setting [108].

Both guided and unguided ICBT for depression have shown effects on depression [99, 109, 110]. However, the literature indicates that guided ICBT may be more effective than unguided ICBT [106, 111]. The effect of ICBT on depression is better compared to control condition and/or waiting list [95, 112] and equal to that of face-to-face CBT [109]. This effect is also reported in studies of ICBT for somatic diseases [100]

In the context of persons with coexisting somatic chronic disease and depressive symptoms, studies suggest that unguided generic ICBT programs for depression have a disadvantage in that they are not adapted for the complex situation of suffering from both somatic disease and depressive symptoms [113, 114], suggesting that adapted ICBT programs for those with somatic diseases may be warranted. However, there are only a few studies that have investigated the effect of CBT on depression in persons with heart failure [115].

CBT and ICBT in Persons with Heart Failure

There are only a few studies on CBT for depressive symptoms in persons with heart failure. None of these studies has investigated ICBT. An overview of studies investigating the effect of CBT in heart failure is presented in table 3.

As seen in table 3, a total of nine studies were found [116-124]. Of these, eight report on depressive symptoms as primary or secondary outcomes [116-122, 124]. The mode of delivery of CBT in all studies was face-to-face. However some interventions also employed telephone and/or booster sessions. The length of interventions ranged from 30 minutes to six months. There was generally one session per week. Four of the nine studies reported significant improvements in depressive symptoms [118-121]. Of these, three were RCT studies [118, 120, 121]. However, in the study of Dekker et al. 2014 [118] the effect on depressive symptoms was only found after one week. Of the nine studies, three included participants independently of the level of depressive symptoms [122-124]. Thus, the few studies that have been published indicate that CBT can have positive effects in persons with heart failure. Freedland et al. 2015 [121], the only study that had a sample size close to that estimated necessary in this type of study, is also the study that provides the most promising results in regard to the effect of CBT on depressive symptoms in persons with heart failure. Excluding self-citations of the author of this thesis, no studies regarding the effect or effectiveness of ICBT for persons with heart failure have been published, stressing the novelty of the topic for this thesis.

Table 3. Overview of studies investigating the effect of CBT in persons with heart failure

Study author year; country; type; sample size; setting	Primary outcome	CBT intervention	Control	Outcome
Gary et al. 2010 [116]; USA; RCT; 74; outpatients	Depression	12-week CBT face-to-face or 12-week CBT plus exercise only	Usual care	No significant difference between groups regarding depressive symptoms.
Cully et al. 2010 [119]; Observational study; 23; outpatients	Depression	6-week face-to-face CBT plus three telephone booster sessions	N/A	Depressive symptoms improved between baseline and the 8-week follow-up.
Dekker et al. 2012 [117]; USA; RCT; 41; inpatients	Depression	One 30 min. face-to-face CBT session plus four telephone session	Usual care	No difference regarding depressive symptoms.
Dekker et al. 2014 [118]; USA; Combined data from pilot studies; 24; inpatients	Depression	One 30 min. face-to-face CBT session plus telephone session	Usual care	Significant between groups favouring CBT, at the one-week follow-up
Cockayne et al. 2014 [124]; UK; RCT; 260; outpatients	Self-management	6 sessions of Cognitive-behavioural self-management program during 6 weeks.	Self-management program without coaching	No significant difference in re-hospitalisation. No significant difference in secondary outcomes.
Freedland et al. 2015 [121]; USA; RCT; 158; outpatients	Depression and self-care behaviour	Up to 6 month of weekly face-to-face CBT	Enhanced usual care	Significant improvement in depressive symptoms in the CBT group compared to control.
Redeker et al. 2015 [123]; USA; Pilot RCT; 52; outpatients	Insomnia	8-week program with four sessions of face-to-face CBT and telephone calls.	Attention control	Significant improvement of insomnia compared to control at 2 weeks after intervention.
Cajanding 2016 [122]; The Philippines; RCT; 100; outpatients	HrQoL	12 weekly session of nurse lead CBT	Usual care	Significant improvement of HrQoL compared to control.
Cully et al. 2017 [120]; USA; RCT; 302; outpatients	Depression and anxiety	6 sessions of face-to-face or telephone CBT, two booster sessions during 4 months.	Enhanced usual care	Significant improvement in depressive symptoms compared to control group at 4 months.

RCT- Randomised Controlled Trail, *CBT*- Cognitive Behavioural Therapy, *HrQoL*- Health-related Quality of Life, *N/A*- Not Applicable

ICBT - Conceptually a Type of Telehealth

The increased interest and implementation of ICBT follows a more general trend in healthcare, namely the interest in employing information and communication technologies (ICT) in healthcare, also known as eHealth. WHO defines eHealth as “the cost-effective and secure use of information and communications technologies in support of health and health-related fields, including healthcare services, health surveillance, health literature, and health education, knowledge and research” [125]. As seen in the WHO definition of eHealth, the concept includes a wide variety of different applications of ICT. A more narrow description of the type of eHealth that includes ICBT is telemedicine or telehealth. There is no overall consensual definition of telemedicine [126]. However, the definition suggested in the report of the WHO group consultation on health telematics is:

“Telemedicine is the delivery of health care services, where distance is a critical factor, by all health care professionals using information and communications technologies for the exchange of valid information for diagnosis, treatment, and prevention of disease and injuries, research and evaluation, and for continuing education of health care providers, all in the interests of advancing the health of individuals and their communities”

WHO 1997 [98] Page 10

With the rapid development of tele-communication (e.g. radio-, telephone-, satellite- and computer-communication), telemedicine has seen a large expansion during the late 20th and early 21st century. Especially, the use of telemedicine by the way of healthcare professionals exchanging information and consulting other healthcare professionals is today well implemented in many healthcare systems around the world [127]. The term ‘telehealth’ is often used interchangeably with ‘telemedicine’. However, telehealth, as a term, has become more used during the early 21st century and can be said to broaden the concept of telemedicine to also (clearly) include health- surveillance, promotion and, public health functions. In this thesis, the terms ‘telemedicine’ and ‘telehealth’ are seen as interchangeable. From this perspective, ICBT can be described as a telehealth intervention, as it provides treatment for health problems without the need for any direct contact between healthcare providers and recipients.

Telehealth interventions are often promoted as cost-effective and with a number of other advantages e.g. increasing access to healthcare [126, 127]. A problem however, is that little is known about how healthcare recipients experience ICBT, and what constitute barriers and facilitating factors for telehealth interventions such as ICBT [128].

Rationale for the Thesis

Depressive symptoms in persons with heart failure are common [46, 48] and have a negative effect on mortality [52, 54], morbidity [48, 55], HrQoL [57, 59] and self-care [27, 61]. However, less is known about the trajectory of depressive symptoms in persons with heart failure and how that trajectory affects the health status of the persons living with heart failure and depressive symptoms. The variation in the reported prevalence of depressive symptoms also underlines the importance of investigating whether there are any differences in respect to health risk associated with the setting and context in which the depressive symptoms are developed and/or maintained. Knowledge about the course of depression and specific groups where depressive symptoms contribute to an increased risk of poor prognosis and diminished health status is important as this will provide information about which groups of persons with heart failure are in most need of interventions in regard to depressive symptoms.

Even though important stakeholders have recognised the importance of addressing depressive symptoms in persons with heart failure [1, 6], the treatment of depressive symptoms in persons with heart failure has been shown to be a challenge. This because traditional first line pharmacological treatment appears less effective [74, 75] and a large treatment- demand gap has appeared due to a lack of psychotherapists [95]. As described in table 2 and in a recent meta-analysis [115] CBT has demonstrated promising results regarding depression for persons with heart failure. However, face-to-face CBT is resource-demanding, and less resource-demanding modalities of CBT, such as ICBT, have not been adapted and tested in persons with depressive symptoms and heart failure.

Finally, even though ICBT for depression is well investigated in the general population [95, 99, 112], only a few studies have investigated the experiences of participating in ICBT [128]. With regard to heart disease, Morton et al. 2017 [129] only found three qualitative studies investigating the experience of participating in telehealth interventions (including tele-monitoring). In all, this clearly indicates a need for knowledge regarding how persons with heart failure and depressive symptoms experience an ICBT telehealth intervention

Overall Aim of the Thesis

The overall aim of this thesis was to describe depressive symptoms over time and to develop and evaluate an ICBT intervention to treat depressive symptoms in persons with heart failure.

Specific Aims

The specific aims were:

Study I: to describe the time-course of depressive symptoms in patients with heart failure over 18 months following hospitalisation due to heart failure, and determine its relationship to the hospital admission rate and mortality. A second purpose was to compare the prognostic information on depressive symptoms assessed 18 months after hospital discharge.

Study II: to (1) describe the development of an ICBT-guided self-help program adapted to patients with heart failure and (2) to evaluate the feasibility of the ICBT program with regard to depressive symptoms, the time used by healthcare providers to give feedback to participants, and participants' perceptions of the ICBT program.

Study III: to (1) evaluate the effect of a nine-week guided ICBT program on depressive symptoms in patients with heart failure; (2) to investigate the effect of the ICBT program on cardiac anxiety and QoL; and (3) to assess factors associated with the change in depressive symptoms.

Study IV: to explore and describe experiences of participating and receiving healthcare through an ICBT intervention on patients with heart failure and depressive symptoms.

METHOD

General Description of Methods in this Thesis

The studies in this thesis employ both quantitative (Studies I, II and III) and qualitative (Studies II and IV) research methods. Quantitative and qualitative research methods both have their advantages and disadvantages. The choice between quantitative and qualitative and the choice of approach and design within these two main research disciplines shall be guided by the research question. Table 4 presents an overview of the research methods used in this thesis.

Quantitative methods was used in Studies I, II, and III, as they all contained research questions implying measurements of different variables, such as symptom severity and number of hospitalisations. The purpose of Studies I and III was also to generate generalisable results by inferring results from the study samples to the population, making quantitative methods suitable. The quantitative research in this thesis adheres to the post-positivistic paradigm, emphasising objectivity, reliability, validity, and replicability as hallmarks for high quality research.

Qualitative research can illuminate the meaning of things and phenomena; it studies in-depth and within a specific context how things work (or do not work) and captures people's stories to understand perspectives and experiences. Thus, a qualitative approach was found suitable in Studies II and IV. This is because they contained research questions that addressed how the ICBT program worked from the perspective of the participants (Study II), and how ICBT was experienced by the participants (Study IV). To assess qualitative research findings and to understand how they may be used it is of importance to take the ontology and epistemology of the research into account. The ontology and epistemology varies, depending on what paradigm the researcher adheres to. In the qualitative studies in this thesis (Studies II and IV) the paradigm of constructivism is adhered to.

Table 4: Overview of study methods and materials (Studies I-IV)

Table 4: Overview of study methods and materials (Studies I-IV)						
	Study I	Study II	Study III	Study IV		
Study design	Quantitative, longitudinal descriptive and comparative	Quantitative and qualitative methods in a proof of concept study to: 1) describe intervention development 2) feasibility test the intervention	Quantitative , open label randomised control design	Qualitative inductive exploratory and descriptive interview study		
Participants	611 persons with heart failure and complete data on CES-D from the COACH study ¹	7 participants with heart failure and depressive symptoms in the feasibility testing. A multi-professional group developed the intervention	50 participants with heart failure and depressive symptoms.	13 participants with heart failure and depressive symptoms that had participated in an ICBT intervention.		
Setting	Baseline: hospitalised persons with heart failure	Non-hospitalised community dwelling adults with heart failure and depressive symptoms	Non-hospitalised community dwelling adults with heart failure and depressive symptoms	Non-hospitalised community dwelling adults with heart failure and depressive symptoms.		
Data source	Questionnaire, interviews, medical records and registers	Research literature and clinical expertise. Questionnaires, semi-structured interviews.	Questionnaires.	Semi-structured telephone interviews.		
Outcomes	Depressive symptoms, hospitalisations and mortality	Depressive symptoms, use of time, participants experience of the program	Depressive symptoms, cardiac anxiety and disease specific QoL, participant activity in program	Participants' experience of participating and receiving ICBT		
Instruments	CES-D	PHQ-9, MADRS-S, Interview guide	PHQ-9, CAQ, MLHF	Interview guide		
Cronbach's α coefficient	CES-D = 0.87	PHQ-9 = 0.82-0.77, MADRS-S = 0.91-0.94	PHQ-9 = 0.81-0.82 CAQ = 0.85-0.87, MLHF = 0.93	N/A		
Data analysis	Chi-square test, Kruskal-Wallis test, multivariable proportional hazard regression, Kaplan-Meier curve analyses	Descriptive statistics. Conventional content analysis guided by Hsieh and Shannon ²	Descriptive statistics, ANCOVA, paired samples t-test, Cohen's <i>d</i> , Pearson's <i>r</i> , Kendall's tau-b, Chi-square, Fisher's exact test, EM method	Qualitative (content) analysis according to the recommendations of Patton ³		
¹ In total, 1023 persons with heart failure was included in the COACH study. Methodology for the trial is published in Jaarsma et al. 2004 [130], Jaarsma et al. 2008 [131], Lesman-Leegte et al. 2006 [132], ² Hsieh and Shannon 2005 [133], ³ Patton 2015 [134]. Abbreviations: ANCOVA Analysis of Covariance, CAQ Cardiac Anxiety Questionnaire, CES-D Center for Epidemiologic Studies Depression Rating scale, COACH Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure, ICBT Internet-based Cognitive Behavioural Therapy, EM Expectation-Maximisation, MADRS-S Montgomery Åsberg Depression Rating Scale – Self-rating, MLHF Minnesota Living with Heart Failure questionnaire, N/A Not Applicable, PHQ-9 Patient Health Questionnaire -9, QoL Quality of Life						

¹ In total, 1023 persons with heart failure was included in the COACH study. Methodology for the trial is published in Jaarsma et al. 2004 [130], Jaarsma et al. 2008 [131], Lesman-Leegte et al. 2006 [132],² Hsieh and Shannon 2005 [133],³ Patton 2015 [134].
Abbreviations: ANCOVA Analysis of Covariance, CAQ Cardiac Anxiety Questionnaire, CES-D Center for Epidemiologic Studies Depression Rating scale, COACH Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure, ICBT Internet-based Cognitive Behavioural Therapy, EM Expectation-Maximisation, MADRS-S Montgomery Asberg Depression Rating Scale – Self-rating, MLHF Minnesota Living with Heart Failure questionnaire, N/A Not Applicable, PHQ-9 Patient Health Questionnaire-9, QoL Quality of Life

Designs and Settings

Study I, had a quantitative longitudinal design. Data was retrieved within the COACH study [130] in which persons that were admitted to hospital due to heart failure symptoms were included for a randomised controlled trial comparing basic and intensive support to standard care of heart failure.

Study II, employed three different patterns of design. I) The development and context adaptation of the ICBT program were performed within a multi-professional team. The ICBT program was based on research and literature as well as the team's clinical experience of providing healthcare for persons with heart failure and treatment of depression. A person living with heart disease, representing a patient non-governmental organisation contributed with the user perspective, and laypersons were used to test the readability of the program and technical function of the treatment platform. II) The feasibility of the program from the perspective of limited efficacy and function was investigated with a quantitative pre-post design. III) Participants' perceptions of the ICBT program was investigated with a qualitative content analysis. One interview was conducted in the home of the participant and the remaining interviews were conducted via telephone at a time chosen by the participant.

Study III, was designed as a randomised controlled trial, where ICBT was tested against an online moderated discussion forum. Decisions regarding inclusion were made based on the screening form and a telephone interview. The ICBT program tested in this study was delivered through a web-based treatment platform requiring two-factor authentication for access. The program consisted of seven modules and associated homework assignments to be worked on during a nine-week period. The participants were guided through the program and received personalised written feedback on all homework assignments. If needed, technical support could be given by telephone.

Study IV, had a qualitative design to explore and describe participants' experiences of ICBT. To ensure that all recruited participants had experience of ICBT, they were identified from the sample of Study III. Thus, all participants in Study IV had experiences of working with the ICBT program. Participants consenting to be interviewed for this study were asked to provide a time and date when they could participate in a telephone interview. They were asked to choose a time when they had at least one hour to spare and would not be disturbed during the interview. Most participants had the interview at home but a few chose other locations such as their workplace.

Participants, Sample Size, Inclusion Criteria, and Procedures

Participant and Socio-Demographical Information

Three different samples of persons with heart failure were used in this thesis. The mean age was similar in all four studies, varying between 62 and 69 years of age. With the exception of Study II, the participants were predominantly men. In all studies, most participants were married or were living with a partner in a long-term relationship (Table 5).

In **Study I**, a subsample from the COACH study [130] was used. The COACH study was a multicentre RCT testing basic or intensive support versus standard treatment of heart failure, conducted in the Netherlands. In the COACH study, persons hospitalised due to symptoms of heart failure were included, in total 1023 persons. The subsample constituting the sample in Study I was created by extracting all participants with complete data on depressive symptoms at both baseline (performed before discharge from hospital) and the 18-month follow-up, in total 611 participants. For these persons, additional data was also collected at a 36-month follow-up. Compared to the 412 persons without complete data on depressive symptoms, the participants in Study I were significantly younger (mean age 69 years versus 73 year). However, there were no significant differences in the distribution of men and women between persons included and not included in Study I. Of the 412 persons not included due to missing data, 347 had depressive symptoms assessed at baseline. There was a significant difference regarding depressive symptoms between those excluded but with depressive symptoms assessed at baseline ($n=347$) and the included participants ($n=611$) with those excluded having higher levels of depression. In addition, the 412 persons not included in Study I had significantly more diabetes and Ischaemic heart disease, and a higher NYHA class.

The participants in **Study II** were recruited for feasibility testing through advertisements in local newspapers in southeast Sweden. The sample consisted of seven persons living at home. All had a self-reported diagnosis of heart failure and screened positive for (at least) mild depressive symptoms.

Table 5. Socio- demographic and clinical characteristics of study participants (Studies I-IV)

	Study I	Study II	Study III*	Study IV*
Participants, n	611	7	50	13
Male, n (%)	379 (62)	3 (43)	29 (59)	9 (69)
Age in years, mean (SD)	69 (11)	62 (10)	63 (13)	65 (14)
Living alone, n (%)	220 (36)	0 (0)	13 (26)	4 (31)
NYHA^a, n(%)				
I	-	-	11 (22)	4 (31)
II	335 (55)	4 (57)	20 (40)	7 (54)
III	253 (41)	3 (43)	18 (36)	2 (15)
IV	16 (3)	-	1 (2)	-
Baseline depressive symptoms^b, n (%)				
No	382 (62.5)	-	-	-
Mild		3 (43)	17 (34)	7 (54)
Moderate	229 (37.5)	2 (29)	21 (42)	3 (23)
Moderately -Severe		2 (29)	12 (24)	3 (23)
Comorbidities, n (%)				
Pulmonary disease	165 (27)	1 (14)	6 (12)	0 (0)
Diabetes	146 (24)	2 (29)	7 (14)	2 (15)
Stroke or TIA	91 (15)	1 (14)	11 (22)	2 (15)
Renal disease	39 (6)	1 (14)	1 (2)	0 (0)
Ischaemic heart disease	243 (40)	3 (43)	18 (36)	6 (46)
Medication				
Beta-blocker	413 (68)	6 (86)	44 (88)	12 (92)
ACEI / ARB	522 (85)	7 (100)	47 (94)	12 (92)
Diuretics	584 (96)	5 (71)	34(68)	8 (62)
Antidepressant	39 (6)	3 (43)	9 (18)	1 (8)
Place of recruitment	Hospital	Community	Community	Community

* The sample in Study IV was recruited within the sample in Study III. ^a NYHA class not reported for seven participants in Study I. ^b In Study I, depressive symptoms were measured by CES-D which lack well-established cut-off scores for different levels of depressive symptoms.

NYHA New York Heart Association functional classification, TIA Transitory Ischaemic Attack, ACEI Angiotensinogen Converting Enzyme Inhibitor, ARB Angiotensin Receptor Blocker

Studies III and IV: The sample consisted of persons actively registering their interest in participating in a study testing ICBT for persons with heart failure and depressive symptoms. The participants were living in their own homes and had not been hospitalised due to heart failure for at least one month. Information about the study was sent out by mail to persons with a diagnosis of heart failure (ICD I50 and I42) and who had made contact at

least once with clinics of cardiology or medicine at four different hospitals in the south east of Sweden. In total, 50 persons were included in Study III. All participants had been diagnosed with heart failure and screened positive for (at least) mild depressive symptoms. Comparing the participants in Study III to the excluded persons who completed online screening ($n=14$), the ones excluded had significantly more renal disease and stroke or TIA, and significantly lower levels of depression. The sample in Study IV consisted of a subsample from Study III. Participants that had experience of the ICBT program (defined as having taken part in at least one module in the ICBT program), were invited to participate in Study IV. Twenty-seven invitations were sent out and 13 participants were interviewed.

Sample Size

To ensure robust and generalisable results the sample size needs to be considered in quantitative studies. In qualitative studies the sample size, expressed as the number of study participants is not relevant in the same way as in quantitative studies. Instead, the richness and variation in the data is of interest. Thus, in both quantitative and qualitative studies estimating how many participants are needed and including a sufficient number of participants contributes to the quality of the study.

Study I, was a secondary analysis performed on already collected data from the COACH study, a multicentrel study evaluating different models of follow-up after hospitalisation in persons with heart failure. The sample size calculation in the original article [130] indicated a need to include 1050 participants (given an effect size of 0.5 and alpha (α) set to 0.05) for the hard endpoints of mortality or unplanned hospitalisation. No new sample size calculation was made, instead all available data was used to gain the best generalisable result possible.

In **Study II**, no sample size calculation was performed, as the aim of this study was to describe the development of the ICBT program and test its feasibility.

In **Study III**, the sample size calculation was based on previous studies [102] of ICBT. An effect size of 0.5 was assumed and α was set to 0.05, rendering a need for a sample of 104 persons. Due to dropout of participants, we aimed to recruit 120 persons to Study III.

In **Study IV**, an approximation of the required number of participants was made based on literature on qualitative methods [131, 132] and taking the tradition of the research discipline into consideration. With this in mind, approximately 20 participants were the targeted number of participants to include in study IV.

Recruitment Procedure and Inclusion and Exclusion Criteria

Study I: Eligible participants were recruited during their hospitalisation due to symptoms of heart failure. Based on the criteria in the COACH study, the inclusion criteria were: at least 18 years of age and had been admitted to hospital due to heart failure symptoms, NYHA II-IV, evidence of underlying structural heart disease. Exclusion criteria were: concurrent inclusion in a study requiring additional visits to research health care personnel, restrictions that made the person unable to fill in data collection forms, invasive intervention within the last six months or planned during the following three months, ongoing evaluation for heart transplantation, inability or unwillingness to give informed consent [130]. To be included in Study I, participants also had to have complete data on depressive symptoms at baseline and at the 18-month follow-up.

In **Study II**, the participants were recruited via advertisements in local newspapers in southeast Sweden. The ads stated that persons with heart failure and depressive symptoms who felt motivated to seek support for their depressive symptoms using ICBT could register their interest on the study website. The recruitment process was then performed in three steps. First, potential participants registered and confirmed their interest in participation. Second, the potential participants filled in the online screening questionnaire. Third, all potential participants with a positive screening for depressive symptoms were telephone-interviewed to verify the online screening. Based on the inclusion and exclusion criteria, a decision was then taken on whether to include or exclude the participant. For the qualitative part of Study II, all participants involved in the testing of the program were recruited for a semi-structured interview. Recruitment in **Study III** started with an information letter that was sent to all persons (n=2855) with heart failure that had at least one health care contact with the departments of cardiology or medicine at four hospitals in southeast Sweden. The letter contained the same information as the ad used for Study II and an explanation of why the recipient had been mailed the information. The rest of the recruitment process was then identical to the three-step process used in Study II.

Studies II and III shared inclusion and exclusion criteria, with two exceptions. 1) In Study II, the participants were not to have been hospitalised due to heart failure for the last three months. In Study III, this period was shortened to one month. 2) In Study II, the participants had a self-reported diagnosis of heart failure and in Study III the diagnosis of heart failure was based on ICD codes in the medical record. Beside from this, the same inclusion criteria were used: age of at least 18 years, at least mild depressive symptoms defined as a score of five or more on the PHQ-9, access to a computer with an Internet connection during the intervention period, access to a mobile phone able to receive text messages, ability to read and write Swedish. The exclusion criteria were: other health problems assessed as hindering participation in the program (e.g. planned major

surgery), severe depressive symptoms or other psychiatric health problems requiring specialist psychiatric treatment or making the intervention unsuitable, high risk of suicide.

In **Study IV**, the participants included in Study III that had worked with the ICBT program (defined as actively worked on at least one module of the program) were recruited for a qualitative interview. Variation in the experience of ICBT was sought by inviting participants who had completed different numbers of modules. In total, 27 invitations were sent out and 13 participants were interviewed.

Procedures

In **Study I**, baseline data including depressive symptoms was retrieved while participants were hospitalised and participants' health records were scanned for comorbidities. Follow-up data on depressive symptoms and data on hospitalisation and cause of hospitalisation was collected at 18 months after discharge from hospital. Data on mortality was collected after 18 and 36 months from hospital registers, general practitioners and the municipality. The collection of data at 36 months was an additional long-term follow-up not originally scheduled in the COACH study.

In **Studies II and III**, baseline data was collected before the start of the intervention. The participants in Study III were randomised to either ICBT treatment or an online moderated discussion forum (control group intervention). For safety reasons, all participants in Studies II and III were asked to self-report depressive symptoms including suicidal ideations weekly during the intervention phase of the study.

All included participants in Study II and those randomised to ICBT in Study III received a nine-week ICBT program consisting of seven consecutive modules. Each module included text and homework assignments. Written feedback on homework assignments was provided, along with answers to questions posted by the participants. Participants receiving ICBT were also reminded by personalised written messages if they did not hand in homework assignments.

The online moderated discussion forum (used as a control group in Study III) included questions and discussion topics regarding heart failure, depressed mood, self-care and contact with healthcare. Each week during the intervention phase, a new topic was presented. The participants in the discussion forum were encouraged to discuss the topics with each other by writing in a discussion thread. The moderator monitored the discussion but did not provide answers to questions and was not to intervene in the discussion unless any post contained statements that could result in a health risk for the participants.

All participants could seek technical support regarding the web-platform hosting the ICBT program and the discussion forum via an encrypted message system or ordinary e-mail.

Follow-up data was collected after the end of the ICBT intervention, approximately ten weeks after the intervention started. During the intervention phase in Study II the feedback providers' use of time for feedback and technical support was logged.

Qualitative interviews (**Studies II and IV**) were carried out after the participants had ended the ICBT intervention.

All participants received written and oral information regarding the studies before providing their consent. In Studies II-IV, consent was given in a two steps. First, the participants consented to the collection of data necessary for the screening procedure by clicking a consent button on the study website. Second, if screening resulted in an inclusion decision, oral information was given via telephone and a consent form for participating in the intervention study as well as for being contacted for qualitative interviews was sent by mail. The participants then returned the signed consent form before the start of the intervention. The participants invited to the qualitative studies (part of Study II, and Study IV) were contacted by e-mail or telephone regarding participation in the interviews. Consent for the interviews was obtained before the interviews were conducted. No financial compensation was given to the participants and all participants had to provide their own computer, mobile phone and access to the Internet.

Development of the ICBT Program

The ICBT program used in this thesis (Studies II-IV) was developed based on previously used ICBT programs for depression. Literature on depressive symptoms, depression, heart failure, the combination of heart failure and depressive symptoms, and the experience of living with heart failure and depressive symptoms was reviewed. A multi-professional team (consisting of nurses specialising in heart failure care, psychiatric and mental health care and patient education, a psychologist, and a cardiologist) adapted the ICBT program to the context of heart failure and depressive symptoms based on the literature review and the clinical experience. A person living with cardio vascular disease (volunteering for the Swedish Heart and Lung Association) was included in the development process to incorporate the perspective of potential users of the program. To increase readability and intelligibility, laypersons without experience of heart failure care and ICBT proofread the ICBT program and tested the functions in the web-based treatment platform.

Data Collection and Measurements

In this thesis, data was collected using standardised questionnaires (Study I), standardised self-administered web-based questionnaires (Studies II and III) and qualitative interviews (Studies II and IV). Three automated reminders were sent out to the participants in Studies II and III that did not complete the questionnaires. In Study I, medical records and municipality registers were used for extracting data on mortality and morbidity. Demographic and medical background data including age, sex, marital status, NYHA class, comorbidities, and medication was collected in Studies I-III. Cronbach's α coefficient was used to calculate the reliability coefficient for CES-D (Study II), CAQ (Study III), MADRS-S (Study II), MLHF (Study III) and PHQ-9 (Study II and III).

Center for Epidemiologic Studies Depression Rating Scale

The CES-D was used to measure depressive symptoms in Study I. The CES-D is a 20-item self-report questionnaire designed to measure depressive symptoms in the general population and in the medically ill [133]. A total sum score is used (0–60), with higher scores indicating more depressive symptoms. A cut-off point of 16 is generally used to define patients at risk of clinical depression [133, 134]. Internal consistency reliability is reported with an alpha varying from 0.84-0.90 in different samples [133]. CES-D has been reported as suitable for screening of depressive symptoms in persons with coexisting physical disability [134]. Cronbach's α coefficient in Study I was 0.87.

Patient Health Questionnaire -9

PHQ-9 was used to measure depressive symptoms in Studies II and III. PHQ-9 is a nine-item self-administered instrument designed for detecting depression. It detects both threshold disorder (major depression) corresponding to DSM-IV and sub-threshold disorders (other depressive disorders) [135]. The nine items are based on the diagnostic criteria for major depressive disorder in DSM-IV [136]. The items are rated on a four-graded scale (not at all - 0, several days - 1, more than half the days - 2, nearly every day - 3) giving a total score range from zero to 27. A higher total sum score indicates more severe depressive symptoms. Kroenke et al. 2001 [137] suggest the following categories for points scored in correlation to level of depression severity for PHQ-9: 0-4 no or minimal depressive symptoms; 5-9 mild depressive symptoms, 10-14 moderate depressive symptoms, 15-19 moderately severe depressive symptoms, and 20-27 severe depressive symptoms. A score of ten or more is frequently used to identify persons with major depressive disorder [136].

PHQ-9 has been validated and tested in a primary care context, on obstetrics-gynaecology outpatients, and on patients with heart failure [135, 136, 138]. The internal reliability in the primary care context is reported to

have a Cronbach's α of 0.89, 0.86 in obstetrics-gynaecological patients and 0.85 in patients with heart failure. The correlation between PHQ-9 and diagnosis determined by a blinded mental health professional using a structured diagnostic interview via telephone was 0.84. PHQ-9 has also shown good construct validity when compared to functional scales known to relate to depression (mental health, social, overall and role functioning) [137]. In patients with heart failure, sensitivity and specificity have been reported as acceptable [136]. PHQ-9 has been tested for inter-format reliability between pen-and-paper and computerised versions [139]. Cronbach's α coefficients in this thesis were 0.77-0.82.

Montgomery Åsberg Depression Rating Scale –Self-rating

In Studies II and III, MADRS-S was used as a security measurement for depressive symptoms and suicidal thoughts. MADRS-S is a self-rating version of the Montgomery Åsberg Depression Rating Scale (MADRS) and has been reported to have a high correlation with the original MADRS scale [140, 141]. MADRS is designed to measure the severity of depression in patients and has been shown to be sensitive to change in patients' depressive state [142]. MADRS-S consists of nine items. In each item, describing statements are given. The person rating her/himself has to indicate the statement with the best fit for the situation over the last three days. Indications can also be given between two statements. This gives a seven-point scale for each item, ranging from zero to six. The maximum score for MADRS-S is 54, with higher scores indicating more severe depressive symptoms [143, 144]. The following interpretation of MADRS-S scores has been proposed: 0-12 no depression, 13-19 mild depression and, 20-54 moderate/severe depression [143]. As MADRS avoids major emphasis on somatic symptoms of depression, it has been recommended for assessment of depression/depressive symptoms in settings with physical illness [145]. MADRS-S has been tested for reliability and validity. In a sample of persons with major depressive disorder Cronbach's α was reported as 0.84 and the construct validity was assessed as satisfactory [146]. No significant changes in the psychometric properties have been shown when MADRS-S is delivered via the Internet compared to pen-and-paper ratings [147]. Cronbach's α coefficients in Study II were 0.91-0.94.

The Minnesota Living with Heart Failure Questionnaire

In Study III, the MLHF was used to measure HrQoL. The MLHF is a disease-specific, self-administered instrument for HrQoL used by persons with heart failure. The instrument consists of 21 items scored on a six-point Likert-scale (0-5). The range of scores is 0-105 with a higher score indicating worse HrQoL [148]. The scoring of the MLHF can be divided into two dimensions, physical and emotional, and a total score [149]. For the physical dimension the scale ranges between zero and 40 and for the emotional dimension the scale ranges from zero to 25 [150]. A change of five points in the MLHF has been suggested to indicate a clinically

significant change [151] and the MLHF has been reported to detect change over time with a medium effect size (Cohen's $d \geq 0.50$ to 0.79) [150] but may not detect more subtle changes [152]. In a meta-analysis, Garin et al. 2009 [153] reported an internal consistency with a Cronbach's α of 0.94 for the MLHF as a total. Test-retest reproducibility was 0.84 . Furthermore, Garin et al. 2009 [153] reported that MLHF has a good responsiveness to change in HrQoL, and recommended the use of the instrument in longitudinal studies where responsiveness is an issue and self-administration is preferable. The inter-format reliability of the MLHF between Internet and pen-and-paper versions has not shown equivalence [154]. Cronbach's α coefficient in Study III was 0.93 .

The Cardiac Anxiety Questionnaire

The CAQ is an 18-item instrument measuring heart-focused anxiety in one total score and three dimensions, fear, avoidance and, heart-focused attention. Each item is scored on a five point Likert-type scale, from zero (never) to four (always) giving a total score range from $0-72$. As each dimension consists of a different number of items, the mean score for the dimensions and the total score is often calculated and reported, enabling comparison between dimensions and total score. The CAQ has demonstrated good psychometric properties [155]. The Cronbach's α coefficients in Study IV were $0.85-0.87$ for the total CAQ, $0.79-0.82$ for the fear dimension, $0.88-0.89$ for the avoidance dimension, and $0.68-0.69$ for the heart-focused attention dimension.

Qualitative Interviews

In Studies II and IV, qualitative data was collected by interviews. To direct the interviews in alignment with the aims of the studies, interview guides were used (Table 6). Both interview guides were designed with open-ended questions. In addition to the main questions, a number of topics or areas of interest were listed in each interview guide, enabling the interviewer to ensure these topics were covered during the interview, either by the informant spontaneously addressing the topic during the interview or if necessary, by asking questions about the topic. To increase the depth and richness of the interviews, both interview guides also had a number of probing questions. All interviews except one were performed via telephone. Telephone interviews were chosen because they facilitated a purposeful sampling from the geographically spread study population. All interviews were booked in advance via e-mail and/or telephone contact between the informant and the interviewer. Informants were asked to choose a time of their convenience for their interview so that they had sufficient time (at least one hour) and would not be disturbed by others during the interview. All interviews were digitally audio-recorded with the consent of the informant.

Table 6: overview of interview guides

Type of question	Study II	Study III
Main questions	<ul style="list-style-type: none"> - How did you experience the program? - Were there parts of the program that you experienced as helpful and/or supportive? - Were there parts of the program that you experienced as complicated or unhelpful? 	<ul style="list-style-type: none"> - You have (recently) participated in an Internet based CBT program. Can you please tell me about this?
Topics to follow up	<ul style="list-style-type: none"> - With respect to the content/technology/implementation, can you tell me something positive about the program? - With respect to the content/technology/implementation, can you tell me something negative about the program? - Can you please estimate how much time you spent working with the program? 	<ul style="list-style-type: none"> - Advantages/ disadvantages with the treatment program - Positive aspects with treatment through the Internet? - How would you describe what the program were/is? - Contact with the feedback provider - Experience of the feedback - Use of the Internet for any other type of healthcare? - What do you think about the healthcare system using the Internet more and more for information and interventions? - In your experience what is the difference between healthcare provided face-to-face compared with healthcare provided through the Internet? - What are the advantages/disadvantages? - Integrity and healthcare through the Internet.
Probing questions	<ul style="list-style-type: none"> - Can you please tell me more about that? - Can you please elaborate on what you mean? - Can you please give an example - Can you explain/clarify what you mean...? - Earlier you said...? 	

Data Analysis

Quantitative Data Analysis

Statistical analysis was performed using the Statistical Package for Social Science (SPSS) version 18.0 (Study I) and IBM SPSS Statistics 22 (Study II and III).

General Statistical Principles and Tests on Background Data

Categorical variables are described as frequencies (Studies II and III) and as percentages (Studies I and III). For continuous variables, mean values and standard deviations were reported (Studies I and III). Due to the small sample size, the median was reported in Study II. Normally distributed data was analysed with parametric tests. Non-parametric tests were used on non-normally distributed data and in small samples or subgroups (Studies I-III). Differences in sociodemographic and clinical data between groups were tested with bivariate analysis (One-way analysis of variance and Kruskal-Wallis test) (Study I) and Student's t-test (Study III) and Chi-square test (Studies I and III) or Fisher's exact test if the expected number of observations in each group was less than five (Study III).

Study I

The main purpose of the statistical test in Study I was to report risks and mortality associated with depressive symptoms. To achieve this, first a comparison of different categories of depressive symptom status (ongoing, recovered, new episode, and non-depressed) with outcomes (days to first hospitalisation and mortality) were analysed with chi-square test (categorical variables) or Kruskal-Wallis test (continuous variables). Second, multivariable proportional hazard regression was used to evaluate the independent association between depressive status and outcomes. This was performed in two steps: 1) the change in depressive score over the 18-month follow-up period was evaluated, 2) then the outcomes were evaluated by the four depressive status groups. The multivariable proportional hazard analysis was adjusted for known covariables (i.e. age, sex, chronic obstructive pulmonary disease, diabetes, ischaemic heart failure, baseline brain natriuretic peptide level, and history of heart failure related hospitalisation). Lastly, a Kaplan-Meier curve analysis was performed on depression status groups regarding mortality after 36 months. (Study I)

Study II

Frequencies, median and range were calculated for the outcome of depressive symptoms. The mean was calculated for the outcome of time used by healthcare provider. (Study II)

Study III

The main purpose of the statistical test in Study III was to report the differences between groups and changes in depressive symptoms. Intention to treat analysis was employed, including all participants randomised to either study group, regardless of their completion rate of the intervention. The between groups analysis was performed by analysis of covariance (ANCOVA) adjusting for baseline scores and regression to the

mean. The change within each group was tested with a paired samples *t*-test. Effect size was calculated with Cohen's *d*, with a small effect size defined to be between 0.2 and 0.5, medium effect size between 0.5 and 0.8 and large effect size above 0.8. To investigate factors associated with changes of depressive symptoms, Pearson's *r* was used for interval-scale variables and Kendall's tau-b for ordinal-scale variables.

Missing values analysis was performed and Little's test for missing completely at random was conducted. Missing values were imputed using the Expectation-Maximisation method. However, subgroup analysis was conducted on cases with complete data due to the small subgroups.

Qualitative Data Analysis

The analysis method of qualitative data in Studies II and IV was the same as described above, qualitative content analysis. Both Studies (II and IV), were mainly descriptive and explorative, and employed an inductive approach. However, there are variations in method descriptions between different references, and there are rarely any clear "cookbook-style" instructions on how to perform qualitative content analysis [132]. The qualitative analysis in Study II is guided by conventional content analysis as it is described by Hsieh and Shannon 2005 [156]. In Study IV, the analysis was guided by Patton's [132] description of qualitative analysis. Figure 4 illustrates the general analysis process in Studies II and IV.

Data analysis started with transcription and/or an accuracy check of the transcripts (Studies II and IV). In this early phase of analysis, the researcher started to familiarise himself with the data. This was followed by further familiarisation by reading all transcripts several times (Studies II and IV). Coding then started by identifying words or text extracts capturing central concepts relevant to the aim of the study. In Study II, the researcher highlighted these texts extracts and labelled them. In Study IV, coding was carried out several iterative steps: first, two researchers read and independently coded one interview and a group of PhD student coded parts of three anonymised transcripts. A coding scheme was then constructed. All transcripts were then systematically coded in accordance with the coding scheme.

After coding, the codes were then inductively sorted into patterns forming categories (Studies II and IV) and sub-categories (Study IV). In Study IV, categories and sub-categories were formed in an iterative process where the researcher made a preliminary categorisation that was then triangulated with a second researcher. The two researchers discussed similarities and differences between themselves to reach a consensus decision regarding categories and sub-categories. When all categories had been described, they were investigated once more to see if themes could be constructed. Finally, the findings were triangulated with a third researcher for confirmability.

Figure 4: The general qualitative analysis process in studies II and IV

Ethical Considerations

All studies were approved by an independent ethical review board. Ethical approval for Study I was obtained from the Central Ethics Committee, the Netherlands (reference numbers: METc 2002/047, METc 2002/047: Amendement5). Studies II-IV were approved by the Regional Ethical Review Board in Linköping (reference number: 2011/166-31). Study III is registered as a clinical trial (clinicaltrials.gov NCT01681771). The studies were carried out in accordance with the Declaration of Helsinki [157]. Informed consent was obtained from all participants in Studies II, III and IV. For Study I, informed consent was obtained at inclusion in the original study (the COACH study [130]) and renewed consent were not considered

necessary for Study I as the study was conducted within the limits of the purpose of the COACH study and the informed consent given by the participants at that time. All participants were informed that participation was voluntary, and that they could withdraw their participation at any time during the study without any consequences and without having to state any reason for their decision.

To minimise the risks for participants in Studies II and III, all participants were assessed for suicidality based on their individual scores of depressive symptoms at screening (PHQ-9) and a structured assessment using section C in the MINI version 5.0.0. Furthermore, all participants were asked to complete MADRS-S weekly during the intervention period. This was done as a safety monitoring procedure to ensure that participants that deteriorated in their depressive symptoms or became increasingly suicidal were identified. If persons were excluded due to being severely depressed, having a high risk for suicide, or due to suspicion of other psychiatric disorders that made the treatment program unsuitable, they were recommended and guided to make contact with an appropriate healthcare provider.

To protect sensitive information regarding participants' health, the ICBT program was delivered via a website that used secure encryption of all information. A two-factor authentication system (password and single-use codes delivered via mobile phone) was used to access the parts of the website containing the ICBT program and all personal information regarding participants. All quantitative data in Studies II and III was collected using the same secure website as the ICBT program.

All qualitative interviews were digitally recorded on a password-protected smartphone. Interviews were transferred to a password protected computer system as soon as possible after each interview and then deleted from the smartphone. Transcripts were kept in a locked location and only members of the research group had access to them. All data published or made available for persons outside the research group was anonymised and scrutinised to ensure that it was not possible to identify individual research participants.

RESULTS

The mean age in the samples (Table 5) in this thesis varied between 62 and 69 years of age, with the highest mean age among the hospitalised persons included in Study I (Studies I-IV). Concerning symptom severity of heart failure, most persons reported NYHA class II (40-57%) followed by NYHA class III (36-41%). In all samples, ischaemic heart disease was the most common comorbidity (36-43%). In persons hospitalised at baseline (Study I) 27% had pulmonary disease and 24% had diabetes. In community-dwelling persons, stroke or TIA, and diabetes were more common comorbidities compared to pulmonary disease (Studies II and III). The majority were receiving pharmacological treatment for their heart failure. Six percent of the persons in Study I used pharmacological antidepressants. The corresponding figures in Studies II and III, which only included persons with at least mild depressive symptoms, were 43% and 18% respectively.

Depressive Symptoms in Heart Failure over Time

Depressive symptoms were reported in 38% (n=229) of persons (n=611) hospitalised due to symptoms of heart failure. After 18 months, 26% (n=160) reported depressive symptoms (CES-D ≥ 16). Four different paths (Figure 5) can describe the course of depressive symptoms: 1) Non-depressed, with no depressive symptoms at baseline and the 18-month follow-up. 2) Remitted depressive symptoms, with symptoms at baseline but not at the 18-month follow-up. 3) Ongoing depressive symptoms, with depressive symptoms at both baseline and the 18-month follow-up. 4) New depressive symptoms, with no depressive symptoms at baseline but symptoms at the 18-month follow-up. (Study I)

Figure 5. Illustration of the four trajectories of depressive symptoms between baseline and follow-up.

An increase of depressive symptoms between discharge and the 18-month follow-up was associated with a small but significant increase of risk for re-hospitalisation due to cardiovascular disease (HR 1.02, 95% CI 1.01-1.04)

and all-cause hospitalisation (HR 1.02, 95% CI 1.01-1.04). Persons in the groups with ongoing and new depressive symptoms were readmitted to hospital significantly more often compared to persons without depressive symptoms and those with remitted symptoms. However, the adjusted hazard ratio, for increased risk for hospitalisation, among persons with depressive symptoms was only significant in the group with new depressive symptoms (HR 1.5, 95% CI 1.2-3.5 for all-cause hospitalisation and HR 1.7, 95% CI 1.1-2.6 for hospitalisation due to cardiovascular disease). There were no significant differences in risk regarding hospitalisation due to heart failure. (Study I)

Mortality after 36 months from discharge was significantly higher in persons depressed at the 18-month follow-up compared to non-depressed persons. Of persons with depressive symptoms at the 18-month follow-up, 26% had died at the 36-month follow-up compared to 15% among non-depressed persons (Log rank $p=0.001$) (Figure 6).

When comparing each depressive status group (non-depressed, remitted, ongoing, and newly developed) Kaplan-Meier curves (Figure 7) showed significant differences in mortality at the 36-month follow-up (Log rank $p=0.008$) with 25% (ongoing) and 28% (newly developed) deceased at 36 months compared to 15% (remitted) and 16% (non-depressed). An adjusted hazard ratio showed a significantly higher risk for all-cause mortality in persons with newly developed depressive symptoms (HR 2.0, 95% CI 1.2-3.5) and a non-significant ($p=0.056$) trend of increased risk for persons with ongoing depressive symptoms (HR 1.7, 95% CI 0.98-3.1). (Study I)

Figure 6. Unadjusted Kaplan Meier curve of depressive symptoms status 18 months after discharge and all-cause mortality 36 months post discharge.

Figure 7: Unadjusted Kaplan Meier curve of depressive symptoms status groups 18 months after discharge and all-cause mortality 36 months post discharge.

To summarise, most persons with depressive symptoms at discharge (68%) had a natural or spontaneous remission of symptoms at the 18-month follow-up. There were no significant differences regarding mortality or morbidity between persons with remitted depressive symptoms and those that were non-depressed (CES-D score lower than 16 at baseline and the 18-month follow-up). Among those with depressive symptoms at the 18-month follow-up (both ongoing and newly developed), there was an increased risk for re-hospitalisation and death. However, when adjusting for other known risk factors the increased risk associated with depressive symptoms was only statistically significant among those with newly developed depressive symptoms. The results in Study I suggest that interventions targeting depressive symptoms should primarily be directed at those persons that develop depressive symptoms as they are community dwelling and/or those persons that have remaining depressive symptoms for a period of time after discharge from hospital. (Study I)

ICBT in Persons with Heart Failure and Depressive Symptoms

The Program

A nine-week ICBT program for depressive symptoms in persons with heart failure was developed. The program was developed based on a similar ICBT program previously tested in other studies (e.g. Andersson et al. 2005 [158]) but was context-adapted to persons living with heart failure.

A theoretical framework according to CBT theory was used [87, 91-93]. Figure 8 shows a CBT model of how heart failure can cause depression. The inner circle of the model describes perceived losses, threats and stressful symptoms caused by heart failure. This causes negative emotions and creates distorted thoughts leading to the formulation of a negative belief. In turn, the belief affects behaviours that may reinforce the negative emotions and confirm the belief. Overall, this is a process leading to the development of depression (the outer circle). In the model, a vicious circle can be seen since the negative thoughts, emotions and behaviours in turn can reinforce each other or give rise to new negative thoughts, emotions and behaviours.

The nine-week ICBT program aims to help the participant to be active, and to perform homework assignments that enable them to become aware of, and modify, as well as to learn skills to cope with negative thoughts. In the program this therapeutic process is mainly done by helping the participant to make changes in their behaviour. Thus the nine-week ICBT program (Studies II and III) is predominantly focused on behavioural activation, but also includes content related to cognitive-oriented CBT. The program consists of the components of psycho-education, relaxation (only Study III), problem-solving and behavioural activation. Figure 8 describes how the four components in the ICBT work to decrease depression.

Figure 8. A CBT model describing how heart failure leads to the development of depression. The figure also describes how the four components in the ICBT program (1) psycho-education, (2) problem-solving, (3) behavioural activation and (4) relaxation can help to decrease depression by modification of negative thoughts, behaviours and emotions.

The program consists of seven consecutive modules employing different CBT components (i.e. values and goals, psycho-education, behavioural activation, and problem-solving) that have previously been demonstrated to be effective in the treatment of depression. Each module in the program was designed to address different aspects of living with depressive symptoms and heart failure, and contained text and one or more exercises that were assigned as homework (Table 7).

Table 7: Overview of the developed and tested ICBT program (Studies II and III)

Module (week)	Content (CBT component)	Aim	Homework assignment
1 (1)	Introduction (Values and goals)	To inform the participant about the program, how to work with it, and to involve the patient in the intervention.	Identifying values and setting goals for participation in the program.
2 (2)	Living with heart failure (Psycho-education)	To convey knowledge about heart failure, how it is treated, and what it is like to live with heart failure.	Identifying symptoms of heart failure and proposing possible alternative coping strategies. Multiple-choice questions about heart failure.
3 (3)	Depression/depressive symptoms and heart failure. (Psycho-education)	To convey knowledge about depression and the link between depression and heart failure, treatment of depression, and what it is like to live with depression.	Identifying symptoms of depression. Multiple-choice questions about depression associated with heart failure. Identifying fears and worries connected to heart failure and depression.
4 (4 & 5)	Behaviour activation 1 – to enable change (Behavioural activation)	To become aware of how behaviour, thoughts and mood are linked, and to help the patient identify his/her own behaviour.	Mapping activities in a weekly schedule, rating all activities as positive or negative. Making a list of desirable activities, and implementing new desirable activities.
5 (6 & 7)	Behaviour activation 2 – to implement change (Behavioural activation)	To identify what the participant wants to change and to provide training to reduce negative behaviour and increase positive behaviour.	Eliminating negative activities and/or reducing the negative effect of undesirable activities.
6 (8)	Problem-solving: a tool for dealing with problems (Problem-solving)	To identify perceived problems, and to provide training in problem-solving.	Practicing problem-solving.
7 (9)	Consummation	To summarise the program and help the participant to maintain the changes.	Creating a checklist for coping with future setbacks, identifying tools perceived as helpful by the participant.

A healthcare provider gave personalised written feedback on homework assignment, answered questions from participants, and provided guidance to participants regarding progression through the program. (Study II and III)

Based on the qualitative findings in Study II a non-mandatory relaxation exercise (Figure 8) was added to the program before it was used in Study III. No other changes were made to the program between Studies II and III.

Each module was designed with a specific aim. The introduction (module one) provided practical information about the program and how to work with it, and gave an overview of the program content. In the homework assignment for module one, participants were asked to identify their expectations and goals regarding their participation in the intervention. (Studies II and III)

The psycho-education (modules two and three) was used to provide knowledge about different aspects (e.g. explanations of causes and possible treatment strategies) of the participants' health problems (heart failure and depressive symptoms). The psycho educative components in the program were also used to counter the asymmetric relation between participants and healthcare providers about knowledge concerning health problems, thus creating a shared knowledge base regarding depressive symptoms and heart failure between the participants and the healthcare providers. As knowledge about one's health problems is an important aspect of self-care, this and other self-care aspects were also addressed in modules two and three. Homework assignments helped participants to learn to recognise symptoms (of heart failure and depression), and to formulate their own suggestions regarding self-care activities. The participants were also asked to perform knowledge checks in the form of multiple-choice questions. (Studies II and III)

Behavioural activation (modules four and five) was divided into two stages. First, the concept of behavioural activation was explained and the program focused on mapping and assessing activities in the everyday life of the participants. Furthermore, participants were encouraged to identify new and desirable activities and implement one of these activities in their activity plan. Second, the program focused on how to reduce negative activities by providing strategies for either stopping a negative activity or modifying the activity so that it had a less negative influence on the participant's mood. To allow sufficient time for participants to do homework assignments and start to implement behavioural activation, modules four and five were both two-week modules, creating a period of one month for the participants to work on behavioural activation. (Studies II and III)

Problem-solving (module six) was used to provide the participants with a systematic way of identifying, planning and implementing new ways of addressing problems. In the homework assignment, participants were encouraged to test the introduced tool for problem-solving on a number of situations. (Studies II and III)

Module seven contained a summarisation of the program, and the participants created their own plan for handling setbacks in depressive symptoms by reviewing their work in modules one to six and identifying those parts of the program they had gained the most benefit from. (Studies II and III)

Effects of the Program

ICBT decreased the level of depressive symptoms among participants receiving the intervention. In Study II the median level of depression (measured by PHQ-9) decreased from 11 to 8.5. No participant in Study II reported an increase of depressive symptoms when comparing baseline to the post intervention nine-week follow-up. In an intention to treat analysis comparing ICBT against a control group (participating in an online moderated discussion forum) no significant difference regarding depressive symptoms was demonstrated [$F(1,47)=1.63$, $p=0.21$]. However, a within-group analysis in Study III (Figure 9) comparing depressive symptoms at baseline with post intervention follow-up showed a significant decrease in depressive symptoms in the ICBT group (baseline $M=10.8$, $SD=5.7$ vs follow-up $M=8.6$, $SD=4.6$, $t(24)=2.6$, $p=0.02$, Cohen's $d=0.43$). Within-group analysis of the control group showed no significant change of depressive symptoms ($t(24)=0.93$, $p=0.36$). (Study III)

Figure 9. Comparison of level of depressive symptoms between and within groups. Based on data from Study III.

Figures 10 and 11. Comparison of cardiac anxiety and HrQoL between and within groups. Based on data from Study III

Secondary outcomes of cardiac anxiety (measured by CAQ) and HrQoL (measured by the MLHF) showed no significant differences between groups (Figure 10 and 11). Within-group analysis of CAQ showed a significant decrease between baseline and follow-up in the subscale of fear (baseline $M=1.55$, $SD=0.73$ vs follow-up $M=1.35$, $SD=0.60$, $t(24)=2.18$, $p=0.04$, Cohens $d=0.31$). Differences in the CAQ total score, subscales of avoidance and heart-focused attention, as well as in the MLHF (including dimensions of emotional and physical factors) were statistically non-significant in both the ICBT group and the control group. However, the change of six points (baseline $M=41.8$ vs follow-up $M=35.8$), with lower values indicating better HrQoL, in the MLHF within the ICBT group may indicate a clinically significant improvement. The corresponding change in the control group was 1.9 points (baseline $M=47.1$ vs follow-up $M=45.3$). (Study III)

Time Used by Healthcare Provider and Participants

In total, approximately 31 hours, or 29.5 minutes per participant and week (Figure 12) were spent on feedback and support to participants during the nine-week interventions period in Study II. The used time was categorised as treatment-related feedback and support regarding questions on how to use the web platform. Treatment-related feedback required approximately 20 minutes per participant per week. Support regarding use of the web platform required approximately 10 minutes per participant per week. Most support questions were asked during the first week of the intervention and individual need for support varied considerably between participants, ranging from 40 to 170 minutes (Figure 13). (Study II)

Healthcare providers average use of time during the intervention in minutes per week and participant

Figure 12. Illustration of the distribution of time used by the healthcare provider divided into feedback and support.

Figure 13. Illustration of the individual support time for each participant in Study II. Dotted lines are mean and median values.

Factors Related to Outcomes of Depressive Symptoms

Activity in the ICBT program, measured as the number of log-ins by participants, was associated with a decrease in depressive symptoms in participants in the ICBT group ($r = -0.50$, $p = 0.02$). A similar non-significant trend was observed among participants in the control group ($r = -0.32$, $p = 0.17$). In the ICBT group, age had a negative correlation with the number of log-ins ($r = -0.67$, $p < 0.001$) while in the control group the association between age and number of log-ins was not significant ($r = -0.24$, $p = 0.25$). In the ICBT group, women had a significantly larger reduction of depressive symptoms compared to men ($t(19) = 2.12$, $p = 0.048$). The number of completed modules and NYHA class was not associated with change in depressive symptoms. (Study III)

Participants’ Experiences of ICBT

One overarching theme was identified among participants’ experiences of ICBT: ‘ICBT- an effective, but also challenging tool for self-management of health problems’. This theme was constructed based on six categories that were identified during the analysis process (Table 8). (Study IV)

Table 8. Categories and themes describing participants’ experiences of ICBT	
Categories	Theme
Something other than usual healthcare	ICBT – an effective, but challenging tool for self-management of health problems
Relevance and recognition	
Flexible, understandable and safe	
Technical problems	
Improvements by live contact	
Managing my life better	
ICBT- Internet-based Cognitive Behavioural Therapy	

Something Other Than Usual Healthcare

Participants experienced ICBT as something other than what they usually thought of as healthcare. The most prominent difference between ICBT and other forms of healthcare was the experience that participants had to be active agents in ICBT. They described ICBT as something they did (themselves) in contrast to many other forms of healthcare that they thought of as something they received. (Study IV)

Relevance and Recognition

Most participants described at least some parts of the ICBT program as relevant and useful, although there were a few participants that did not experience any benefits from the ICBT program. One important factor contributing to finding the ICBT program relevant was to recognise oneself in the program, to experience that the program matched the health problems of the participant. Finding parts of the program hard to understand (e.g. behavioural activation) or experiencing that the program did not address health problems that participants struggled with

contributed to describing the program, or parts of the program as less relevant or to having problems in recognising one's own situation in the program. (Study IV)

Flexible, Understandable and Safe

Working through the Internet was experienced as flexible. Most participants described it as positive to be able to work at a location of their own choice (mostly the home). Another aspect experienced as mainly positive was to be able to work with the ICBT at a time that suited the individual participant (Studies II and IV). However, the experience of freedom to choose the time and place was also described as challenging by some participants, as it was easy to postpone work with the ICBT (Study IV).

Flexibility was also experienced as participants said that they could adapt the program to their personal needs by focusing time and energy on the parts of the program that they found relevant for themselves and could dedicate less time to parts that addressed topics that they already knew about. (Study IV)

Most participants described the ICBT program as understandable, but working via the Internet was also challenging. This was because they were not used to healthcare being delivered by this medium. Most participants described that it was demanding to read large amounts of text, especially on screen. (Studies II and IV) They also experienced that they had to learn new ways of communicate with the healthcare provider, because such communication was not usually in writing. The written communication also meant that participants had the experience of being anonymous. The experience of anonymity was double-edged as it meant that participants could feel reduced to a number but also that they could be honest and write exactly what they felt and could address sensitive topics more freely (Study IV).

The ICBT program was experienced as safe concerning computer security and integrity towards unauthorised third party access to sensitive data. However, it was described as a challenge to know how to handle personal integrity towards family members when working with ICBT at home. (Study IV)

Technical Problems

Different types of technical problems were described. These problems could be divided into those due to participants' own computer equipment (e.g. old computers) and problems due to the web platform of the ICBT program being perceived as complicated or not providing sufficient automated feedback (i.e. not clearly communicating if homework assignments had been handed in or saved). Postponing work and trying again at a later point, testing different potential solutions, seeking support from other persons

such as family members or the healthcare provider were all described as strategies to handle different technical problems. (Study IV)

Improvement by Real Time Contact

Several participants stated that they would have preferred more real time contact (i.e. direct communication through voice and/or picture) during the ICBT. Real time contact was described as enhancing the experience of feeling cared for. However, the written delayed communication used in the program was also described as valuable and the need for real time communication was described as dependent on the circumstances and the aim of the communication. Participants that described the ICBT program as a learning process also mostly described the written delayed communication as suitable and sufficient. On the other hand, real time communication was described as important as a backup in case something did not work, and was described as desirable as a complement to the written delayed communication. (Study IV)

Managing My Life Better

ICBT was experienced as contributing to managing one's life in a better way. The participants said that they did new things or had taken up old interests to manage their health problems in a more effective way or to experience health (e.g. the participants described that they had learned to think about and address problems in new ways, and had started or restarted hobbies). Some participants had also stopped doing or had changed things they did not feel contributed to their health (e.g. they had changed the way they talked about health problems with their family members or had changed jobs). The participants also described the program as a revelation and said that it had contributed to making them see that they themselves could take an active role in improving their health. (Study IV)

DISCUSSION

This thesis has shown that the proportion of persons with depressive symptoms decreases over time after discharge from hospital. Still, depressive symptoms occur in 26% of community-dwelling persons with heart failure. Moreover, the highest risk of re-hospitalisation and death was found in the group of persons that developed depressive symptoms when not hospitalised. ICBT in the form of a guided self-help program adapted to persons with heart failure is feasible, and the results in this thesis do not show any risk regarding worsening of depressive symptoms. Moreover, this thesis does not show any significant difference between ICBT and the control group participating in a moderated online discussion forum. However, there was a significant reduction of depressive symptoms in those receiving ICBT, when comparing baseline and post-intervention assessments. The change in depressive symptoms (baseline versus post-intervention) was not significant in the control group.

Depression in Persons with Heart Failure

In Study I, 38 % of all persons with heart failure had depressive symptoms at discharge. At the 18-month follow-up, 26% had depressive symptoms. This is similar to other studies on the prevalence of depressive symptoms among persons with heart failure [46, 48, 51]. Worsening of heart failure and hospitalisation can be seen as stressful events, that may trigger depressive reactions [30]. This may explain some of the higher prevalence of depressive symptoms at discharge compared to the 18-month follow-up. Moreover, the natural trajectory of depression means that many depressive episodes resolve within a period of three months to one year [159]. This may provide an explanation for the lower prevalence of depressive symptoms found at the 18-month follow-up compared to baseline in Study I. Another possible explanation for the higher prevalence in hospitalised persons is that overlap of symptoms between heart failure and depression occurs more when someone is hospitalised due to heart failure symptoms.

An increased risk of death and re-hospitalisation was found among persons with depressive symptoms 18 months after discharge from hospital. This risk increase was highest among those that had developed depressive symptoms after discharge from hospital (i.e. in the newly depressed group) (Study I). This suggests that interventions targeting depressive symptoms should be focused on persons developing depressive symptoms when not hospitalised or who retain depressive symptoms for a period of time after discharge from hospital. The exact 'wash-out time' needed after a hospitalisation has not been investigated in this thesis. One indication of

the challenge of distinguishing depressed mood due to stressful life events (such as hospitalisation) from the clinical diagnosis of depression can be found in the DSM 5 [38], which suggests making a diagnosis of depression with great caution in close proximity to a stressful life event. Nevertheless, the emotional response (including depressed mood) in relation to a hospitalisation due to worsening of heart failure is arguably a natural emotional response (cf. Scherer and Mehu 2015 [33]) and allowing natural recovery may be ethical and beneficial, as persons affected would not be subjected to unnecessary treatment and the healthcare system can focus its resources on those in most need of support to regain their health.

The results of Study I, with 26% of the sample having depressive symptoms that were associated with high health risk at the 18-month follow-up, indicate that there is a large group in need of treatment for depressive symptoms. Based on epidemiological data, approximately 222 000 individuals suffer from heart failure in Sweden [3]. Assuming that approximately 20% of those have depressive symptoms [46] the number in need of professional treatment for depressive symptoms, would be approximately 44 000 persons. Most of these are managed in primary care settings [160] and have depressive symptoms that largely go undetected [161]. Pharmacological treatment of depressive symptoms in heart failure is associated with difficulties due to the doubtful effectiveness of SSRI [74, 75] and the risk of severe cardiovascular side effects of TCA [1]. This emphasises the need for alternative treatment strategies, such as psychotherapies. This large group of persons in potential need of treatment and the problems related to pharmacological treatment all leads to a challenge for the healthcare system and calls for new means to provide care. Arguably, ICBT is one such treatment modality with high capacity compared to face-to-face psychotherapies, and with a high degree of accessibility for the community-dwelling population [102], including most persons with heart failure.

As shown in this thesis (Study I) and other studies (Table 2), depressive symptoms have a negative impact on morbidity and mortality in persons with heart failure. Hard end points (e.g. mortality and morbidity) may therefore be seen as logical outcomes of investigating depressive symptoms in heart failure. However, there is a demanding challenge in demonstrating positive effects of interventions on hard endpoints in heart failure. Recent pharmacological trials in heart failure populations show a need for large sample sizes to be able to demonstrate the effects on mortality and morbidity, e.g. McMurray et al. 2014 [162] used a sample with more than 8000 participants. This in combination with the difficulties in recruitment of persons with heart failure and depressive symptoms would post a challenge in the research design. Equally important as the effect on mortality and morbidity is the intervention's ability to improve health. Because health is more than the absence of illness and death, hard outcomes say little about the effect on health. Especially in sever chronic

diseases were some persons may prioritise their QoL over survival. Outcome measures such as depressive symptoms and health-related quality of life describe health related outcomes significantly better, and can therefore be considered better suited as outcomes. This is also in alignment with the ESC, which suggests that interventions aimed at decreasing depressive symptoms should focus on evaluating the effect on depressive symptoms, HrQoL and other outcomes related to changes in health status [1]. Focusing on health-related outcomes also implies that qualitative findings are important outcomes that can be used to improve healthcare (cf. Watson 2012 [163]).

Internet-Based Cognitive Behavioural Therapy

The Impact of ICBT and the Challenges in Recruitment

In this thesis, no significant difference was shown between ICBT and the control condition (online moderated discussion forum) regarding depressive symptoms. However, there was a significant decrease in depressive symptoms between baseline and follow-up in the ICBT group. There was also a significant reduction of fear and what can be described as a clinically important improvement of HrQoL in the ICBT group (Study III). There are a number of possible explanations for these results.

The effect of ICBT for depression has been reported in meta-analysis, with a large pooled effect favouring ICBT over a waiting list [95] and with smaller but significant effects for unguided ICBT [99]. ICBT has also been shown to have similar or equal effect compared to face-to-face CBT [100]. However, in a meta-analysis on publication bias regarding CBT for depression, Cuijpers et al. 2010 [164] reports that the effect size for CBT appears to be substantially smaller when the pooled effect size is controlled for publication bias. Moreover Johnsen and Friberg 2015 [165] reported a decline of the effect of CBT on depression in their meta-analysis, though notably this decline appears to have levelled out in studies published after 1995 as shown by Ljótsson et al. 2017 [166] in their re-analysis of the data from Johnsen and Friberg 2015 [165]. Thus, one has to acknowledge the possibility that ICBT is not effective or have a smaller effect than anticipated in treatment of depressive symptoms in persons with heart failure. Nevertheless, based on the significant decrease of depressive symptoms in the ICBT group and the tendency towards an increased between group difference over time, as well as the improvement of HrQoL (Study III), another plausible explanation for the results is that the study was underpowered. This thesis showed that recruitment of participants was a challenge, due to fiscal circumstances we had to stop recruitment after 50 participants (Study III). Other studies on CBT and ICBT has reported similar challenges in recruiting participants [121, 167].

Despite the fact, as pointed out above, that approximately 44 000 persons in Sweden can be expected to have depressive symptoms and heart failure, the recruitment of participants was slower than expected. Based on experiences from previous ICBT studies (cf. [168] advertisements in newspapers were first used (Study II). As this was not effective, the recruitment method was changed in Study III. Even though personal letters by mail generated a better response compared to newspaper advertisements, the response rates were still lower than expected.

Depression in itself can result in a reduced capacity to make decisions [30], e.g. whether to participate in a research study. The relative novelty of ICBT and similar telehealth interventions may also contribute to low recruitment rates. Among older Swedes, 49% of 66-75 year olds and 24% of those 76 years and older state that they have good computer knowledge. A majority of Swedes over the age of 65 also do not feel included in the information society [169]. Both low perceived computer knowledge and not feeling included in the information society may constitute barriers to the recruitment of persons living with heart failure in studies on ICBT. Other recruitment strategies, such as professional referrals and prevalence recruitment may appear attractive, but have also been reported as less successful. In one ICBT study using prevalence recruitment within primary care, an estimated sample of 11504 eligible persons was assumed based on point prevalence for depression and anxiety disorders. However, the clinicians responsible for recruitment only identified 1606 eligible participants. Thus 1606 study information packs were sent out. Of those receiving an information pack ($n=1606$) only 21 persons completed the consent and screening process and seven were actually included in the study [170]. As recruitment methods that have a high degree of access to potential study participants do not appear to result in equally high recruitment rates, there appear to be other factors involved in the decision-making process regarding participation in ICBT studies. One such factor may be low perceived computer knowledge among the elderly. A plausible solution could be to combine recruitment via information letters with information meetings in which potential participants could see and test the intervention platform, and thus be better able to make a decision regarding whether their individual computer knowledge was sufficient for participating in an ICBT study.

An alternative or contributing factor to the non-significant difference between ICBT and the control condition is that there was a small nominal (but non-significant) decrease in depressive symptoms in the control group. This small decrease of depressive symptoms may have been due to natural variation in depressive symptoms, spontaneous remission of depressive symptoms, or due to a potential antidepressant effect of the online discussion forum that participants in the control group took part in. The online discussion forum contained elements such as encouraging active participation, sharing experiences about health problems, and

strategies to handle health problems, and may have provided social support to the participants. Thus, the online discussion forum share some similarities to psycho-education and behavioural activation, both known to have effects on depressive symptoms [90, 94]. Furthermore, social support has been demonstrated to protect against depression [171] and online social support has been suggested as a nursing intervention to alleviate distress [172]. Thus, future research on the specific effects of online discussion forums for persons with heart failure and depressive symptoms would be of interest, especially research investigating if there are any specific characteristics distinguishing persons that gain health benefits from this type of intervention. As an online discussion forum requires less resources from the healthcare system compared to ICBT it appears a potentially attractive alternative for persons with a high likelihood of having beneficial outcomes from online discussion forums. Another subject for future research to investigate is whether the combination of peer-support (e.g. via discussion forums) and ICBT has any effect on depressive symptoms compared with ICBT only.

Feasibility of ICBT and the Need for Context-Adapted Programs

The results in this thesis suggest that ICBT is feasible for persons with heart failure (Study II) but needs further refinement before implementation in clinical practice. Nevertheless, this is an important result since few studies have investigated ICBT in this population, which is older and has less computer skills compared to other populations in which ICBT has previously been evaluated. The mean ages of the participants involved in ICBT in this thesis (Studies II and III) were 62 and 63 years respectively. Persons with heart failure are generally older, with a mean age of 77 years in the Swedish population [3]. However, the age of the participants in this thesis was considerably higher compared to the mean age of 38 years in previous studies of ICBT (mean age in 38 studies of Internet-delivered psychological treatment [95]). In Sweden, 88% of all 66-75 year olds use the Internet and for persons aged 76 or older, 48% are Internet users. This can be compared with Swedes 65 years old or younger, of whom 96-100% use the Internet [173]. Even though most persons use the Internet in their daily life, the use of telehealth interventions such as ICBT is not as common [173], and may therefore be associated with barriers. In Study IV, the participants described encountering technical problems, and ICBT was experienced as something they were not used to, indicating the need for more implementation research regarding how to successfully implement ICBT into the healthcare system for persons with heart failure.

The ICBT program used in this thesis was adapted to fit the context of heart failure and depressive symptoms (Study II). Experiences of recognition and perceiving the program as relevant were reported in the findings. However, there were also participants that experienced a lack of recognition and relevance in the program (Study IV). Previous studies have shown that participants want an ICBT program to acknowledge health problems due

to chronic somatic disease as this would increase the perceived relevance of the ICBT [113, 114]. There are only a few studies on ICBT in the context of persons living with chronic somatic disease [113, 114, 174]. Thus, there is little knowledge about how recognition and relevance is created in ICBT for persons living with chronic somatic disease. Findings in this thesis revealed that some of the participants experienced that the ICBT program did not sufficiently address some of their health problems e.g. stress and worries, and non-heart failure-related physical health problems (Study IV). As indicated in Study IV, it is a challenge to balance the requirements for contextual and individual adaptation with the benefits in terms of accessibility that a more generalised treatment program offers. One way to deal with this could be to use a person-centred care approach (cf. Ekman et al. 2011 [175]), by enabling the participant, in discussion with the healthcare provider, to construct an individualised program. However, such a solution would require access to a large number of treatment modules or advanced software that could create "new" treatment programs tailored to each individual. A more realistic alternative may be to develop a possibility to establish communication between therapists and those treated so that they can agree on the purpose and extent of treatment. It is also important to critically evaluate ICBT and, through continued research, create a better picture of which people can benefit from ICBT treatment and for whom ICBT may not contribute to increased health.

Role and Requirements on Feedback Providers in ICBT for Persons with Heart Failure and Depressive Symptoms

Persons living with heart failure and depressive symptoms often have complex health problems. In this thesis, many participants had at least three coexisting health problems (or diseases) (Studies I-III). Other studies report that multimorbidity is common in heart failure. Chamberlain et al. 2015 [176] reported that most persons with heart failure had at least two additional chronic conditions, with other cardiovascular diseases being the most common. Taylor et al. 2017 [177] reported that 99.1% of all persons presenting with heart failure in a primary care context had at least one other chronic condition, and 53.4% had six or more conditions. Providing guiding and feedback to persons with complex health conditions may be challenging and may require a broad competence profile. At the same time, research shows that though feedback in ICBT is important, the professional background of the feedback provider in ICBT for depression appears to be less important [178]. One study comparing clinician-guided ICBT with ICBT supported by a technician showed no difference in outcome between the therapist group and the technician group [107]. Even though the formal education and clinical experience of CBT may not be important factors in ICBT feedback, other therapist factors have been identified as important. Feedback that affirms and encourages the participant and includes self-disclosure about the feedback provider correlates with a decrease in depressive symptoms in ICBT [179]. Furthermore, task reinforcement, task

prompting, self-efficacy shaping and empathic reinforcement are correlated with module completion, and deadline flexibility is negatively associated with outcome [180](such as reduction of depressive symptoms). Thus, providing feedback to persons with heart failure and depressive symptoms requires a broad knowledge base regarding both physical and psychological health problems. The provider should also have basic knowledge regarding CBT and important factors related to giving feedback in ICBT, and be able to consult different specialists, e.g. cardiologists and psychologists. Thus, nurses and other healthcare professionals used to working with a holistic perspective on health may be suitable as feedback providers in ICBT for persons with heart failure and depressive symptoms. However, if ICBT were to be implemented in heart failure care there would be a need for shorter education regarding ICBT and the role of the feedback provider among clinical staff.

ICBT – an Effective, but Challenging Tool for Self-Management of Health Problems

Two fundamental aspects of CBT are learning (e.g. new behaviours or strategies) and implementing new ways of behaving and thinking in everyday life, both requiring the participants in ICBT to be active [85]. In Study IV, participants' experiences of ICBT were mostly positive. ICBT was described as helpful and had contributed to participant changing the way they thought about their own situation and what they themselves could do to improve their health (Study IV). However, the participants had to be actively engaged in ICBT and self-management, something that was experienced as challenging and demanding (Study II and IV). Many ICBT programs are described as self-help programs [181], as is the case with the ICBT program in this thesis. From the theoretical standpoints of both CBT [87] and self-care [18], ICBT may be seen as a type of healthcare intervention aimed to improve self-care and make the participant take an active part in the treatment. In Study IV, ICBT was experienced as something one did for oneself; as a tool for self-management of health problems. However, not all persons in need of treatment and support will be able to take an active role in their treatment. Thus, there is a need for the development of other treatment strategies. Face-to-face interventions may be one option in these situations since some persons are used to and therefore prefer such interventions [182]. Nevertheless, ICBT may still be an important tool in the treatment of depressive symptoms in persons with heart failure. This as implementation of ICBT programs in clinical praxis could be an option to free up more therapy resources for persons that not can draw advantage of ICBT.

One challenge with ICBT was that participants experienced it as unusual (Study IV). Lately, there has been a shift towards telehealth [183] and self-care [184] within the professional healthcare system. However, this shift may not have been fully adopted by the users of health services [185]. Thus, it appears that healthcare and the users of healthcare in some situations

are out of step with each other, even though there is research demonstrating that persons that take an active role and have good knowledge regarding their treatment often have better outcomes in self-care [186] and HrQoL [187]. Thus, there is no benefit gained if the healthcare system does not support the users in how to become active participants in their own healthcare and the use of telehealth.

In this thesis, the participants described it as an advantage that they could adjust the ICBT to their needs, e.g. by skipping parts of the program that they perceived they knew or had already completed (Study IV). However, persons sometimes tend to overestimate their own capacity and knowledge in many situations. This may lead to persons taking decisions that are known to have a negative effect on their health [188]. Thus, healthcare personal is often faced with a complex dilemma of balancing between respecting the decisions made by persons seeking healthcare and the obligation to provide evidenced based healthcare and support persons in taking informed decisions. One way of reducing the risk of misconceptions could be to improve the readability and understandability of ICBT programs. Health literacy research indicates that well designed written information contributes to improved understanding of health problems [189].

ICBT challenges the traditional view of the caring relationship, as this is dependent on the physical presence of nurses and patients [183]. Methods and experiences from a predominantly face-to-face based healthcare system may not be possible to transfer to ICBT and other similar forms of telehealth. Though not explored in this thesis, a possible way to tackle this challenge could be by learning from other areas such as research on mass and social media. Mass media has illustrated the possibility for persons to establish relationships even with fictional characters [190]. Social media have shown the ability to activate persons [191]; for example, using behaviour modifications and positive feedback through likes and positive status updates could be one option in ICBT. Another example could be the use of positive role models in alignment with fictional characters in literature and film.

Rumination over the Positive Progress in this Thesis

In writing a discussion one tends to focus on areas and topics in the results that are in need of further development and contain challenges. This may be necessary to help in pointing out a direction for future research and to prevent others from repeating mistakes already made. However, it can also appear to reduce the importance of positive results and properly working strategies. A short summary reflection also on the positive aspects on the results may therefore be warranted. At the start of the project constituting the basis for this thesis, there was an awareness that depressive symptoms in heart failure are common [46]. Furthermore, little was known about how to effectively treat depressive symptoms in heart failure. Pharmacological

treatment had not been shown to be effective [74], and although CBT appeared a possible treatment option only a small number of mostly small studies had evaluated it in persons with heart failure and depressive symptoms [116, 117, 119]. Although ICBT for depression had demonstrated a good effect [102], there were no known attempts to adapt and use ICBT in a heart failure context. This thesis has contributed by showing that persons that develop depressive symptoms outside hospital care are the ones with the highest mortality and morbidity risk. Furthermore, a feasible ICBT program for depressive symptoms in persons with heart failure has been developed and tested. Though the efficacy of the program has not been fully clarified, important lessons regarding the recruitment of participants have been learned, and the experience of participating in ICBT has been described. Thus, arguably, this thesis contributes a small but important step in improving healthcare for persons with heart failure and depressive symptoms.

Methodological Considerations

Generalisation, Reliability, and Validity

When quantitative research methods are used, as in Studies I, II and III, there is often an ambition to generate a result that can be generalised by inferring results from the sample to the population. In this thesis, there are a number of limitations to consider when it comes to generalisation of the quantitative results.

In Study I, the data collection ended five years before the publication and may today be considered as old. An important concern in regard to generalisation is therefore to consider if there have been any considerable changes in the treatment of heart failure, and such changes have indeed occurred (cf. Ponikowski et al. 2016 [1], Swedberg et al. 2005 [192], Dickstein et al. 2008 [193], McMurray et al. 2012 [194]). Nevertheless, the prevalence of heart failure [195] and of depressive symptoms in heart failure and the association of these symptoms with mortality and morbidity in persons with heart failure appear to be relatively constant over time (cf. Rutledge et al. 2006 [46], Jani et al. 2016 [48]). Thus, from the temporal perspective, the sample in Study I appears to be representative of the heart failure population of today. Another important aspect when considering the generalisation of quantitative results is the sample size, as this must be sufficiently large to infer results from the samples to the population [196]. In Study I, the included sample was considerably smaller compared to the sample size calculation for the original COACH study, and no new sample size calculation for Study I was performed, indicating a need for caution in interpreting the results. However, in a recent study on the prognostic impact of depression screening on four-year mortality in persons with heart failure, Deveney et al. 2016 [197] calculated a need for 372

participants. Though the design of Deveney et al. 2016 [197] differs from that of Study I in this thesis, the similarities in sample and follow-up time suggest that the 611 persons included in Study I represented a sufficient sample size. As the purpose of Study II was not to generate generalisable quantitative results, but to test the feasibility of the ICBT program, the small sample is justifiable. A sample size calculation in study II may have improved the quality of the study. However, sample size calculations are rarely reported in feasibility studies [198]. Moreover, from a research ethical perspective [199], including a large number of participants in newly developed and untested interventions may not be justifiable as the potential risks are not yet known. In Study III, the small sample size is a considerable limitation of the results. Thus, the results have to be interpreted with caution. However, depressive symptoms and HrQoL are strongly associated [22]. The significant decrease of depressive symptoms together with the trend of improvement of HrQoL within the ICBT group, and the lack thereof in the control group suggest that lack of statistical power and the small sample size are plausible explanations for the non-significant between group results.

The age of the participants and the countries that they live in may affect the possibility of generalisation the quantitative results of this thesis. To enable generalisation, the sample must be representative of the population [200]. The samples were recruited in the Netherlands and Sweden, which are two north European countries with similar educational level [201], health status [202], access to healthcare, and allocated healthcare resources [203]. From this perspective, generalising results to other similar contexts, such as north European high-income countries, appears justifiable. In this thesis, the age of the participants was considerably younger (mean age 62-69 years of age) than the mean age of the heart failure population (mean age 77 years of age [2]). Moreover, the sample in Study I significantly differed from excluded persons that did not have complete data on depressive symptoms, and in Study III the sample was self-selected. This may have caused a bias in the results. Thus, it appears appropriate to interpret the results in terms of efficacy [204], bearing the limitations of generalisation in mind, and not effectiveness, which implies that the results are generalisable to the populations of persons with heart failure and depressive symptoms.

Valid and reliable instruments were used in all quantitative studies. In this thesis the interest has been to investigate the effect of ICBT on depressive symptoms among persons that were affected by such symptoms. Thus, the validity of the results in this thesis is strengthened by the fact that the included samples in Studies II and III consist of participants with depressive symptoms at baseline. Scoring and interpretation of scores were handled according to the instructions for each instrument. In Studies II and III, web-based self-assessment instruments were used. This may have an impact on how the results are interpreted. Even though the used self-

assessment instruments have shown acceptable validity and reliability, there are some variations reported between self-assessments and assessments made by clinical experts regarding depressive symptoms [205]. Thus, comparing results in this thesis with results based on clinical assessments may require some caution. The instruments administered via the web, and used in this thesis (CAQ, MADRS-S, MLHF, and PHQ-9) were all originally developed as pen-and paper questionnaires. The inter-format reliability for CAQ has not been specifically reported. However, studies of other instruments reports largely equivalent psychometric properties between pen-and-paper and Internet versions [206, 207].

Trustworthiness of Qualitative Findings

In this thesis, qualitative data was collected by interviews. The qualitative research interview is one of the most common ways of collecting qualitative data and is known to be able to generate rich data [132]. There are also other possible sources of qualitative data that could have been used in this thesis. The written materials in the form of homework assignments and messages between study participants and the feedback provider could have been included in a qualitative content analysis. If other data sources had been included in the qualitative analysis, the findings would probably have provided a broader construct of the findings.

The use of telephone interviews as a way of collecting qualitative data may have reduced the richness in the data compared to interviews performed face-to-face. However, there are some studies suggesting that telephone interviews can generate sufficient data comparable with traditional face-to-face interviews [208, 209]. The interviews in this thesis were assessed to be rich in data. Furthermore, face-to-face interviews would have reduced the number of participants in Study IV. In the trade-off between variation and purposeful sampling, and the richness of individual interviews, the telephone interview was assessed to be a suitable tool for data collection.

Findings from qualitative research strive to increase and broaden the in-depth understanding of a phenomenon, usually within a certain context. Thus, findings are generally not generalisable, but may be transferable from one situation and sample to another [132]. The qualitative findings in this thesis are constructed from data generated by participants that all had experiences of the investigated phenomena (the ICBT program and ICBT). Furthermore, the participants were asked to share their own experiences of the ICBT program and/or ICBT. Thus, there is a clear link between the participants' human world experience of ICBT and the findings in this thesis, all contributing to establishing the credibility of the findings [132]. A possible limitation of the findings in this thesis is that they were not member-checked, something that is often recommended within the social constructive paradigm [210]. However, it has been proposed that there is a paradox in the use of member-checking within a social constructive paradigm. Member-checking implies one reality or that the construct of the

human world of the participants is truer compared to the construct described by the authors. Furthermore, it has been proposed that member-checking leads to confusion about the findings rather than confirmation [211]. In the present study no member-checking was conducted; however it should be acknowledged that the findings would probably have reflected a somewhat different construction of the human world if it had been performed.

To provide a transparent and clear description of the research process, the analysis process has been described in detail, and memo writing was used to document the analysis process. To establish that findings and interpretations are based on the data, triangulation between three different researchers was used during the data analysis. This was also done to present understandable and reasonable findings.

By describing the context, the characteristics of the participants, and the data analysis process, an assessment of the transferability [132] of the findings to other contexts and samples is facilitated.

Design Challenges in Evaluating Complex Interventions

Study III had a self-selected sample, which may have biased the results. However, virtually all intervention research on humans consists of self-selected samples, as it would be unethical to include participants that do not or cannot consent to participation [199]. Self-selection bias is a research problem that in some situations may be more realistic to handle with transparent reporting and acknowledgement of its existence. From the perspective of the medical research paradigm, RCT studies are generally considered to provide the strongest evidence [212]. However, when it comes to complex interventions, where the effect of the intervention is not only dependent on variables that can be controlled by the researcher, one needs to consider if other research designs may be more suitable in providing meaningful results. Arguably, ICBT and other forms of psychotherapies are such interventions. This because the effect of ICBT is not only dependent on the intervention but also on factors such as the motivation of the participant. One way to address the problem with evaluating the effect of complex interventions could be to use preference-based recruitment and sampling techniques in which study participants are referred to different interventions based on their own preference [213]. Ideally, RCT studies can be used to demonstrate efficacy, then RCT studies can be followed by preference-based studies to evaluate the effectiveness of different sub-populations, thus generating results that are meaningful in the clinical context and can be used to improve healthcare.

Implications

The results and findings in this thesis will contribute to a better understanding of depressive symptoms in persons with heart failure. Depressive symptoms are common among persons with heart failure and have a negative impact on mortality, morbidity, and Hr-QoL, especially among community-dwelling persons. Thus, depressive symptoms among persons with heart failure need to be assessed and addressed continually in the clinical routine. ICBT is a plausible solution for treatment of depressive symptoms in heart failure, and can be facilitated by healthcare personnel with basic knowledge of CBT. ICBT also seems feasible for a young-old population. However, further refinements of ICBT programs are needed and their efficacy and effectiveness needs to be established in further research. As active participation is experienced as core in ICBT, both nurses and other healthcare personnel, and persons that may be eligible for ICBT must thoroughly informed about the active role of the patient in ICBT before it can be implemented in clinical praxis. The purpose of such information is to achieve consensus with the participating persons about roles and activity before and during ICBT interventions.

Future Research

During the work on this thesis, several ideas for future research developed. These were ideas originating from both results and findings in the studies and from identified gaps in the literature.

To establish the efficacy (or lack thereof) of ICBT for treating depressive symptoms in persons with heart failure there is a need for larger scale studies with sufficient sample sizes. Furthermore, the long-term effect of ICBT needs to be investigated.

The specific effect of online moderated discussion forums by themselves or in combination with ICBT needs to be investigated. Also, it would be of interest to evaluate the use of CBT-inspired telehealth interventions as tools for patient education regarding health problems (both physical and psychological) and primary prevention in heart failure care.

Further research is also needed to better understand the characteristics of persons that can benefit from ICBT, in order to discriminate between persons likely to have a good ICBT outcome and those in need of other types of intervention.

Finally, there is also a need to better understand barriers and facilitators for telehealth interventions among both healthcare users and healthcare personnel. How caring relations are best formed when healthcare providers and recipient are at a distance from each other is an important aspect to investigate. Also, more concrete aspects such as overcoming technical problems and clarifying how ICBT could best be implemented in the healthcare system need to be addressed.

CONCLUSIONS

After discharge from hospital, depressive symptoms decrease spontaneously among a large proportion of persons with heart failure, though depressive symptoms are still common in persons with heart failure that are community dwelling. Depressive symptoms in persons with heart failure are associated with increased risk of death and hospitalisation. The highest risks are found among persons with long-term ongoing depressive symptoms and those developing depressive symptoms while not hospitalised.

ICBT for depressive symptoms in heart failure is feasible. An intervention with a nine-week guided self-help program with emphasis on behavioural activation and problem-solving skills appears to contribute to a decrease in depressive symptoms and an improvement of HrQoL.

When ICBT is delivered to persons with heart failure and depressive symptoms, the participating persons request contextual adaptation to health problems related to heart failure and depressive symptoms. ICBT is experienced as a useful tool for self-care and as something other than usual healthcare. ICBT also requires active participation by the persons receiving the intervention, something that sometimes was experienced as challenging by the persons participating in ICBT.

SVENSK SAMMANFATTNING

Depressiva symtom är vanligt förekommande hos personer som har hjärtsvikt, betydligt vanligare än i grupper av människor med jämförbar ålder och könsfördelning. Hjärtsvikt är förenat med oförutsägbara symtom, en dålig prognos och låg hälsorelaterad livskvalité. Dödligheten och sjukligheten hos personer med hjärtsvikt är också hög. Kombinationen av depressiva symtom och hjärtsvikt ökar såväl dödlighet som sjuklighet samtidigt som den hälsorelaterade livskvalitén sjunker jämfört med personer som enbart har hjärtsvikt. De negativa hälsomässiga konsekvenserna som depressiva symtom i samband med hjärtsvikt innebär är väl kända. Dock saknas kunskap om hur man på ett bra sätt hanterar och behandlar depressiva symtom hos personer med hjärtsvikt. Läkemedelsbehandling med de vanligast förekommande antidepressiva preparaten, Serotonin återupptagshämmare, har inte visat sig effektiv. Kognitiv beteendeterapi (KBT) har i ett fåtal studier visat positiv effekt på depressiva symtom hos personer med hjärtsvikt. Dock råder det brist på utbildade KBT terapeuter vilket försvårar sådan behandling. För att lösa problemet med brist på KBT terapeuter har användningen av internetbaserad KBT (IKBT) föreslagits. IKBT har visat sig effektiv vid behandling av milda och måttliga depressiva symtom men är inte utvärderat hos personer med hjärtsvikt.

Avhandlingens övergripande syfte var att beskriva hur depressiva symtom utvecklas över tid hos personer med hjärtsvikt, samt att utveckla och utvärdera ett IKBT program för behandling av depressiva symtom hos personer med hjärtsvikt. Vidare skulle erfarenheterna av IKBT utforskas hos personer som deltagit i IKBT.

Avhandlingen bygger på studier med såväl kvantitativ som kvalitativ utformning. I studie I rekryterades de 611 deltagarna i Nederländerna. De sju deltagarna i studie II rekryterades via annonser i svenska dagstidningar. Deltagarna i studie III (50 deltagare) och IV (13 deltagare) kom från samma grupp av personer som rekryterade via brev som skickades till alla personer som haft en vårdkontakt på grund av hjärtsvikt vid någon av fyra kardiologiska eller medicinska kliniker på fyra olika sjukhus i sydöstra Sverige.

Studie I hade en kvantitativ longitudinell utformning där data samlades in i samband med utskrivning från sjukhus och efter 18 månader. Ytterligare data rörande sjuklighet och dödlighet samlades in 36 månader efter utskrivningen från sjukhus. I studie II användes tre olika designmodeller: I) Behandlingsprogrammet utformades och anpassades till den specifika situationen för personer med depressiva symtom och hjärtsvikt genom att

forskning, litteratur och klinisk erfarenhet sammanställdes inom en multiprofessionell grupp. II) Programmet genomförbarhet utvärderades kvantitativt genom datainsamling rörande depressiva symtom före och efter genomförandet av behandlingen samt tidsåtgången för behandlaren. III) Studiedeltagarnas erfarenheter av IGBT programmet undersöktes genom intervjuer som analyserades med en kvalitativ innehållsanalys. Studie III var utformad som en randomiserad och kontrollerad studie där ett nioveckors IGBT program anpassat till personer med hjärtsvikt och depressiva symtom prövades mot ett modererat diskussionsforum via internet. Data rörande depressiva symtom, hälsorelaterad livskvalité och hjärtrelaterad ångest samlades in före och efter interventionerna i de båda grupperna. I studie IV användes en kvalitativ metod för att utforska studiedeltagarnas erfarenheter av IGBT. Data samlades in genom kvalitativa telefonintervjuer och analyserades genom kvalitativ innehållsanalys.

Medelåldern bland studiedeltagarna varierade mellan 62 och 69 år, i de i avhandlingen ingående studierna. De flesta studiedeltagarna upplevde hjärtsvikts symtom vid måttlig eller lätt ansträngning, motsvarande funktionsklasserna NYHA II och III. Den vanligaste kroppsliga samsjukligheten var ischemisk hjärtsjukdom och de allra flesta var läkemedelsbehandlade för sin hjärtsvikt. Sex procent av deltagarna i studie I och 43% respektive 18% av deltagarna i studie II och III behandlades med antidepressiva läkemedel.

Hos de personer som lagts in på sjukhus på grund av hjärtsvikts symtom hade 38% depressiva symtom. Vid uppföljning 18 månader efter utskrivning förekom depressiva symtom hos 26% av deltagarna. Symtomutvecklingen av depressiva symtom kunde kategoriseras i fyra olika grupper: 1) Inga depressiva symtom. 2) Depressiva symtom som gått tillbaka. 3) Pågående depressiva symtom. 4) Nyutvecklade depressiva symtom. Den högsta risken för återinläggning på sjukhus och död fanns hos personer i grupperna med pågående och nyutvecklade depressiva symtom.

Ett nioveckors IGBT program bestående av sju moduler som alla inkluderade hemuppgifter utvecklades och testades. Under behandlingen fick deltagarna skriftlig återkoppling på sitt arbete av en behandlare. Gällande IGBT programmets effekt på depressiva symtom så kunde ingen signifikant skillnad visas mellan de båda behandlingsgrupperna (IGBT och diskussionsforum). Dock fanns det en signifikant minskning gällande depressiva symtom inom IGBT gruppen när baslinjevärden och uppföljningsvärden jämfördes. Motsvarande förändring i diskussionsforumsgruppen var inte signifikant.

Studiedeltagarnas erfarenheter av IGBT beskrevs i ett tema: IGBT- ett effektivt men också utmanande verktyg för egenvård av hälsoproblem. Temat baserades på sex kategorier: Något annat än vanlig hälso- och

sjukvård; Relevans och igenkänning; Flexibelt, förståeligt och tryggt; Tekniska problem; Förbättringar genom direktkontakt; Att hantera sitt liv på ett bättre sätt.

Sammanfattningsvis visar avhandlings resultat att flertalet av de som har depressiva symtom i samband med utskrivning från sjukhus förbättras spontant. Dock är depressiva symtom vanligt även hos personer med hjärtsvikt utanför sjukhus. Depressiva symtom medför en ökad risk för död och sjukhusinläggningar, med den högsta risken hos de personer som har depressiva symtom som pågår över lång tid eller som utvecklar depressiva symtom när de inte är inlagda på sjukhus.

IKBT för personer med depressiva symtom och hjärtsvikt är genomförbart. Användandet av ett nioveckorsprogram med fokus på beteendeaktivering och problemlösning tycks bidra till minskade depressiva symtom och förbättrad hälsorelaterad livskvalité.

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Sökord

Depression, Egenvård, Hjärtsvikt, Internetbaserad kognitiv beteendeterapi, Kognitiv beteendeterapi, Patienters upplevelse, Telehälsa

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