Diagnosis, mortality, and professional life in patients with heart failure

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Varje år ska hjärtat slå
Ungefär 30 miljoner gånger
Men så slå då!
Slå
Slå
Slå

Ur *Det här är hjärtat*, 2015
Bodil Malmsten

To Hjalmar

ABSTRACT

Background:
Heart failure (HF) is a common and severe disease with an increasing incidence among young adults. An emerging composite endpoint is home-time. Little is known, on how living with HF affects professional life.

Methods and results:
In Paper I, we used medical records of 965 of patients 20-100 years with HF 2000-2012 to validate the diagnosis according to the European Society of Cardiology´s current guidelines. The diagnosis was validated as definite, probable, and miscoded HF in 601 (62.3%), 310 (32.1%) and 54 (5.6%) cases, respectively. In Paper II and III, we used the National patient register, the Cause of Death Register, and the Longitudinal integrated database for health insurance and labour market studies (LISA). In Paper II, home-time during 4-years follow-up was calculated for 388 775 patients 18-84 years, 1992-2012. Home-time increased over the study period for both age groups. Patients 18-64 years had more home-time than those 65-84 years (83.8% vs. 68.2%), mainly due to lower 4-year mortality rate (14.2% vs. 29.7%). In Paper III, time on sickness benefit during 2-year follow-up was estimated for patients and controls 18-60 years, 1995-2016. Sickness benefit time declined over the study period for both groups, with a steeper decline for patients. In Paper IV, patients 16-<55 years diagnosed with HF or dilated cardiomyopathy 1997-2016, had their records examined and 294 patients still alive and living nearby, participated. Two thirds of patients were male, mean BMI was elevated. Patients in blue-collar, compared to white-collar occupations were significantly more weighed down by thoughts of work at home, and had a lower working capacity in relation to physical demands, but were not more often on current sick leave.

Conclusion:
Validity of the HF-diagnosis was high, supporting the use of this register in HF-research. Patients with HF in Sweden had an increasing home-time over two decades and young patients had more home-time than older patients. Time on sickness-benefit was higher for HF-patients than for controls and decreased in both groups, but steeper in patients than controls. Most young adults with HF were male, had an elevated BMI and patients of blue-collar occupations reported more job strain than patients of white-collar occupations.

Keywords: Heart failure, young adults, home-time, sick leave, working condition

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LIST OF PAPERS

This thesis is based on the following Papers, referred to in the text by their Roman numerals.

I Schaufelberger Maria, Ekestubbe Sofia, Hultgren Simon, Persson Hans, Reimstad Ann, Schaufelberger Mattias, Rosengren Annika. Validity of heart failure diagnoses made in 2000-2012 in western Sweden.
ESC Heart Failure 2020; 7: 37-46

II Ekestubbe S, Fu M, Giang KW, Lindgren M, Rosengren A, Schioler L, Schaufelberger M. Increasing home-time after a first diagnosis of heart failure in Sweden, 20 years trends.
ESC Heart Failure 2022; 9: 555-563

III Ekestubbe S, Lindgren M, Basic C, Giang KW, Rosengren A, Thunström E, Schiöler L, Schaufelberger, M. Decreasing time on sickness benefit days for patients with heart failure over two decades.
In manuscript

IV Ekestubbe S, Lindgren M, Giang KW, Rosengren A, Schaufelberger M. Impact of heart failure on professional life, in young adults.
In manuscript

CONTENTS

ABBREVIATIONS

BMI	Body Mass Index
CDR	The Cause of Death Register
CHARM	The Candesartan in Heart failure Assessment of Reduction in mortality and morbidity
COPD	Chronic obstructive pulmonary disease
DAOH	Days Alive and Out of Hospital
DCM	Dilated CardioMyopathy
ECG	ElectroCardioGram
ESC	European Society of Cardiology
HF	Heart Failure
HFmrEF	HF with mildly reduced ejection fraction
HFpEF	HF with preserved ejection fraction
HFrEF	HF with reduced ejection fraction
HR	Hazard ratio
ICD	International Classification of Diseases
IPR	In-Patient Register
KM	Kaplan-Meier
LISA	Longitudinal integrated database for health insurance and labour market studies
LVEF	Left Ventricular Ejection Fraction
MAGGIC	Meta-Analysis Global Group in Chronic
NPR	National Patient Register
PARADIGM-HF	Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PIN	Personal Identity Number
PPV	Positive Predictive Value
QoL	Quality of Life
TPR	Total Population Register
US	United States
WHO	World Health Organization

INTRODUCTION

Definition of heart failure

Heart failure (HF) is a medical syndrome caused by structural and/or functional abnormalities of the heart causing elevated intracardiac pressure and/or inability to produce enough cardiac output to maintain adequate oxygenation in the tissues of the body (1). This causes typical, yet unspecific symptoms and clinical signs that could also have many other causes, especially in older patients (2). The most typical symptoms of HF are breathlessness, orthopnea, paroxysmal nocturnal dyspnea, reduced exercise tolerance, fatigue, and ankle swelling, and the most specific clinical signs are elevated jugular venous pressure, hepatojugular reflux, third heart sound, and laterally displaced apical impulse, even if pulmonary rales and ankle swelling are more common (1).

Several diagnostic criteria are available such as the Framingham criteria (3), the Boston criteria (4), and the Gothenburg criteria (5). In addition, the European Society of Cardiology (ESC) regularly produces guidelines on the diagnosis and treatment of HF. In the latest (2021) three types of HF are defined: HF with reduced ejection fraction (HFrEF), HF with mildly reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF) (1). All types of HF require typical symptoms (clinical signs can be absent in the early stages) and objective evidence of cardiac dysfunction, usually in the form of echocardiography with a different cut-off value of left ventricular ejection fraction for the different types; ≤40%, 41-40% and ≥50%. HFpEF also requires objective evidence of left ventricular diastolic dysfunction.

The epidemiology of heart failure

HF is a common disease with severe consequences and high health care costs globally (6-8). The incidence of HF varies between studies; in Sweden it was estimated to 3.8/1000 person-years in 2010 and the prevalence was estimated to 2.2% (9). In Western countries, in total, the age-adjusted incidence is decreasing while the prevalence is increasing, this discrepancy is likely caused by an ageing population since incidence and prevalence of HF increase with age (10-12).

Despite advances in diagnostics and therapy, the mortality of HF remains high, with mortality rates comparable to those of some of the most common cancers (13). The estimated 1-year mortality is about 25% (11, 14) and the 5-year mortality about 50% (9, 13, 14). A study combining data from the Framingham Heart Study and the Cardiovascular Health Study, found an estimated 4-year mortality of 57% (15). Reports on the trends of mortality over the last decades are conflicting. A Swedish study comparing patients with HF of ischaemic and non-ischaemic aetiologies from 1987 to 2003 found a marked decrease in 3-year mortality in men aged 35 to 64 years with ischaemic etiology and a less marked reduction in 3-year mortality for women (16). This study found no further reduction in mortality after 2001 (16) while other studies from Sweden have found a decrease in mortality from 2006 to 2010 (9), from 2005-

2013 (17) and from 1987-2014 (18). From the United States (US), there are several concerning reports that the mortality rates have recently begun to increase (19-21).

Young adults

HF is primarily a disease of the elderly, and most studies reflect this. However, studies of younger patients have emerged recently. Young adults with HF differ from older patients in many aspects, from etiology to prognosis; they are more likely to be obese, to have dilated cardiomyopathy (DCM) (22-24) and congenital heart disease (24). The prevalence of DCM was 63% in patients <40 years old in the pooled data from register studies and randomized clinical trials from the Meta-Analysis Global Group in Chronic (MAGGIC) consortium (22). In the three randomized clinical trials with a broad range of HF-patients in the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM)-program, the prevalence of DCM was 62% in patients <40 years old (23).

In a Swedish study based on the national hospital discharge register, the prevalence of cardiomyopathy was 19.7% and 12.6% in patients 18-44 and 45-54 years, respectively (25). In a Danish study using the Danish nationwide registers, an increase in prevalence of cardiovascular risk factors and cardiomyopathies was observed (26). The increase in DCM was especially steep with a rise in prevalence from 5% to 10%, between 1995 and 2012. It has been estimated that 25% of cases in a Western population are hereditary, but the underlying cause for DCM is often unknown (27). Other possible etiologies are, e.g., chronic inflammation secondary to systemic inflammatory diseases, myocarditis, drugs, alcohol or peripartum cardiomyopathy. Overall, the incidence of HF in young adults has increased over the last decades (25, 26, 28, 29). Two studies found an increase in the age-adjusted first HF-hospitalization rates for young men, 20-44 years (30) and 20-64 years (31), while the incidence for all other groups decreased, including women <65 years. Two of the proposed reasons for this increase in young adults are the increasing prevalence of obesity (32, 33), and decreasing cardiorespiratory fitness (34) in this group.

The mortality of young adults with HF is lower than for older patients (22, 23), but still high and the estimated loss of life-years increases with decreasing age. A study from the Swedish Heart Failure Register reported 1-year all-cause mortality for patients <55 years corresponding to 4.2% (24). Also, for 50% of patients aged 20, the number of life years lost was estimated at 36 or more. A recent nationwide Swedish study comparing patients with HF to controls, found that patients 16-64 years had a higher risk of long-term mortality (>11 years) than controls with hazard ratio (HR) 3.16 and 4.11 in 1987-2000 and 2001-2014, respectively (18). However, the reports of trends in mortality among young adults are conflicting. In Denmark 1-year mortality rates declined for middle-aged patients but remained constant for patients <45 years (26), and in Sweden 1-year case fatality was reduced in both younger and older patients but no further significant improvement in case fatality occurred in the <55 year age group after 2001 to the end of the study period 2006 (25). However, another recent Swedish study found decreasing short- and long-term mortality for patients with HF 18-64 years 1987-2014 (18). In the US, HF-related mortality increased for patients 15-44 years from 2012 to 2019 (35).

Home-time

In addition to the frequently reported endpoints incidence, prevalence and mortality for HF, Days Alive and Out of Hospital (DAOH) or home-time, has been used sparingly to illustrate HF outcomes. In stroke research, this endpoint is reported more often, and has been shown to correlate well with functional level after stroke (36, 37). Since it is easy to calculate, it represents a cost-effective approach to the follow-up of large cohorts (36-39). For stroke patients, being "alive at home, without recurrent stroke, and without being hospitalized for complications" was the most important outcome, which was translated into home-time (40).

In a study from the CHARM-program, DAOH was proposed as an alternative composite outcome and a mean increase in DAOH for patients on candesartan vs. placebo of 24.1 days was reported (41). This corresponds to a mean increase in percent DAOH (percent of total follow up time spent alive and out of hospital) of 2.0%. Furthermore, significant differences in percent DAOH were observed for Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) and the CHARM overall program (42). DAOH increased for patients with HF in New Zealand 1988 – 2008, despite an ageing population (43). More recently it was reported that home-time in patients with HF >65 years, correlated well with more commonly used endpoints such as mortality and hospital readmissions, in a US population (44). The mean home-time in this population was 244 days at 1-year follow-up and the largest contributor to reduced home-time was death. Chronic obstructive pulmonary disease (COPD), dementia and renal deficiency were associated with less home-time.

To improve care for patients with HF, or any other disease, studies of the disease and its effect on populations is necessary. It can be done in different ways, with epidemiologic register studies being one piece of the puzzle. This requires that we agree on how to classify the disease. To be able to rely on the registers where diagnoses are reported, a validation of the most important diagnoses is necessary.

International classification of diseases – a brief history

To invent, for statistical purposes, a classification of diseases which cause death has been attempted many times. François Bossier de Lacroix (1706-1777) is suggested as the first person who attempted to systematically classify diseases (45). A century later, John Graunt wanted to estimate the proportion of liveborn children who died before age six, this was complicated by the fact that he had no records of age at death. Therefore, he totalled the number of deaths attributable to conditions known to commonly cause death in young children (e.g., thrush, rickets, abortives), and half of the deaths attributable to conditions known to cause death in both younger and older children (e.g., smallpox, measles, swinepox). His estimate, 36% mortality before the age of six, was later confirmed by more accurate evidence.

The current International Classification of Diseases (ICD) was preceded by the first International Classification of Causes of Death. In 1891, The International Statistical Institute appointed a committee lead by the Chief of Statistical Services of the City of

Paris, Jacques Bertillon, with the making of a classification of causes of death (45). This was later used by an increasing number of countries and revised many times. Gradually, the need for an internationally recognized classification of non-fatal diseases grew and at the Fifth Decennial Revision Conference a resolution was adopted to compile an International List of Diseases. Since the sixth revision of the ICD, which was conducted in 1948, the World Health Organization (WHO) has overseen the classification. The latest revision, ICD-11, was adopted by the 72nd World Health Assembly in 2019 and entered into force on 1st January 2022 (46). ICD-11 includes, for the first time, codes for traditional medicine. ICD is available in 43 languages and are being used by all member States of the WHO. The most common use of the system is to report mortality data, 177 countries use the ICD for this purpose (47).

Validity of the diagnosis of HF

National register based epidemiological studies offer valuable real-life-data from large populations provided that the coverage and quality of the registers are high. One important quality aspect is the validity of the studied diagnosis, that is whether the diagnosis is correct or whether there is an under- or overdiagnosis. The reported validity of the diagnosis of HF varies between studied populations and the methods used in the validation. Studies using the ESC criteria reported high specificity (99%) and high positive predictive values (PPV) (77% and 84%), but lower sensitivity (29%) (48-50) while a study using three clinicians' assessments as "gold standard" reported high specificity and PPV (99.7% and 85.9%, respectively) and slightly higher sensitivity than studies using the ESC criteria (48.5%) (51). Higher validity was reported among cardiologists (97.5%) and internists (85.0%), but lower among general practitioners (73.1%) and other physicians (69.1%) (52).

In Sweden, the validity has been sparsely studied. A study found a high validity for cardiomyopathy diagnoses (86.6%) in Western Sweden (53). In a primary care population, the ESC diagnostic criteria were fulfilled in only about 30% of the patients and the diagnosis was based on symptoms alone or in combination with a pathologic chest X-ray and/or electrocardiogram in 69% of the patients (54). The validity in the Swedish hospital discharge register was higher (95%) among men with HF as a primary diagnosis 1976-2001, reported by Ingelsson et. al. (55).

Sick-leave and return to work for patients with heart failure

Despite having an equal or lower symptom burden than older patients, young adults with HF report a lower quality of life (QoL) (22, 23). One aspect of life that differs between young and old patients is workforce participation and, specifically, expectations concerning physical capacity. This might explain some of the variation in QoL observed between age groups.

Studies investigating the effect of HF on sick-leave or the capacity to return to work are scarce. Following a first myocardial infarction, the greatest risk factor for not returning to work was co-existing HF (56). In a Danish study of patients aged 18-60 years with a first hospitalisation for HF, only 42% of patients had fully returned to the workforce after one year (57). Predictors of returning to work was being male, of younger age or having a higher education level or income. More than a third of patients were still on part-time sick leave after three years. In addition, the same research group found that being treated with target and near target doses of evidence-based therapy, was associated with a lower risk of becoming detached from the work force following a first hospitalisation for HF (58). In a third study from the same research group, being unemployed at the time of the first hospitalization for HF was associated with increased mortality and risk of readmission (59). Furthermore, low cardiorespiratory fitness in adolescent Swedish males predisposed to receiving a disability pension for HF later in life (60).

Patients on sick leave due to HF in Sweden, reported inequalities in social supports between different socioeconomic groups; patients with low income, lower level of education and who were unmarried, needed more support than they received (61). HF-patients on sick leave also graded their health as worse compared to other people of the same age and having a good self-rated health was strongly associated with positive encounters with healthcare professionals (62).

Occupational level and health

There are several differences in health parameters between blue- and white-collar populations, however the findings are sometimes complex.

White-collar workers were more sedentary at work than blue-collar workers, but the amount of sedentary time was comparable on weekends (63). Sedentary behavior, such as sitting or watching television, is associated with cardiovascular and all-cause mortality (64, 65). However, while the increased risk of mortality for prolonged sitting, was eliminated with a higher level of physical activity, this was not true for watching television (66). Contrary, a high level of occupational physical activity (more common in blue-collar occupations) in men was associated with an increased risk of early mortality (67).

In a Swedish study, high job strain was associated with an increased risk of cardiovascular disease in blue-collar workers but not in white-collar workers (68). Another Swedish study found a higher risk for cardiovascular disease in people of blue-collar and low-skilled occupations compared to white-collar occupations (69). Around half of the increased risk was mediated by lower cardiorespiratory fitness, higher body mass index (BMI), less exercise, and more smoking in the blue-collar and low-skilled group.

Regarding sickness absence, low occupational class have been reported to be associated with higher prevalence of sickness absence overall in a large population in Finland (70) and cuts in sickness benefit mainly affected sickness absence for blue-collar workers (71). However, despite different job demands, white- and blue-collar workers reported similar health complaints (72).

AIMS

The overall aims of this thesis were to investigate different aspects of living with HF, more specifically home-time, time on sickness benefit and working conditions, with an emphasis on patients of working age. A valid diagnosis is key for HF-research, thus Paper I provides a basis for the other Papers. The aims of the individual studies are listed below:

I To validate the diagnosis of HF according to the ESC guidelines among patients hospitalized in Gothenburg, Sweden.

II To compare trends in home-time for patients with HF between 18-64 and 65-84 years in Sweden 1992-2012.

III To compare trends in sickness benefit days for patients with HF and controls in Sweden 1995-2016 and to investigate predictors for sickness benefit days for HF patients.

IV To compare patient characteristics and perceptions of job strain for patients with HF of blue- and white-collar occupations.

PATIENTS AND METHODS

The national Swedish registers

Epidemiological studies on HF incidence, prevalence and mortality are often based on national registers. Sweden is a leading country on register-based studies due to the long history of keeping registers of their population and that the Swedish personal identity (PIN) number enables linkage between different registers and thus studies of large populations (9, 10). There are several national registries frequently used in medical research in Sweden the ones used in this thesis is described as follows.

The Total Population Register

The Statistics Sweden are responsible for the Total Population Register (TPR), created in 1968. The registry is an extract from the National registration of the population and contains information on PIN, age, sex, name, address, citizenship, country of birth, births, deaths, immigration, emigration, residence permits and family relations (73). This register can be used for different research purposes such as follow-up of study participants regarding date of death and immigration, selection of controls and study participants in cohort studies. Strengths of the TPR are its completeness, consistency of definitions over time and the possibility to link this register to others via the PIN (74). Limitations include over- and under-coverage. The latter may for example occur when immigrants and deaths are not reported to the register. Over-coverage on the other hand, could occur when the death of emigrants is not reported. Furthermore, some emigrants may not report having emigrated since they believe they might benefit from remaining in the registers, by receiving social benefits for example. Foreign-born individuals have a lower mortality than people born in Sweden in the register, which may suggest that a substantial number of foreign-born individuals in the register are not truly residing in Sweden (75).

The National Patient Register

The National Patient Register (NPR) was founded by the National Board of Health and Welfare in 1965 but did not reach national coverage until 1987 (76). The purpose of the register is stated as to follow the development of the health of the public over time, improve the possibility to prevent and treat diseases, contribute to the development of the healthcare and to follow the quality of the healthcare. From 2001 and onwards, the register also holds information on out-patient care, but only from specialized care and not from primary health care. The National Inpatient Register (IPR) is a part of the NPR containing information from the hospital discharge registers only. The NPR also contains information from private caregivers from 2001 since it became mandatory for all caregivers within specialized healthcare to report to the NPR. The validity of the IPR is high for many, but not all, diagnoses (77). For example, comparison between the IPR and other separate quality registers found a high proportion of cases, >95%, identified through IPR for a first stroke, heart surgery, cholecystectomy, and carotid artery surgery. However, a lower proportion of cases, <79%, were found in the IPR for endoscopic retrograde cholangiopancreatography, multiple sclerosis, and cataract surgery (77).

The Swedish National Cause of Death Register

Sweden has one of the oldest records of causes of death in the world. A system with national coverage for registering population statistics was launched in 1749 (78). The clergy compiled information on deaths and cause of death from parish registers and this was then aggregated on county level followed by national level. The priests were responsible for reporting the cause of death and since there were very few doctors, the priests mostly had to decide on what caused a death themselves. This was a very unpopular task among the priests and thus, in 1831, the register was limited to only contain deaths due to smallpox and other epidemics, childbirth, accidents, crime or suicide. In 1911, all deaths were again mandatory to report and in 1951 the register was adapted to the ICD-6 from WHO.

Since 1991 the reporting is based on two forms filled in by one or more doctors: a notification of death and medical death certificate. The first is a legal obligation and must be completed before burial can take place while the second one must be made within three weeks of the death and is the basis of the Cause of Death Register (CDR). Most certificates are not based on autopsies today. The frequency of autopsies in Sweden has decreased from 41% to 14% and 31% to 7% for men and women, respectively, between 1987 and 2021 (79). The general accuracy of the death certificates was estimated to 77%, when comparing diagnoses listed on the cause of death certificate to diagnoses reported to the IPR 1995 for patients who died in the hospital (80). The accuracy differed between diagnoses and was highest for malignant neoplasms (90%) and ischaemic heart disease (IHD) (87%) and was lowest for benign, other and unspecified tumors (40%) and for chronic obstructive and other pulmonary diseases (47%). For "other heart disease" the accuracy was estimated to 65%. The Statistics Sweden reported that in 2020, only 0,9% of deaths did not receive a medical death certificate with cause of death specified (79).

The Longitudinal integrated database for health insurance and labour market studies

The Longitudinal integrated database for health insurance and labour market studies (LISA by Swedish acronym) is an integration database of several different national registers provided by Statistics Sweden and covers the population >16 years (>15 years since 2010) registered in Sweden every December 31 since 1990 (81). The register provides annual data for statistics in labor market and health research, and it is based on individuals present in the TPR. It was founded as a response to the rising sick leave numbers in Sweden. In medical research it is most used to retrieve information on educational level, sick leave and disability pension, and unemployment, but it also contains information on for example marital status, migration, foreign background, occupation and income. Some variables are available both on individual and family level.

Sickness compensation in Sweden

Commissioned by the Swedish Government, the Swedish Social Insurance Agency [Försäkringskassan] published a report in 2020 analysing the development of sick leave in Sweden (82). Sick leave rates were generally record high in the beginning of the 21st century, with almost 800,000 people receiving some kind of reimbursement for sickness absence in January 2005. Hence, the Swedish government set a goal to reduce paid sick leave by 50% by 2008. Consequently, the administration for public health insurance initiated several changes resulting in a decline in the paid sick leave rate from 2003. Concomitantly, there was an increase in the sickness compensation rate (formerly known as early retirement due to sickness) with a peak of approximately 10.5% of the population receiving sickness compensation in 2005, thereafter the sickness compensation rates also declined (83).

Overview of the thesis

Paper I and IV were cross-sectional studies, Paper II was a retrospective study and Paper III was a case-control study. An overview of the four Papers is shown in Table 1.

Study populations

The Sahlgrenska University Hospital is a teaching hospital in Sweden's second largest city, Gothenburg, that receives around 350 000 patients each year (84). It is the largest hospital in Sweden and one of the largest in Europe. In Paper I, all patients with a discharge code I50 (ICD-10) from a cardiology or internal medicine ward, 2000-2012 were identified. Patients discharged alive and deceased were included in the search and this comprised 27 517 patients from which a sample of 1100 patients was randomly selected - half with HF in a primary position and half in a contributory position. Paper IV used discharge codes from the Sahlgrenska University hospital to identify patients 16-54 years with a first hospitalization for HF (I50) or DCM (I42) 1997-2016. In the first part of the study, the records for these patients were reviewed and those considered to have a correct diagnosis of HF were registered in a special form. Patients alive and still living in the area were invited to the second part of the study: a visit to a research nurse.

In Paper II and III, patients alive 1 day after discharge for a first hospitalization for HF were identified in the NPR using the codes 428.A, 428.B, 428.X (ICD 9) or I50 (ICD 10) and in addition for Paper II: 427.00, 417.10 (ICD 8). We defined a first hospitalization as not having a preceding diagnosis of HF in the NPR seven years prior. The study period was 1992-2012 and 1995-2016 for Paper II and III, respectively. In Paper II, patients were then divided into two age groups: 18-64 and 65-84 years. For Paper III, patients 18-60 years and alive one day after discharge were included, and we also recruited five controls per patient, matched for age, sex and municipality. Patients and controls were divided into two age groups: 18-44 and 45-60 years.

Methods

Paper I

Medical records were reviewed, using the digital record system when available. This was however not fully introduced until 2002 so when records were lacking in the digital version, the hospitals local and regional archives were contacted and provided fur-

Table 1. Overview of the four Papers

	Paper I	Paper II	Paper III	Paper IV
Study design	Cross-sectional	Retrospective cohort	Case-control	Cross-sectional
Data sources	Medical records	NPR, LISA, CDR	NPR, LISA, CDR	Medical records, clinical and laboratory data, questionnaires.
Study population	Patients 20-100 years, hospitalized for HF at internal medicine or cardiology clinics at the SU 2000-2012	Patients 18-84 years with a first hospitalization for HF in Sweden 1992-2012	Patients 18-60 years with a first hospitalisation for HF in Sweden 1995-2016 and control subjects matched by age, sex, and municipality	Patients 16-54 years with a first hospitalization for HF or DCM at the SU 1997-2016
Exclusion criteria	Having a scheduled procedure, missing diagnosis, missing digits in PIN, transfer between hospitals, severe dementia, missing medical records	Reused PIN, missing in LISA, died at index hospitalization or the day after	Immigrated/emigrated within 7 years prior to index hospitalization, missing in LISA, lacking matched controls, early retirement up to 2 years prior to index	Being deceased, living too far away from the hospital, insufficient knowledge of the Swedish language
Statistical methods	Descriptive statistics, T-test, Mann-Whitney U test	Descriptive statistics, Kaplan-Meier estimator, Cox proportional hazard regression	Descriptive statistics, zero-inflated negative binominal regression	Descriptive statistics, T-test, Mann-Whitney U test
Main outcome	Validity of the HF diagnosis	Percent home-time of 4-year follow-up, by sex, age group and year of first hospitalization	Percent sickness benefit days of 2 years follow-up, by age group	Patient characteristics and patient perceptions regarding professional life by occupational class
Covariates	N/A	Age, duration of index hospitalization, educational level, marital status, IHD, cancer, atrial fibrillation/flutter, diabetes mellitus, COPD, stroke, hypertension, cardiomyopathy, valvular disease, asthma, congenital heart disease.	Male sex, Swedish citizenship, educational level, marital status, unemployment, hypertension, diabetes mellitus, IHD, atrial fibrillation/flutter, valvular disease, cardiomyopathy, congenital heart disease, stroke, pulmonary embolism, chronic kidney disease, cancer, non-psychotic mental illness, psychotic mental illness, alcohol abuse, substance abuse, stress-related disease, musculoskeletal disease	N/A

Abbreviations: N/A; non applicable, NPR; national patient register, LISA; longitudinal integrated database for health insurance and labour market studies, CDR; cause of death register, PIN; personal identity number, HF; heart failure, DCM; dilated cardiomyopathy, SU; Sahlgrenska University Hospital.

ther information. Information from the index hospitalisation was collected on a form and generated in total 65 variables. For patients with HF as a contributory diagnosis, information on examinations and comorbidities were also collected from previous medical records.

The ESC guidelines were used as basis of the validation. New updates of the guidelines were published several times during the study period (2000-2012). Thus, several different versions were used in the validation. We stipulated that it took a year for a new version of the guidelines to be implemented in the clinics and therefore we used the 1995 (85), 2001 (86), 2005 (87) and 2008 (88) guidelines for patients with an index hospitalisation 1992-2001, 2002-2005, 2006-2008 and 2009-2012, respectively. The 1995, 2001 and 2005 version of the guidelines required appropriate symptoms and cardiac dysfunction on imaging for a diagnosis of HF while the 2008 version also required appropriate clinical signs for a definitive diagnosis. Some clinical signs were now also considered equivalent to cardiac dysfunction on imaging: third heart sound, cardiac murmur, and elevated natriuretic peptides. Table 2 shows an overview of how the ESC guidelines were used in the study.

Table 2. Diagnostic assessments supporting or opposing the heart failure diagnosis from the different ESC guidelines used in the study

	1995	2001	2005	2008
	Supports if present/ Opposes if normal or absent	Supports if present/ Opposes if normal or absent	Supports if present/ Opposes if normal or absent	Supports if present/ Opposes if normal or absent
Appropriate symptoms	+++*/---	+++*/--	+++*/---	++*/--
Appropriate signs	+++/-	+++/-	+++/-	++*/-
Response to treatment	+++/---	+++/---	+++/---	+++/--
Pathological ECG	/---	/---	/---	++/--
Cardiac dysfunction on imaging	+++*/---	+++*/---	+++*/---	+++**/--
Chest X- ray	+/-	+/-	+/-	+++/-
Natriuretic peptides	n/a	+ (if elevated) /---	+ (if elevated) /---	+++ (if elevated) /---

Abbreviations: +/- of some importance, ++/-- of particular/ considerable importance, +++/--- of major importance, ECG; electrocardiogram, ESC; European society of cardiology. * Necessary for definite diagnosis. ** Considered objective evidence of cardiac dysfunction. This assessment is adapted from the heart failure diagnostic guidelines edited by the ESC in 1995, 2001, 2005 and 2008. *Reprinted with permission from the publisher. Schaufelberger et. al. ESC Heart Failure 2020; 7: 37–46*

The HF diagnosis was classified as definite, probable, or miscoded. Where the initial validation caused uncertainty, two cardiologists examined the records and made a final decision together.

Paper II

Information on baseline variables were collected from the NPR and the LISA-register. Comorbidities were obtained from the NPR; all discharge codes 7 years prior to index and from the index hospitalisation were searched for relevant codes from ICD 8, 9 and 10 (Appendix 1). Educational level and civil status were obtained from LISA, from 2 years before the index hospitalisation. If data was missing in LISA, we used information from 1 year before or from the index year instead.

The outcome variable was home-time, calculated as time spent alive and out of hospital. Thus, information on all days spent at hospital and deaths were collected from the IPR and the CDR, respectively. The total follow-up was 4 years. When a patient died, the remaining days until 4 years had passed were registered to enable the calculation of home-time.

Paper III

Information regarding age, sex and comorbidities was collected from the NPR using the same principle as in Paper II. In addition, we included non-psychotic and psychotic mental illness in this Paper since psychiatric diseases are a common reason for sick leave. ICD-codes for non-psychotic and psychotic mental illness were adapted from a study by Robertson et al. (89). From LISA, data regarding citizenship, educational level and marital status was obtained. Date of death was collected from the CDR.

The outcome variable, sickness benefit days, was also collected from LISA. The information was available as net sickness benefit days for one year, i.e., total days receiving some form of sickness benefit from the Swedish welfare system that is obtainable from the 15^{th} day of each sick leave period. The variable is net days, for example four days with 25% sickness benefit each day equals one net sickness benefit day. Patients were followed yearly from index and the two subsequent years.

Paper IV

In the first part of the study, patient records were reviewed, and discharge ICD-9 codes and EF were collected from the index hospitalisation while all subsequent records were examined for eventual cardiac resynchronization therapy, implantable cardiac defibrillator and heart transplantation.

In the second part of the study, a research nurse examined patients and collected anthropometric measurements, blood tests, information on current medication and handed out three questionnaires. Two of the questionnaires were adapted from the INTERGENE/ADONIX-study and have been previously described (90). The third questionnaire contained supplementary questions regarding socioeconomic factors. All questions used in this study are listed in Table 3.

Table 3. A compilation of the questions and answer options used in Paper IV

Are you currently on sick leave?				
Yes	No			
Have you ever smoked cigarettes regularly?				
Yes	No			
Have you become unemployed?				
Yes, both the last year and earlier	Yes, both the last year and earlier	No		
Have you been forced to change jobs?				
Yes, both the last year and earlier	Yes, both the last year and earlier	No		
In the past 12 months, have you had difficulties meeting expenses for food, rent, bills, etc.?				
Yes, on one occasion	Yes, on several occasions	No		
Do you use snuff or smoke a pipe/cigarillos/cigars daily?				
Yes, I snuff	Yes, I smoke pipe/cigarillos/cigars	No		
What is your current marital status?				
Married or co-habiting	Unmarried	Divorced	Widow or widower	
Where were you born?				
In Sweden	In Norway, Denmark, Finland, or Island	In another European country	In another country outside of Europe	
Do thoughts of work weigh you down when you are at home?				
Never	Seldom	Sometimes	Often	Nearly always
When the work becomes physically troublesome, do you have the opportunity to slow down or work differently, so that the discomfort is reduced?				
Yes	Often/yes	Sometimes/no	Seldom/no	Never or almost never
Do you have the opportunity to decide on your planning of work tasks/working hours?				
Never	Seldom	Sometimes	Often	Almost always
Do you feel rested and recovered when you start work?				
Yes	Often/yes	Sometimes/no	Seldom/no	Never or almost never
How do you assess your current work ability to be in relation to the physical demands of the work?				
Very good	Good	Acceptable	Poor	Very poor

The questionnaires could be filled out at the visit or taken home to be completed and mailed in at a later occasion.

Based on patients stated occupation (in free text), they were classified as blue- or white-collar workers (Table 4), based on the Swedish Standard Classification of Occupations (91).

Table 4. Classification of blue- and white-collar workers by subgroups, adapted from the Swedish Standard Classification of Occupations

White-collar occupation	Blue-collar occupation
Managers	Agricultural, horticultural, forestry and fishery workers
Operation managers in service industries	Building and manufacturing workers
Occupations requiring advanced level of higher education	Mechanical, manufacturing and transport workers
Occupations requiring higher education qualifications or equivalent	Non-commissioned officers
Administration and customer service clerks	Other military ranks (e.g., privates)
Service care and shop sales workers	
Commissioned officers	

Stastistics

Common to all Papers was that descriptive statistics was used to present the distribution, central tendency, and variability of the baseline data. The distribution of frequencies was presented as number (percentage). Symmetrically distributed continuous variables were presented as mean (standard deviation) and continuous variables of skewed distributions were presented as median (interquartile range). Pearson's Chi-Square test were used to compare categorical variables and the Mann-Whitney U test was used to compare ordinal variables or continuous variables with a skewed distribution. Normally distributed continuous variables were compared using the Independent samples T-test. A two-tailed p-value of <0.05 was considered statistically significant in all Papers.

In Paper II, the Kaplan-Meier (KM) estimator was used to estimate cumulative mortality (92). The KM estimator is an estimator of the survival function, i.e., the probability of being event free past a certain time. It is frequently used to handle differing times-to-event, especially when not all subjects continue in the study until the event takes place. The studied outcome must be dichotomous and in medical research it is often used to analyze survival, but it is also used to study other time-to-event outcomes. The cumulative mortality was presented as Kaplan-Meier curves (a plot over the Kaplan-Meier estimator over time) by sex and time-period.

To analyze mortality over the study period and to enable adjustment for other covariates, Cox proportional hazard regression was used (93). This semi-parametric regression model is the most used in medical research since it is powerful and easy to use. The outcome generated by the model is the hazard ratio: an estimate of the ratio of the hazard rate in two groups compared. An easily understood description of the HR has been proposed by Spruance et. al. “The difference between hazard-based and time-based measures is analogous to the odds of winning a race and the margin of victory. The hazard ratio is the odds of a patient’s healing faster under treatment but does not convey any information about how much faster this event may occur.” (94). The model requires several assumptions to be made. Firstly, the censoring in the data must be random or noninformative and this assumption must be considered in the study design and the data collection. Secondly, the model assumes that the hazards are proportional meaning that the hazard ratio is constant over time. This assumption can be tested by comparing the Kaplan-Meier curves or plotting the scaled Schoenfeld residuals. To avoid making assumptions regarding linearity we modelled the continuous variables using cubic restricted splines.

In Paper III, Cox regression could not be used since the outcome was not binary but a count (percent time on sickness benefit). The dependent variable also had an excess of zeros; patients who had zero days on sickness benefit predominated. Furthermore, there was overdispersion, i.e., an excess variability, in the data. A zero-inflated negative binominal regression was chosen – the zero-inflation to account for the excess zeros and the negative binominal regression to account for the overdispersion (95). This model also assumes that the excess zeros are due to a separate process from the count values – in Paper III all patients not eligible for sickness benefit days could not be completely excluded and were likely partly a reason for the excessive number of patients with zero sickness benefit days.

Ethical commentary and reflection

The main ethical risk in this thesis is the risk of integrity violations. In all Papers, PIN was used to access medical records or link different registers. To minimize the risks, the data collected from registers and medical records was not marked with the PIN but with new serial numbers created specifically for each study and thus the data was always kept and handled de-identified. The keys, connecting the PIN to the anonymized serial number, are stored on a USB flash drive, locked into a safe. Informed consent was gathered for Paper IV but not for Papers I-III. With nationwide register-based studies, informed consent is not needed which is argued for in the ethics application. Firstly, due to the retrospective design many patients are deceased at the time of the study. Furthermore, the register used are national registers maintained by different parts of the government and no consent is needed to be included in the register. With large population sizes it is also impossible to identify any of the individuals included in the study based on published data.

In Paper IV, informed consent was gathered for patients accepting to participate in the study visit. However, many patients declined to participate when invited by the study nurses and we wanted to ask them the reasons for declining and record them. This gives us possibility to better analyse any potential bias this might lead to. An additional application was filed and approved by the ethics committee, also approving that this second invitation was made by doctors over the phone.

The Papers conform to the Declaration of Helsinki (96) and are approved by the Ethical review board, see Table 5.

Table 5. Ethical approvals

	Ethical review board	Diary number
Paper I	Gothenburg	588-11, 582-12
Paper II	Gothenburg	540-11, T063-13, 026-12, T908-16
Paper III	Gothenburg	540-11, T063-13, 026-12, T908-16
Paper IV	Gothenburg	865-12, 504-15, T306-16, T606-16, T413-18

RESULTS

Validity of heart failure diagnoses 2000-2012 in Western Sweden

In Paper I, we investigated the validity of the HF diagnosis in patients discharged from internal medicine or cardiology wards at the SU, 2000-2012.

Of the 1100 patients randomly selected for the study, a total of 135 were excluded, 22 for having a scheduled procedure, 53 for missing the HF diagnosis/clinic other than cardiology/internal medicine/outside the selected age range/missing digits in PIN, 12 for transferring to another hospital, 37 for missing medical records and 11 for having severe dementia or another similar condition affecting the possibility to report symptoms. After exclusions, 965 patients remained, and their records were validated.

In total, 487 (50.5%) patients were women and 535 (55.4%) had HF as a primary diagnosis (Table 6). The mean EF was 41.9% for the 681 who had an EF recorded.

Validity

Cases were classified as definite, probable and miscoded HF for 601 (62.3%), 310 (32.1%) and 54 (5.6%) cases, respectively. In total, the diagnosis was considered valid (definite or probable HF) in 94.4% of cases. The years 2009-2012 where the 2008's ESC guidelines were used, had 82.6% definite cases compared to the other 3 time periods with around 55% cases classified as definite. Most miscoded cases had died from sudden cardiac arrest or had a malignancy.

Patient characteristics by group of validity

The most frequent co-morbidities were IHD, atrial fibrillation/flutter and hypertension. Cases with definite HF had significantly less thyroid disease (6.8% vs. 12.9%) and more renal failure (17.6% and 11.9%) and elevated creatinine (57.4% vs 52.8%) than cases with probable HF (see Table 4 in Paper 1). Dyspnea, orthopnea, and weight gain were significantly more often reported by cases classed as definite than probable HF (Table 7). Echocardiography was performed in 96.7%, 34.2% and 57.4% of patients with definite HF, probable and miscoded HF, respectively (Table 6).

Not having performed an echocardiography was the most common reason to be classified as probable rather than definite HF. Pathological ECG (definite 96.6%, probable 96.0% and miscoded 79.2%) and congestion on chest X-ray (definite 71.5%, probable 73.0% and miscoded 38.6%) were more common in definite and probable cases than in miscoded cases.

Increasing home-time after a first diagnosis of heart failure in Sweden, 20 years trends

In Paper II, we estimated home-time and compared trends in home-time over the study period for patients 18-84 years with a first hospitalisation for HF in Sweden 1992-2012.

Table 6. Patients' characteristics according to validity of diagnosis

	Total	Definite HF	Probable HF	Miscoded HF	Definite vs. probable	Definite vs. miscoded	Probable vs. miscoded
	n=965	n=601	n=310	n=54	p-value	p-value	p-value
Age (years), mean (SD)	78.7 (11.2)	76.9 (11.4)	81.9 (9.6)	81.1 (12)	.000	.009	.615
Female sex, n (%)	487 (50.5)	273 (45.4)	186 (60)	28 (51.9)	.000	.364	.262
Diagnostic position[a], n (%)							
Primary	535 (55.4)	350 (58.2)	165 (53.2)	20 (37)	-	-	-
Contributory	430 (44.6)	251 (41.8)	145 (46.8)	34 (63)	-	-	-
Echocardiography performed, n (%)	718 (74.4)	581 (96.7)	106 (34.2)	31 (57.4)	.000	.000	.001
Ejection fraction, mean (SD)	41.9 (15.3)	39.5 (14.7)	52.0 (13.6)	56.7 (8.1)	.000	.000	.029
	n=681	*n=560*	*n=95*	*n=26*			
NT-proBNP (ng/L), median (IQR)	3620 (1638-8492)	3770 (1875-9420)	2820 (1258-6250)	2400 (-)	.194	-	-
	n=194	*n=165*	*n=26*	*n=3*			
Pathologic ECG[b], n (%)	850 (95.5)	547 (96.6)	265 (96.0)	38 (79.2)	.644	.000	.000
	n=890	*n=566*	*n=276*	*n=48*			
Congestion on x-ray, n (%)	635 (70.4)	402 (71.5)	216 (73)	17 (38.6)	.654	.000	.000
	n=902	*n=562*	*n=296*	*n=44*			
Positive response to treatment, n(%)	622 (92.8)	408 (93.8)	195 (92.4)	19 (82.6)	.352	.000	.001
	n=669	*n=435*	*n=211*	*n=23*			
Hospital[a, c]					.000	.047	.850
Sahlgrenska hospital, n (%)	353 (36.6)	184 (30.6)	144 (46.5)	25 (46.3)	-	-	-
Mölndal hospital, n (%)	194 (20.1)	129 (21.5)	54 (17.4)	11 (20.4)	-	-	-
Östra hospital, n (%)	418 (43.3)	288 (47.9)	112 (36.1)	18 (33.3)	-	-	-
Speciality[a]					.000	.028	.915
Internal medicine clinic, n (%)	777 (80.5)	455 (75.7)	274 (88.4)	48 (88.9)	-	-	-
Cardiology clinic, n (%)	188 (19.5)	146 (24.3)	36 (11.6)	6 (11.1)	-	-	-

Abbreviations: n; total number of subjects, HF; heart failure, ESC; European Society of Cardiology, NT-proBNP; N-terminal pro brain natriuretic peptide, ECG; electrocardiogram, SD; standard deviation, IQR; interquartile range. When the total value of a variable was less than five no comparison between the groups was made due to statistical reasons. [a] P-values for all subcategories. [b] In 19 cases the ECG could not be located and the journal text was not specific enough to confirm or rule out any pathology so these patients were not included in the analysis. [c]The Sahlgrenska University Hospital is constituted by three different hospitals. *Reprinted with permission from the publisher, Schaufelberger et. al, ESC Heart Failure 2020; 7: 37–46*

Table 7. Symptoms and clinical signs in patients with a diagnosis of heart failure, n (%)

	Total	Definite HF	Probable HF	Miscoded HF	Definite vs. probable	Definite vs. miscoded	Probable vs. miscoded
	n=965	n=601	n=310	n=54	p-value	p-value	p-value
SYMPTOMS							
Dyspnoea	804 (83.3)	536 (89.2)	243 (78.4)	25 (46.3)	.000	.000	.000
Fatigue	303 (31.4)	201 (33.4)	94 (30.3)	8 (14.8)	.378	.007	.004
Weight gain	78 (8.1)	58 (9.7)	16 (5.2)	4 (7.4)	.014	-	-
Coughing	168 (17.4)	112 (18.6)	48 (15.5)	8 (14.8)	.247	.727	.805
Ankle swelling	299 (31)	194 (32.3)	89 (28.7)	16 (29.6)	.392	.733	.932
Orthopnoea	195 (20.2)	136 (22.6)	51 (16.5)	8 (14.6)	.002	.225	.029
CLINICAL SIGNS							
Raised jugular venous pressure	46 (4.8)	32 (5.3)	12 (3.9)	2 (3.7)	.337	-	-
Pulmonary percussion, dull	44 (4.6)	28 (4.7)	14 (4.5)	2 (3.7)	.93	-	-
Cardiac murmur	237 (24.6)	162 (27)	60 (19.4)	15 (27.8)	.012	.896	.158
Peripheral oedema	463 (48)	294 (48.9)	151 (60.3)	18 (33.3)	.915	.286	.037
Pulmonary rales	593 (61.5)	381 (63.4)	187 (60.3)	25 (46.3)	.396	.013	.054
Tachycardia >90 beats/min	373 (38.7)	243 (40.4)	119 (38.4)	11 (20.4)	.575	.004	.011
Hepatomegaly	23 (2.4)	16 (2.7)	5 (1.6)	2 (3.7)	.321	-	-
Tachypnoea >20 breaths/min	236 (24.5)	161 (26.8)	70 (22.6)	5 (9.3)	.175	.005	.026
Third heart sound	12/1.2)	9 (1.5)	2 (0.6)	1 (1.9)	-	-	-
Ascites	35 (3.5)	25 (4.2)	7 (2.3)	3 (5.6)	.142	-	-
Cyanosis	34 (3.5)	22 (3.7)	10 (3.2)	2 (3.7)	.740	-	-

Abbreviations: n = total number of subjects; HF = heart failure. When the total value of a variable was less than five no comparison between the groups was made due to statistical reasons. *Reprinted with permission from the publisher, Schaufelberger et. al, ESC Heart Failure 2020; 7: 37–46*

Patients with a first hospitalisation for HF (n=651 961) in Sweden during the study period were identified using the NPR. After excluding patients with a record of HF in the 7 years prior to 1992 (n=32 736), incomplete register data (n=1526), age <18 or >84 (n=184 295), who died in hospital or one day after discharge (n=44 629), 388 775 patients were included in the study. Two age groups were created, 18-64 years and 65-84 years, containing 62 428 and 326 347 patients, respectively.

Patient characteristics

The mean age for patients in age groups 18-64 and 65-84 years were 58 years (53-62) and 77 years (73-81), and 31.2% and 47.4% were women, respectively. Most patients of both age categories had a primary or secondary level of education, 41.5% and 41.3%. IHD, atrial fibrillation/flutter and hypertension were the most common co-morbidities in both groups, 43.8% vs. 43.2%, 23.8% vs. 34.9%, and 29.1% vs. 31.8%, respectively. Cardiomyopathy and congenital heart disease had a higher prevalence in the 18-64 years age group, 10.0% vs. 1.6% and 1.3% vs. 0.3%, respectively.

Home-time

Mortality was calculated to enable determination of home-time. The overall 4-year all-cause mortality rate was 44.5% (compared to 23.3% and 48.5% for patients 18-64 and 65-84 years, respectively). Mortality rates decreased over the study period for all groups but to a lesser degree for women than for men (Figure 1 and 2). A cox regression adjusted for the other covariates in the study provided decreasing HR for women 65-84 years until the period 2001-2003, after which the decrease ended (Figure 3).

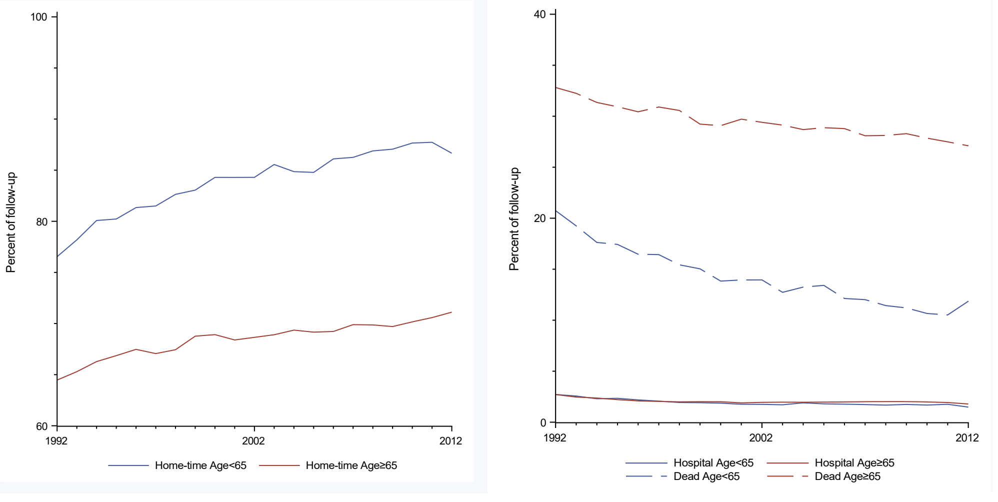

Figure 1. Home-time, in-hospital time, and time deceased during 4-year follow-up by year of first hospitalization and age group.

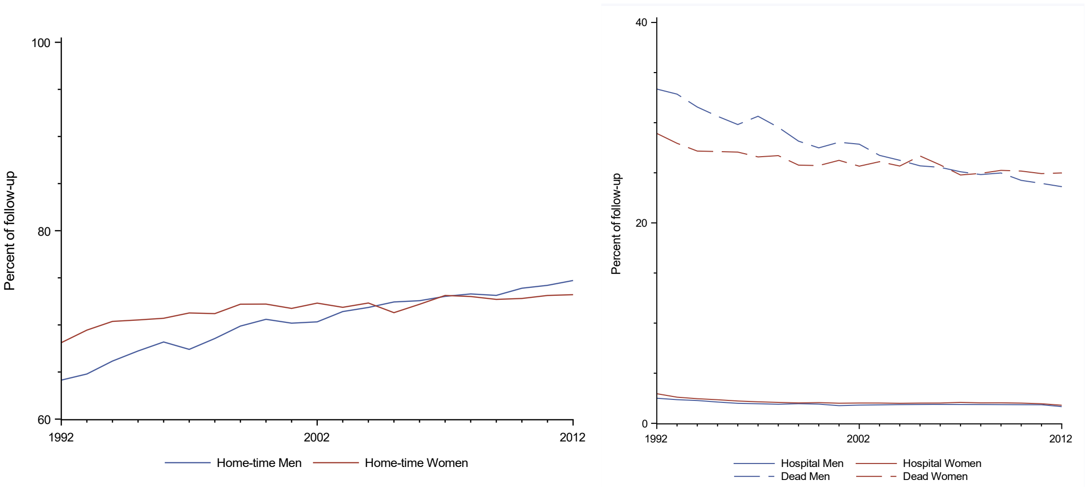

Figure 2. Home-time, in-hospital time, and time deceased during 4-year follow-up by year of first hospitalization and sex

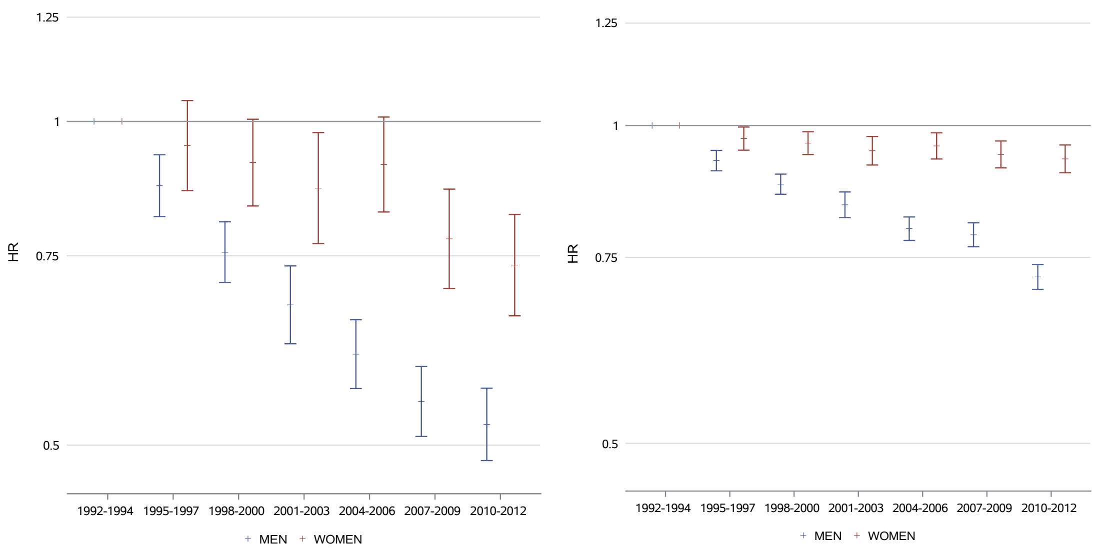

Figure 3. Forest plot of adjusted association between mortality risk and year of first hospitalization by sex and age group.

The overall home-time for all patients was 70.7% and they spent 2.1% of their time in hospital. Death accounted for 27.2% of the 4-year follow-up period. Patients 18-64 years had more home-time than those 65-84 years (83.8% vs. 68.2%, respectively). This was primarily due to a lower mortality rate for patients 18-64 years than 65-84 years (14.2% vs. 29.7%, respectively), see Figure 1. Both age groups and sexes had increasing home-time over the study period, however, this increase stalled in women after 2007 (Figure 2).

Decreasing time on sickness benefit days for patients with heart failure over two decades

In Paper III, we estimated time on sickness benefit for patients 18-60 years in Sweden with a first hospitalisation for HF 1995-2016 compared with controls. Follow-up time was 2 years. Patients and controls were divided into four groups by age: patients 18-44 years, patients 45-60 years, controls 18-44 years and controls 45-60 years (for details on patient selection please see Paper III).

Patient characteristics

Approximately one third of patients and controls 18-44 years were women. Fewer cases than controls were married or had less than 10 years education, in this age group. In patients 45-60 years, the proportion of women was lower, approximately one in five patients, and fewer cases compared to controls were married, or had less than 10 years education. Patients had higher rates of all comorbidities than controls in both age groups (number and percentages are presented in Paper III).

Sickness benefit

Patients in both age groups had a larger percentage of time on sickness benefit days than controls over the entire study period. Patients 18-44 years had a more pronounced difference in time on sickness benefit than controls.

There was a declining trend in sickness benefit for patients and controls of both age groups with some temporary increases (trends in time on sickness benefit is presented in Figure 2 in Paper III). For both age groups, the differences between patients and controls decreased over the initial part of the study period, 1995-2009, but then increased again 2009-2016.

Predictors for increasing or decreasing time on sickness benefit are presented in Paper III. For patients 18-44 years, stroke and cardiomyopathy had the strongest positive association with sickness benefit while educational level >12 year had the strongest negative association. For patients 45-60 years the strongest positive and negative associations were found for stroke and cancer vs. educational level >12 years and atrial fibrillation/flutter, respectively.

Impact of heart failure on professional life, in young adults

In Paper IV, we investigated clinical and socioeconomic characteristics regarding professional life for around 300 young patients with HF, comparing blue-collar workers to white-collar workers. Around one third and one quarter of patients were classified as white- and blue-collar, respectively. The remaining patients could not be classified regarding occupational class due to lacking or insufficient information on occupation.

Patient characteristics

In total, around two thirds of patients were male and born in Sweden. Patients were overweight with a mean BMI >25 kg/m^2. Patient characteristics regarding mean age and laboratory parameters are shown in Paper IV. The most common comorbidities were DCM, cardiac ischaemia, hypertension or atrial fibrillation/flutter. One in ten in patients had an implantable cardiac defibrillator on the most current follow-up. The most commonly used medications were beta-blockers, and renin-angiotensin-blockers including angiotensin receptor/neprilysin inhibitor (RAS-blockers).

Professional life

In total, around half of patients were currently on sick leave when filling out the questionnaires, and around one in ten reported to have had difficulties meeting current expenses for food, rent and bills. Regarding work capacity and strain, around one in ten patients reported being frequently weighed down by thoughts of work at home while around half of patients reported that they often or almost always had the possibility to decide over work tasks or working hours. In Paper IV, bar charts of the questions regarding working conditions are shown.

When comparing white- and blue-collar workers they did not differ significantly in most baseline characteristics apart from that white-collar patients had a higher prevalence of implantable cardiac defibrillators. Blue-collar patients were significantly more often foreign-born, had more often lost their job and reported a higher job strain than white-collar patients, presented in Paper IV.

DISCUSSION

The validity of the diagnosis of heart failure – Paper I

A valid diagnosis is the key in register-based research and thus Paper I lays the foundation on upon which the other Papers rest. The main finding in Paper I was that the diagnosis of HF had a high validity according to the ESC guidelines, in any position, and was considered valid (definite or probable HF) in 94.4% of cases. The accuracy of the diagnosis increased over the study period, 2000-2012. Importantly, the main reason for being classified as probable rather than definite HF was an incomplete or missing echocardiography report.

Ingelsson et. al found 96% of patients with a primary diagnosis of HF treated at a cardiology or internal medicine clinic, to have definite HF (55). For patients at any clinic, the validity was 95%, 76% and 63% when the diagnosis was in primary, secondary or third to sixth position. In our study, 58.4% and 33.7% of contributory diagnoses were classified as definite and probable HF, respectively, indicating that these diagnoses also may be used for register-based studies on HF (Table 6).

In our study, 62.3% of all cases were classified as definite HF. We argue that the patients classified as possible HF very likely truly had HF but lacked a complete echocardiography report, thus mostly could not be diagnosed as definite HF according to the ESC guidelines in current use. Guidelines for HF are an important tool for cardiologists, 98% of a sample of European cardiologists were aware of some version of HF guidelines and up to 92% perceived that they adhered to the ESC guidelines (97).

A typical diagnosis classified as probable HF had characteristic symptoms and signs combined with a pathological ECG or had congestion on chest X-ray but lacked cardiac imaging. In the Ingelsson study, as much as 51% of the patients were diagnosed without an echocardiography (55). A pathological chest X-ray or a pathological ECG was accepted as objective evidence of cardiac dysfunction, which did not comply with the current ESC guidelines (85). Therefore, we argue that probable HF in our study, compares to definite HF in the Ingelsson study.

The effect of mandatory cardiac imaging on validity is also evident in the difference in validity between the versions of the guidelines. In the 2008 guidelines, objective evidence of cardiac dysfunction was not limited to cardiac imaging (88). Cardiomegaly, a third heart sound, cardiac murmurs and raised natriuretic peptides were also considered objective evidence. In the period of our study using these guidelines (2009-2012), the proportion of diagnoses considered definite was 82.6%, compared to 56.9%, 54.5% and 54.7% in the period using the 1995, 2001 and 2005 guidelines, respectively (see Figure 2 in Paper I). Furthermore, a much larger proportion of patients had performed an echocardiography in the definite than in the probable group when using the 1995, 2001 and 2005 guidelines than when using the 2008 version, further illustrating the importance of cardiac imaging (see Table 5, Paper I).

Another important limitation of the study by Ingelsson et al was that the diagnosis was only validated in male patients. In our study, 50.5% of patients were women, making the results more generalizable. A significantly smaller proportion of women had definite than probable HF, likely due to fewer women having the presence of an echocardiography report.

The validity of the HF diagnosis in Swedish hospitals was high in our study, supporting the use of the NPR in register-based studies of HF-patients. In primary care in Sweden, however, the diagnostic criteria from the ESC were only fulfilled for about 30% of patients since many lacked adequate cardiac imaging (54). That study recruited patients 2004-2006 and the use of natriuretic peptides and echocardiography has likely increased over the following decades and the validity of the diagnosis might be different today. However, it is likely that most patients with HF are seen by the secondary care, in-patient or out-patient. One Swedish study found that only 9% of HF-patients had exclusively diagnoses from the primary care (17).

Home-time for patients with heart failure – Paper II

The concept of home-time, or alternatively time spent alive and out of hospital, have been sparsely used in HF research. However, stroke patients themselves have identified spending time at home and out of hospital, as a prioritized outcome (40). Home-time has also been shown to correlate well with more traditional outcomes in HF-patients (44). Therefore, we wanted to examine and compare trends in home-time for patients 18-64 and 65-84 years, to investigate how HF-patients spend their time after the diagnosis.

In Paper 2, the main finding was that patients with a first hospitalisation for HF spent only 70.7% of the subsequent 4 years, alive and not admitted to a hospital. Home-time increased over the study period, but this increase stagnated after 2007 for women 65-84 years. The cumulative all-cause mortality decreased over the study period for men of both age groups and for women 18-64 years but for women 65-84 years, the decrease in mortality was less pronounced.

Greene et al. found that HF-patients (≥65 years) spent 57.4% of the 2 years following a hospitalisation for HF at home, while 2.0% were spent in hospital, 3.7% in a skilled nursing facility, 0.2% in a rehab facility and 0.2% in another institution (44). In our study, we could not discriminate between time spent at home or in nursing facility or other institutions. When summing up all time spent alive outside of hospital in the Greene study, the corresponding number for 2 years home-time was 61.5% and the time spent as deceased was 36.5%. For patients ≥65 years in our study, the home-time was 68.2% and the time spent as deceased was 29.7%. In a study from New Zealand, DAOH 2 years following an index hospitalisation increased from 449 to 511 days between 1988-1999 (43), corresponding to an increase in percent DAOH from 61.5% to 70.0%.

Another study of DAOH in HF patients from the CHARM programme (median follow-up 38 months) found higher home-time (41). Percent DAOH was 91.6%, 86% and 81.2% for patients with candesartan aged <65, 65-74 and >74, respectively. The corresponding numbers for patients on placebo were 90.3%, 84.6% and 76.9%, respectively. Patients treated with candesartan, compared to placebo, had a mean increase in home-time of 24.1 days. This was mainly due to lower mortality. Patients 18-64 years in our study had comparatively less home-time, 83.8%. The reason for this is not clear but is has been shown that patients in randomized controlled trials are not widely representative of real-world patients due to a high selection of patients included and might entail for example a lower mortality (98). The patients in the CHARM-programme were also stable patients in out-patient care, while our patients were all first hospitalizations.

Until 2004, men had higher home-time than women, but in 2005 this shifted (Figure 2), most likely due to that the mortality for women levelled off around the same time resulting in a lesser reduction in home-time. For men, the mortality decreased more steeply over the entire study period. The reason for this disparity between men and women is not clear but possible explanations might be that women have more HF with preserved ejection fraction (99). The greatest improvements in treatment for HF over the last decades does not include a reduction in mortality for patients with HFpEF but for patients with HF-rEF, (100-103) and possibly patients with HFmrEF (104, 105). However, the Sodium-Glucose Cotransporter-2 (SLGT-2) inhibitors have later been shown to reduce cardiovascular mortality for patients with HFmrEF/HFpEF in a meta-analysis (106). HF patients with IHD have higher mortality than patients with HF from non-IHD origin (107) and the IHD-mortality have decreased over the last decades (108, 109). As a consequence, the mortality for female patients with HF should have decreased less than for men. In fact, in another work from our group, we showed that patients with HF of non-ischaemic origin had a less pronounced reduction in mortality compared to patients with HF of ischaemic origin (16). This was most prominent among women.

Professional life and characteristics in young adults with heart failure, Paper III-IV

HF is primarily a disease of the elderly but exists in all ages. For young adults, work is often an important part of life, socially and economically, and Paper III-IV therefore investigates characteristics in young patients with HF, sick-leave and working conditions.

Characteristics in young adults with heart failure

In young adults with HF in Paper IV (16-54 years at first hospitalisation) and in Paper III (18-44 years), the most common comorbidities were DCM, hypertension and IHD. IHD, hypertension and atrial fibrillation/flutter were the most common comorbidities in patients 45-60 years, and all three conditions had higher prevalence in this age group than in the younger age groups. This was in accordance with results from MAGGIC (22) and the CHARM-program (23), where the prevalence of MI and atrial fibrillation increased with age while DCM decreased. In Paper IV, we also found a dominance of male patients of around 70%, corresponding to results from MAGGIC where 70% or more males in every age category below 70 years were reported. In the general population a higher prevalence of DCM has been found in men (110). Furthermore, in Paper III, we also found a higher proportion of women in the youngest age groups than in patients 45-60 years, also in accordance with MAGGIC and the CHARM-program. Alcohol abuse was found in around 5% of patients of both age groups in Paper III and in around 1.5% of patients in Paper IV. In Paper III, approximately 5% and 1% of patients 18-44 and 45-60 years had substance abuse, respectively while merely around 2.0% of patients in Paper IV had substance abuse. Comparisons between these numbers in Paper III and IV should be made with caution. However, since Paper IV only included comorbidities reported at the index hospitalisation and diagnoses from other hospitalisations prior to index were not included. MAGGIC and the CHARM-program did not report substance abuse but also found a higher prevalence of alcohol-related HF in the very young than in patients 45-60 years.

The mean BMI of patients <55 when diagnosed with HF in Paper IV was 28.8 kg/m^2, with no significant difference between white- and blue-collar workers. In the CHARM-program, the youngest patients were more likely to be obese, BMI ≥35 kg/m^2 (23). There is increasing evidence that obesity in young age increases the risk for both HF and cardiomyopathy later in life (33, 111, 112). BMI >20 in adolescent Swedish men was associated with an increased risk of developing early HF, and the risk increased incrementally with increasing BMI, from HR 1.22 (1.10-1.35) for BMI 20.0-22.5 kg/m^2 up to HR 9.21 (6.57-12.9) for BMI ≥35 kg/m^2 (33). For cardiomyopathies, the risk was found to be increased for both men and women, especially for DCM (111, 112).

In Paper IV, HF-patients with white-collar occupations, had a significantly higher prevalence of implantable cardiac devices than blue collar-patients, despite that the two groups did not differ significantly regarding comorbidities, EF, presence of HF-medication, BMI, blood-pressure or in laboratory values. To the best of our knowledge, this has not been shown before. Discrepancies regarding implantable cardiac defibrillators have been shown between the sexes though: an Australian study found that women were less likely to have a cardiac implantable electronic device than men even when adjusting for comorbidities and age (113). Patients with HF of a lower socioeconomic status also received less guideline-directed medical therapy (114, 115).

Sick leave in young adults with heart failure

In Paper III, a case-control cohort study, HF-patients had spent more time on sick-leave than controls continuously over the study period, 1995-2016. Time on sick-leave declined over the study period, for both HF-patients and controls but the decline was steeper for HF-patients. In Paper IV, a cross-sectional study, about half of respondents reported to be on current sick leave.

Trends in sick leave are heavily dependent on changes in political policies regarding compensation for sick leave and thus many of the fluctuations seen in Paper III could be derived from policy changes. Several cuts in sick leave compensation were made in Sweden to minimize costs for society following the financial crisis in 1990-1994, which lead to a reduction in sick leave, and a corresponding decline in sickness benefit rates for both patients and controls was seen in the beginning of the study period (83).

In 2001, the sickness benefit rates peaked for patients in both age groups and in controls 18-44 years. For controls 45-60 years, the peak started in 2000. This corresponds to the record high sick leave in general in Sweden in the beginning of the first century which led to the government setting up a goal that all sick leave should be reduced by 50% until 2008 and that other forms of compensations should instead increase (early retirement and other labour market investments) (116). Among the changes made to achieve this goal, the new Swedish Social Insurance Agency (Försäkringskassan) was founded in 2005. The sick leave rates decreased the following years while the other forms of compensations increased but the decrease in sick leave was more pronounced than the increase for other compensation forms, implying that the net sickness absence in fact did decrease. Indeed, there was a steady decrease in sickness benefit rate for patients of both age groups until 2009-2010 in our study, likely due to these policy changes. In 2009, sickness benefit rate again increased for the younger patients, while the decrease stagnated for patients 45-60 years between 2010 and 2012 and was thereafter followed by an increase. The sickness benefit rates again decreased in the final year of the study period, 2015-2016. However, the younger controls had an increase and controls 45-60 years a stagnation in sickness benefit rates during the final year of the study period.

Even though sickness benefit rates decreased for both patients and controls, the decline was more pronounced for patients, indicating that something had a greater impact on HF-patients than on the general population and that other factors than policy changes might have influenced the sick leave rates seen in Paper III. Psychiatric disease and, as an effect of this, sick leave due to psychiatric disease, increased in Sweden 2010-2016 and was the main reason for the total increase in sick leave during this period (116). Depression is common in HF-patients (117, 118), and we did find a higher prevalence of psychiatric disease in patients than in controls. However, since depression is primarily managed in primary care, this diagnose might be under-reported. Furthermore, the treatment of HF has improved during the study period which also may explain that patients need less time on sickness benefit compensation (86-88, 119).

Working conditions for young adults with heart failure

In Paper IV, HF-patients aged 16-<55 years at diagnosis, were classified by occupation as white- or blue-collar workers and answered questionnaires regarding socioeconomic and working conditions. Approximately one in ten of all patients were frequently weighed down by thoughts of work at home. Around half of all patients had often or almost always the possibility to decide over work tasks and often or almost always had the possibility to decide over work hours. Of all patients, approximately one in five were seldom or never/almost never well-rested when starting work. Working capacity in relation to physical demands were very good for around 40% of patients but also poor and very poor for around one in ten of patients.

When comparing blue- and white-collar patients, blue-collar patients reported lower working capacity in relation to physical demands, more experience of job loss and to be more weighed downed by thoughts of work at home. White- collar patients could decide over work tasks and working hours to a higher degree than blue-collar patients. Despite this, blue-collar patients were not more often on sick leave. To the best of our knowledge, there are no previous studies regarding working conditions for patients with HF. However, several differences between white- and blue- collar patients have also been shown in the general population: blue-collar workers having higher long term sickness absence, being more affected by cuts in sickness benefits, reporting higher physical demands at work and more health complaints and job-demand-control being a stronger correlate of musculoskeletal pain for blue-collar workers (70-72, 120). That social benefit cuts affect blue-collar workers harder (71), might indicate that HF-patients of blue-collar occupations more frequently refrain from sickness absence when sick than HF-patients of white-collar occupations. Blue-collar patients also had experienced job loss more often than white-collar patients, which also might influence the decision to stay home from work when not feeling well.

Limitations

To a varying degree, all four Papers in this thesis had missing data. In Paper I, we were limited to the data collected and available in the medical records. For example, when a certain symptom was not mentioned in the medical records, we had no way of discerning if the patient did not experience the symptom, if they simply had not been asked about it or if the answer had not been noticed in the record. Important signs and symptoms for a certain clinical condition are often negated when not present, however, which would mean that the underreporting of these may be lower. In addition, a report from for example an echocardiography might be mentioned in the records but could not be retrieved from the records. We could then at least use the information reported by the clinician.

Paper II and III were observational studies and though we adjusted for multiple socioeconomic factors and comorbidities, all possible confounders might not have been identified. National registers were used with inherent limitations. The amount of missing data in the NPR, CDR and TPR were very low, while the frequency of missing data was higher for some variables in the LISA-register, with some patients missing from the registers completely. In Paper IV, only around 30% of patients alive and without severe cognitive impairment participated in the study, increasing the risk for selection bias.

Another limitation when using national registers was that they do not contain detailed data on clinical findings, for example ejection fraction. The LISA-register contain aggregated data and for some variables such as sickness benefit compensation, the data is only available on a yearly basis. Thus, in Paper III, with the data from LISA, it was not possible to calculate time on sickness benefit compensation day by day.

In Paper III, the frequencies for some diagnoses are very low in the control group. As the ICD-codes were collected from the NPR, diagnoses from the primary healthcare were not included and since many diseases are primarily managed in primary care, the prevalence of these diseases might be underestimated in this study.

Furthermore, in Paper III, patients with disability pension were excluded since patients with a full disability pension are not eligible for sick leave compensation. The LISA-register did not contain information on whether the disability pension was on full or part time, thus we excluded all patients with any record on disability pension, which might skew the results.

CONCLUSIONS

Paper I in this thesis reported a high validity for HF as a discharge diagnosis in Western Sweden, strengthening the use of the national registers in HF research.

Paper II of this thesis found that patients spent only 70.7% of the 4 years after a first hospitalisation for HF, alive and not admitted to a hospital. Home-time increased over the study period 1992-2012. Women 65-84 years had no further decrease in home-time after 2007, the effect of a less pronounced decrease in mortality in this group.

Paper III of this thesis found that HF-patients spent more time on sickness benefit than controls continuously over the study period, 1995-2016. While time on sickness benefit declined for both patients and controls, it was steeper for HF-patients. The decrease for all groups in the study was likely partly due to policy changes from the government in respond to high sick leave rates. The steeper decline in HF-patients may be due to the improved treatment of HF during the last decades.

Paper IV of this thesis found that of patients aged 16-<55 years when diagnosed with HF between 1997 to 2016, approximately two thirds were male, the mean BMI was elevated and the most common underlying heart conditions were IHD, DCM and hypertension. Blue- collar patients reported significantly more job strain but were not on current sick leave more than white- collar patients, a discordancy that may reflect a difference in economic resources rather than reduced working ability.

FUTURE PERSPECTIVES

This thesis found a high, and increasing, validity for the HF-diagnosis in cardiology and internal medicine wards in Sweden together with an increasing use of echocardiography. The validity in the primary care has been reported to be considerably lower (54), but the diagnoses validated in that study are from two decades ago and much has happened since then regarding the availability of diagnostic tests in the primary care. There is therefore a need for a new validation of more recent HF diagnoses in primary care.

We found an increasing home-time over the last decades, for both patients 18-64 and 65-84 years. The register used did not contain data on time spent in skilled nursing facilities, but the National Board of Health and Welfare keeps separate register with this information and thus future studies could make use of this information and estimate time spent alive, out of hospital and skilled nursing facilities. This would add an extra level to the outcome since being able to continue to live at home is a priority for many people.

This thesis also found decreasing time on sickness-benefit over two decades for patients and controls 18-60 years old, with a steeper decrease for patients than for controls. The decrease being steeper for patients might be a consequence of improved treatment for HF, but it could also hypothetically indicate that patients with HF were hit harder by cuts in the social insurance system. Since we used the LISA-register, only aggregated data on sickness-benefit was available to us. Furthermore, data on which diagnosis that caused the sick leave was not available. Future studies should use register data directly from the Swedish Social Insurance Agency where more detailed data on sick-leave and the causes of it are available. This could bring clarity to the question on whether sick leave specifically for HF is decreasing and how the sick leave after HF is distributed.

SAMMANFATTNING PÅ SVENSKA

Bakgrund:
Hjärtsvikt är en vanlig och allvarlig sjukdom och antalet insjuknande ökar hos yngre personer. Det övergripande syftet med denna avhandling var därför att studera olika aspekter rörande hur det är att leva med hjärtsvikt, med fokus på yngre patienter.

Metoder och resultat:
I delarbete 1 gick vi igenom medicinska journaler för 965 patienter som vårdats för hjärtsvikt på Sahlgrenska universitetssjukhuset (SU) 2000–2012. Med hjälp av riktlinjer för diagnostik av hjärtsvikt från den Europeiska föreningen för kardiologi, bedömdes diagnosens validitet och vi fann att diagnosen var säker eller trolig i 94.4% av fallen.

Delarbete 2 och 3 var registerstudier där vi använde svenska nationella register.

I delarbete 2 beräknades andel ”hemmatid” (tid i livet tillbringad utanför sjukhuset,) under fyra år efter hjärtsviktsdiagnos, för 388 775 patienter i Sverige med hjärtsvikt, 18-84 år gamla, 1992-2012. Patienter 18-64 år hade mer hemmatid än patienter 65-84 år, (83.8% jämfört med 68.2%) till stor del på grund av lägre dödlighet. Hemmatiden ökade över studieperioden för bägge åldersgrupper men ökningen planade ut för kvinnor 65-84 år efter 2007.

I delarbete 3 beräknades tid som sjukskriven, två års uppföljningstid för patienter 18-60 efter en hjärtsviktsdiagnos, jämfört med kontroller från totalbefolkningen och vi fann att sjukskrivningarna minskade under studieperioden 1995-2016 för alla grupper men med en brantare nedgång för patienter än för kontroller.

I delarbete 4, identifierades alla patienter 16-55 år som diagnosticerats med hjärtsvikt eller dilaterad kardiomyopati på SU 1997-2016. De som fortfarande var i livet och bodde i närområdet bjöds in att delta i studien och undersöktes av forskningssjuksköterska och fick fylla i enkäter om arbetsförhållanden. Majoriteten var män och hade ett förhöjt BMI. Vid jämförelse av patienter i arbetarklass och tjänstemän fann vi att de i arbetarklassen var mer tyngda av tankar på jobbet hemma, hade lägre arbetskapacitet i förhållande till fysiska arbetskrav men var inte oftare sjukskrivna, än tjänstemän.

Slutsatser:
Hjärtsviktsdiagnosens validitet är hög, vilket stödjer fortsatt användning av våra nationella register i forskning. Hemmatiden ökade under två decennier och yngre patienter hade mer hemmatid än äldre. Tiden som sjukskriven var högre för patienter än för kontroller men sjönk för bägge grupper, brantare för patienter än för kontroller. De flesta yngre patienter med hjärtsvikt var män och överviktiga och patienter i arbetarklassyrken upplevde större arbetsbelastning än tjänstemän.

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APPENDIX

Apppendix 1. Comorbidites in Paper II according to the International Statistical Classification of Diseases and Related Health Problems (ICD)

	ICD 8	ICD 9	ICD 10
Ischaemic heart disease	410-414	410-414	I20-25
Atrial fibrillation/flutter	427.92	427D	I48
Cardiomyopathy	425	425	I42
Valvular disease	393-398	393-398	I05-09, I34-35
Congenital heart disease	746-747	746-747	Q20-28, Q87, Q89
Hypertension	401-405	401-405	I10-15
Diabetes mellitus	250	250	E10-11, E14
Chronic renal failure	585	585	N18, N26
Stroke	430-438	430-438	I60-69
COPD	490-496	490-496	J44
Asthma	493	493	J45
Cancer	140-208, 230-234	140-208, 230-234	C00-97, D00-09

Abbreviations: COPD; chronic obstructive pulmonary disease.