

Heart failure epidemiology with emphasis on young adults

Carmen Basic



UNIVERSITY OF GOTHENBURG

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carmen.basic@vgregion.se, carmen.basic@gu.se

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"Educating your mind without educating your heart is no education at all"

Aristotle

To my family

ABSTRACT

Background: Heart failure (HF) is a major health problem worldwide with exponentially increasing incidence with age and the majority of patients being elderly. In recent years, an increase in hospitalization and prevalence of HF in younger persons has been documented in Sweden and Denmark, in contrast to an overall decrease in older patients. In addition, an increase in hospital discharge diagnoses of cardiomyopathy has been reported, also most pronounced among the young. New treatment modalities implemented in every day practice have contributed to improved prognosis in heart failure, but the improvement in mortality has slowed down since the beginning of the 21st century.

Aim: The aim of this thesis was 1) to validate hospital diagnoses of cardiomyopathy; 2) to describe characteristics of young patients with HF; 3) to evaluate possible changes in mortality over time by studying mortality rates, mortality risks and estimation of life-years lost compared with matched controls from the general population; and 4) to explore possible sex related differences among young patients with HF.

Methods and Results: Through search of local hospital discharge registers at three hospitals in western Sweden 611 medical records from 1989 to 2009 with the diagnoses of cardiomyopathy were validated against the latest ESC diagnostic criteria. Of all cases a high proportion, 86%, filled the criteria current at the time of diagnosis. In Paper II, III and IV several Swedish registers were combined. In Paper II all patients with incident hospitalization for HF registered in the National Patient Register were included. Over two periods, 1987-2002 compared with 2003-2014, a decrease in mortality rates were observed mainly among patients <65 years while in patients ≥ 65 years only minimal improvement in survival was found. As mortality rates decreased more in matched controls from the general population the relative mortality risk increased in patients <65 years during the observed period. In Paper III and IV, all patients from the Swedish Heart Failure Register were included from 2003 to 2014 and patients <55 years were compared with those ≥ 55 years and matched controls <55 years with regard to patient characteristics, mortality rates and mortality risk. Patients <55 years had higher rates of concomitant cardiomyopathies, myocarditis, obesity, congenital heart disease and reduced ejection fraction (EF) while older patients had more ischemic heart disease, hypertension and atrial fibrillation. Mortality rates were lower among the patients <55 years but when compared to controls they had five times higher mortality risk and patients 18-34 years of age had up to 38 times higher mortality risk. When compared with the estimated life expectancy of the general population the youngest patients lost up to 26 life-years, this declined with increasing age. Women, compared to men, had higher rates of obesity, congenital heart disease, hypertrophic cardiomyopathy, midrange and preserved EF while men had more ischemic heart disease, atrial fibrillation and more often reduced EF. In absolute numbers there was no difference in mortality rates, but women with HF had almost twice as high mortality risk relative to controls than did men (even though not significant) and lost more life-years than men. The most common cause of death was cardiovascular death (CVD) followed by cancer, presence of the latter was associated with doubled mortality risk in men and a 3-fold increase in risk in women, relative to men and women without concomitant cancer.

Conclusion: The validity of the cardiomyopathy diagnoses was high supporting the hypothesis that a real increase of cardiomyopathy might have occurred. Survival of patients with HF improved among patients <65 years while among those older patients the improvement was marginal. The mortality risk relative to age-matched controls increased among the younger group, as the mortality reduction was more pronounced among controls. The younger the patients the higher estimated life-years lost. The most common mode of death was CVD followed by cancer in both sexes. Cancer was associated with increased mortality risk in both sexes.

Key words: cardiomyopathy, validity, heart failure, mortality, epidemiology

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LIST OF PAPERS

This thesis is based on the following papers.

- I Basic C, Rosengren A, Lindström S, Schaufelberger M. High validity of cardiomyopathy diagnoses in western Sweden (1989-2009). *ESC Heart Fail*, 2018 Apr;5(2):233-240.
- II Lena Björck, Carmen Basic, Christina Lundberg, Tatiana Zverkova Sandström, Annika Rosengren, Maria Schaufelberger. Survival in Swedish men and women with heart failure from 1987 to 2014. *In manuscript*
- III Basic C, Rosengren A, Alehagen U, Dahlström U, Edner M, Novak M, Zverkova Sandström T, Schaufelberger M. Young patients with heart failure - clinical characteristics and outcomes. Data from the Swedish Heart Failure, National Patient, Population and Cause of Death Registers. *In manuscript*
- IV Basic C, Rosengren A, Dahlström U, Edner M, Zverkova Sandström T, Schaufelberger M. Sex differences among young patients with heart failure in Sweden. *In manuscript*

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ABBREVIATIONS

ACE	Angiotensin converting enzyme
ARB	Angiotensin receptor blocker
AF	Atrial fibrillation
CHARM	Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRT	Cardiac resynchronization therapy
CVD	Cardiovascular death
DCM	Dilated cardiomyopathy
EF	Ejection fraction
ESC	European Society of Cardiology
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFmrEF	Heart failure with midrange ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HOCM	Hypertrophic obstructive cardiomyopathy
HR	Hazard ratio
ICD	International classification of disease
IHD	Ischemic heart disease
NPR	National Patient Register
MAGGIC	Meta-analysis Global Group in Chronic Heart Failure
MRA	Mineral corticoid receptor antagonists
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PIN	Personal identity number
RAAS	Renin angiotensin aldosterone system
RCT	Randomized clinical trials
SD	Standard deviation
SGLT2	Sodium-glucose cotransporter-2 inhibitor
SwedeHF	The Swedish Heart Failure Register
UK	United Kingdom
US	United States
WHO	World Health Organization

INTRODUCTION

Definition and diagnostic criteria for heart failure

Heart failure (HF) is a common and serious syndrome⁽¹⁾. Over the years the definition of HF has been revised several times. In the latest guidelines of the European Society of Cardiology (ESC) from 2016, HF was defined as “a clinical syndrome characterized by abnormalities of left ventricular function and neuro-hormonal regulation which are accompanied by effort intolerance, fluid retention and reduced longevity”⁽²⁾.

Guidelines provide practical and evidence-based recommendations to medical professionals in everyday clinical practice for management of acute and chronic HF. Historically, several diagnostic criteria for HF have been available including the Framingham criteria from 1971⁽³⁾, Duke criteria from 1977⁽⁴⁾, the Boston criteria from 1985⁽⁵⁾ and the Gothenburg criteria from 1987⁽⁶⁾. In 1995 the ESC presented their first diagnostic criteria for HF⁽⁷⁾ that over years has been updated on a regular basis (in 2001, 2005, 2008, 2012 and 2016). The latest criteria is based on symptoms and clinical signs, measurement of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and echocardiography examination⁽²⁾. The criteria are implemented in the Swedish health care programmes with local adjustments.

The epidemiology of heart failure

HF is a major health problem with high morbidity and mortality, including extensive healthcare costs globally⁽⁸⁻¹¹⁾. The prevalence of HF in an adult population in developed countries has been estimated at about 1-2%⁽¹²⁻¹⁴⁾. Data from Stockholm county based on data from 2.1 million inhabitants showed a HF prevalence of 2.2%⁽¹⁵⁾. HF primarily affects older people and in the population above 70 years of age the prevalence increases to more than 10%⁽¹⁶⁾. Even though HF is more common among the elderly, it may also occur in the young^(3, 8, 16). In previous papers using data from the National Patient Register (NPR) in Sweden, both hospitalization⁽¹⁷⁾ and prevalence⁽¹³⁾ of heart failure increased among young adults. It is reasonable to believe that young patients are hospitalized for comprehensive evaluation when they are diagnosed with HF. Thus the increase in hospitalization rates may mirror true incidence increase. Additionally, the authors showed that hospital discharges with cardiomyopathy diagnoses, a known cause of HF, increased in all age groups, most pronounced among young patients, almost tripling between 1987 and 2006 in the age category 18-44 years of age⁽¹⁷⁾. The prevalence of obesity, a known risk factor for HF, is increasing worldwide⁽¹⁸⁾ and in Sweden⁽¹⁹⁻²¹⁾, in all age groups and recently, an association between obesity and cardiomyopathy has been demonstrated⁽²²⁾.

During the last decades, new treatment modalities were developed resulting in prognostic improvement in selected groups of patients with HF. In addition, improved treatment of hypertension and ischemic heart disease (IHD), the most common causes of HF, may have contributed to decreased incidence of HF in the older subset of the population. Previous reports from Sweden showed improvement in survival up to 2003 especially in men < 65 years with HF of ischemic origin⁽²³⁾. However, changes in mortality trends have been observed recently, where, in contrast to the fast sink-

ing mortality until 2010, a deceleration in the reduction of cardiovascular mortality has been witnessed in the US⁽²⁴⁾, and in the UK only modest improvements in survival were seen in patients with HF from the beginning of 21st century until 2017⁽²⁵⁾. A similar decelerating trend in the mortality reduction in individuals with HF was observed in Sweden after 2003, where only a marginal decrease in mortality was reported from Stockholm county from 2006 to 2010⁽²⁶⁾. A recently published nationwide study showed decreasing both all-cause and CVD related mortality but still combined with high mortality rates⁽²⁷⁾.

It has been speculated on that the aging population may contribute to potential HF “epidemic”⁽²⁸⁾. So far, an epidemic of HF has not been confirmed in Sweden. However, with the increasing trends of HF in the young and increasing life expectancy, an increase in HF might be anticipated in the near future, especially with increasing rates of obesity in the young⁽²⁰⁾, with documented associations with early-onset heart failure and cardiomyopathies^(21, 22). The implementation of evidence-based treatment has led to prognostic improvement, but in patients with HF and preserved ejection fraction (EF), that are more frequently older, women and with obesity⁽²⁹⁻³¹⁾, so far, no trial showed treatment to improve prognosis⁽³²⁻³⁸⁾. This may, to some extent, with an aging population, have contributed to the decelerating mortality trends that have been observed. Even though the overall mortality has improved, the mortality rates still remain high in both stable patients 6-7%^(39, 40) and up to 25%^(41, 42) in patients hospitalized after acute decompensation. Recently published data from Canada presented high mortality rates also in young patients with HF⁽⁴³⁾.

In summary, several factors have changed over time that may have had an impact on the survival of patients with HF in different age categories. It is reasonable to expect a difference in the risk factor profile in the general population as well, as the estimated life expectancy of the general population in most countries is increasing⁽⁴⁴⁾. Consequently, the mortality risk in patients with HF compared with that of the general population still needs to be addressed over time and in different age categories for both sexes.

Causes and co-morbidities in patients with heart failure

There is always an underlying cause of HF, where hypertension and IHD can be found in 75% of cases. In addition, HF can be caused by a variety of other conditions such as congenital heart disease, valve disorders, endocrine disorders, systemic diseases and cardiomyopathies⁽²⁾. Among cardiomyopathies, hypertrophic cardiomyopathy, an inherited disease⁽⁴⁵⁾, is sometimes associated with HF, while in dilated cardiomyopathy it is almost always the case⁽⁴⁶⁾. Dilated cardiomyopathy is a heterogeneous group where idiopathic dilated cardiomyopathy predominates. Also heart failure may arise in conjunction with rapid heart rhythm disorders, general muscle disorders, in conjunction with pregnancy and childbirth in women, and may be due to toxic substances such as alcohol, amphetamine and use of cytostatic⁽⁴⁶⁾. HF may be accompanied with other disorders and sometimes it may be difficult to differentiate between causes and co-morbidities, such as the very frequent co-morbidities in patients with HF represented by IHD, diabetes mellitus, hypertension or atrial fibrillation (AF)⁽⁴⁷⁾.

Classification of cardiomyopathies

Cardiomyopathies represent a heterogeneous group of diseases⁽⁴⁶⁾. Over years the definition and classification has changed as the understanding and knowledge about the entity increased^(46, 48-51). During the 1980s, cardiomyopathies were defined as heart muscle disorder of unknown cause, but with other forms in the group of specific heart muscle disorders with known cause or related with disorders in other systems. Physicians were often challenged with difficulties to distinguish these two categories as cardiomyopathies to a great extent may affect other organ systems⁽⁴⁸⁾. With the growing body of evidence in the area of pathogenesis, genetics and etiology there was recently a new update of the diagnostic criteria from the European Society of Cardiology, where cardiomyopathies were defined as “heart muscle disease with cardiac dysfunction” in the absence of cardiac malfunction due to hypertension, coronary artery occlusion, valve disease or congenital heart disease⁽⁵⁰⁾.

The most recent classification by the ESC was introduced in 2008 with a clinically oriented approach, grouping cardiomyopathies with respect to ventricular morphology and function. Since then cardiomyopathies are defined as: “A myocardial disease in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valve disease and congenital heart disease sufficient to cause the observed myocardial abnormality.” To raise the awareness about hereditary forms all cardiomyopathies were divided into familial or idiopathic forms. Besides, those induced by viral infection, inflammatory disease, tachycardia, in relation to pregnancy or toxic effect of alcohol and/or drug abuse or medications were also included. This resulted in a broader and more comprehensive definition of the cardiomyopathy diagnoses that historically was established with elimination of other major causes of cardiac dysfunction⁽⁴⁶⁾.

Classification of heart failure in regard to ejection fraction

The use of imaging methods, such as echocardiography, enables the evaluation of left ventricular EF. According to the current ESC guidelines, patients with HF may have left ventricular EF $\geq 50\%$, preserved EF (HFpEF), EF 40-49%, midrange EF (HFmrHF), or reduced LVEF $<40\%$, HF with reduced EF (HFrEF)⁽²⁾.

Patients with HFpEF were more often older, women and with history of hypertension and AF, while history of IHD was less common compared with patients with HFrEF^(52, 53). Two previous studies, a clinical trial and a meta-analysis^(54, 55) that compared patients with HF in different age groups, showed that younger patients had higher rates of reduced EF ($<40\%$) than the elderly.

Age categories

In epidemiological studies analysis by age are widely used, mostly to adjust for confounding. When forming age categories, one important aspect is comparability with other studies. One of the recommendations of the international journal of epidemiology for group forming is to use mid-decade to mid-decade groups⁽⁵⁶⁾.

The United Nations Department of Economics and Social Affairs, Population Division has proposed that the population may be divided into following age groups: 1) Children and adolescence 0 to 20 years; 2) “young adults” 20 to 39 years; 3) “middle-aged” adults 40-59 years; older persons ≥ 60 years of age⁽⁵⁷⁾.

A previous national study from the NPR assessing survival of patients with HF relevant for this doctoral thesis used the age of 65 years to define the older (≥ 65 years) and younger (< 65 years) age groups⁽²³⁾. To increase comparability in part II of this thesis the same cut off of 65 years was used. Also, two other studies^(13, 17) showed an increase in hospitalizations and prevalence of HF in the age group 18 to 54 years of age. In order to enable comparison with these studies in part III and IV of this thesis, younger age groups were defined as individuals < 55 years.

Treatment of chronic heart failure

Current recommendations for treatment of HF are based on symptomatology and EF. The use of several drugs and devices has been shown to have beneficial effects on morbidity and mortality in patients with reduced EF. However, all studies to date have been neutral for patients in the EF group $\geq 50\%$ ⁽³³⁻³⁵⁾. For patients with HFmrEF so far there are only subgroup analyses of previous major clinical trials demonstrating an effect on outcomes⁽⁵⁸⁾. Hence, all studies with positive effect on mortality, so far, were performed in patients with HFrEF⁽²⁾.

Treatment with diuretics is recommended in patients with symptoms and signs of congestion^(2, 59), but the effect on mortality have not been studied in randomized controlled trials. Diuretics appear to reduce the mortality risk and risk of worsening heart failure when compared to placebo and when compared to active agents improvement in exercise capacity was noticed in patients with chronic HF⁽⁶⁰⁾.

The neuro-hormonal blocking treatment was established in the 1980s when the inhibition of the renin angiotensin aldosterone system (RAAS) with the angiotensin converting enzyme (ACE) inhibitor, reduced overall mortality in HF^(61, 62). In the following years, the ACE inhibitor enalapril was shown to be beneficial in reducing hospitalizations for HF in asymptomatic patients⁽⁶³⁾.

In addition, the use of beta-blockers is recommended, based on the mortality benefit, for bisoprolol⁽⁶⁴⁾, carvedilol⁽⁶⁵⁾ and sustained-release metoprolol⁽⁶⁶⁾. Angiotensin receptor blocker (ARB) therapy was not proven to be superior to ACE inhibitors⁽⁶⁷⁾ and therefore the treatment with ARB is indicated in case of intolerance of ACE inhibitors and in patients on treatment with an ACE inhibitor but unable to tolerate a mineralocorticoid receptor antagonist (MRA). The MRA spironolactone was proven to reduce mortality in patients with HF with severe symptoms⁽⁶⁸⁾ and in 2011 eplerenone was proven to reduce mortality even in patients with mild symptoms⁽⁶⁹⁾. Ivabradine, which is a sinus node inhibitor, reduced the composite endpoint of CVD or hospitalization for worsening HF in patients with HFrEF and sinus rhythm⁽⁷⁰⁾. In 2014 the combination of ARB (valsartan) and a neprilysin (NEP) inhibitor (sacubitril) has been shown to be superior to enalapril in reducing the risk of death and hospitalization⁽⁷¹⁾.

Studies with hydralazine and isosorbide dinitrate causing vasodilatation, compared with placebo have also shown reduction in mortality⁽⁷²⁾, but the combination was less effective when compared with an ACE inhibitor. On the other hand, treatment with digoxin showed no mortality reduction when compared to placebo but a reduction in hospitalization rates was seen⁽⁷³⁾.

Studies in the area of cardiac devices has shown beneficial effects of cardiac resynchronization therapy (CRT)⁽⁷⁴⁾ and implantable cardioverter-defibrillators⁽⁷⁵⁾ in terms of mortality in selected patient groups where CRT treatment also showed beneficial effects concerning hospitalization rates, even in patients with mild symptoms⁽⁷⁶⁾. After the publication of the most recent guidelines from the European Society of Cardiology (ESC) new treatments, such as sodium/glucose cotransporter 2 (SGLT2) inhibitors that are used to lower plasma glucose in patients with diabetes, have shown favorable effects in patients with HF, also among patients without diabetes⁽⁷⁷⁾.

Differences between men and women with heart failure

Accumulating knowledge about sex differences increases the awareness and a need for different approaches in women and men, when treating cardiovascular disease^(78, 79). Several studies have highlighted the differences between men and women with HF, from clinical presentation to treatment, but the results refer mainly to the elderly⁽⁸⁰⁻⁸³⁾.

Both observational studies and randomized clinical trials (RCT) show that women with HF are older than men⁽⁸⁰⁾. They also describe that women more often have concomitant hypertension, renal failure, obesity and depression whereas men with HF more often have IHD, chronic obstructive pulmonary disease (COPD) and HF with reduced EF⁽⁸⁴⁻⁸⁶⁾. Women have more severe symptoms, but appear to have better overall survival⁽⁸¹⁻⁸³⁾. Also, women are less likely to receive guideline recommended therapy than men⁽⁸⁷⁾. Accordingly, men and women with HF differ in clinical aspects as age, co-morbidities and treatment^(80, 88, 89). Mortality in patients with HF is high, particularly in older patients, but mortality in the young is also substantial^(17, 43). Between 1987 and 2006 young men with HF had a higher mortality than women⁽¹⁷⁾. Mortality risk in elderly patients with HF (mean age 73 years) from the Framingham Heart study was fourfold higher than in age and gender matched control subjects without congestive HF⁽⁹⁰⁾. In a middle-aged community-based population sample with an observation period of two decades women had lower risk of developing HF, they had lower all-cause mortality and death related to HF, but in established HF there was no difference in mortality risk between the sexes⁽⁹¹⁾.

International classification of disease

International Statistical Classification of Diseases (ICD) and Related Health Problems, has existed about one hundred years enabling classification and statistical evaluation of health problems in patients within the health care system. Thus, all diagnoses in medical records are coded using ICD codes. The World Health Organization (WHO) has been responsible for the maintenance of ICD since 1948. Over time, the ICD system has been revised and updated in accordance with advances in science, and since May 1990 ICD-10 version has been acknowledged (used in Sweden since 1997).

Swedish registers

There is a long history of registry holding in Sweden. The first records of demographic data were maintained by church officials already in the 17th century. Since 1947 all persons with residence in Sweden have been assigned a personal identity number (PIN). The use of the current 12-digit PIN, in use since 1967, enables the linkage of different registers⁽⁹²⁾.

All residents in Sweden are registered in the Swedish Population Register, beginning in the 1960s. The register contains demographic data, eg. date of birth, sex and county⁽⁹³⁾.

The Swedish Hospital Discharge Register, also called Swedish National Inpatient Register was established in the 1960s. In 1987 the registrations of hospitalized patients became mandatory on a national level. Currently, the coverage of the register is more than 99%. The register records principal and contributory diagnoses, procedure codes, admission and discharge dates of all hospitalizations. The register has a high validity in general, in particular for HF with an 85–95% accuracy compared with patient records^(94, 95).

The Swedish Cause of Death Register started in 1961 and contains data on time and cause (underlying and contributory) of death for all deceased persons in Sweden. Data that is also available on the location of death, if autopsy was performed or if the cause of death was established through an examination before death, and if the person had had an operation within the last four weeks. Prior to 2012 only Swedish residents were registered⁽⁹⁶⁾.

The Swedish Heart Failure Register (SwedeHF) is a nationwide, voluntary quality register for patients diagnosed with HF. It was introduced throughout Sweden in 2003 including hospitalized patients, outpatient's and in primary care units. Inclusion criterion is physician-judged HF diagnosis. The multisite ethics committee approved the establishment and operation of the register. Individual patient consent is not mandatory but patients are informed and may opt out⁽⁹⁷⁾.

Observational studies

In observational studies the investigator observes what happens, without interfering. They are often used in epidemiological studies to assess the relationship between the factors of interest and disease in the population and may be addressed retrospectively or prospectively. Main types of observational studies are cohort studies and case-control studies. In cohort studies a group of individuals is followed over a defined period of time and the aim is to study whether a factor of interest will affect the incidence of a disease outcome. A comparison of groups of patients with a specific disease (named cases) and individuals without that disease (named controls) is performed in case-control studies and the aim is to investigate if exposure to any factor occurs more or less often in patients than in the control group. Selected controls and controls should be similar in selected characteristics, such as age and sex. This process is called matching. To add power to the study more controls should be included than cases and for

statistical reasons it is usually enough with two controls per patient. In longitudinal studies individuals are followed over a period of time. In cross-sectional studies all information is obtained at a single point in time, providing information on prevalence estimates or current health status of a group of patients. Cross-sectional studies may also be repeated enabling information on changes over time.

Term used to define the occurrence of a condition of interest in the population is prevalence. Incidence is a measurement of the probability of a condition's occurrence in a population within a defined time frame. Mortality is defined as a number of deaths in a population in a specified time period. Prevalence of a chronic disease depends on the rate of newly diagnosed cases (the incidence), potential recovery (for some conditions), and all-cause mortality. These commonly used terms (prevalence, incidence and mortality) may be presented as proportions, percentages or number of cases, per 1,000, 10,000 or 100,000 individuals. Incidence and mortality are often expressed as cases or deaths occurring within a specific number of observation years, eg. per 1000, 10,000, or 100,000 person years.

Survival analysis

Survival analysis is a set of methods to study the time necessary for an individual to reach an endpoint of interest (death, hospitalization). Important features are the length of time for the individual to reach the endpoint and censoring due to incomplete information on the outcome. Data might be left-censored in patients in whom follow up begins after baseline date. Right-censored data comes from patients who has not reached the endpoint at the time point they were lost to follow up, were withdrawn from the study, or where, for some reason, follow up had been stopped before the endpoint was reached. Usually, individuals are included continuously in a study, which means that different individuals have different follow-up times at the end of the study, further complicating survival data.

One way of displaying the survival data is the use of survival curves, usually calculated by the Kaplan-Meier method and presents the cumulative probability of an individual remaining free from endpoint at any point during follow up. An advantage of this method is that it takes into account for example right-censoring, but is not suited to estimate survival adjusted for covariates.

The log-rank test is a non-parametric test used to compare two or more survival curves. Kaplan-Meier curves and log-rank test present univariate analysis of categorical variables, describing the effect of one factor on survival and ignoring the impact of any other factors.

Often used in survival analysis is the alternative proportional hazards regression model (Cox regression) that enables the study of the concurrent effect of a number of explanatory variables on survival. Originally the model was proposed for clinical trials but soon it was embraced in epidemiological observational studies and nowadays it is usually used in cohort and case-controls studies frequently involving long follow up time and numerous known and unknown factors, and works for both quantitative and categorical explanatory variables. This type of model simultaneously addresses the ef-

fect of several factors on survival time. The effect is reported as a ratio for an outcome of interest. In survival analysis hazard presents the immediate risk of reaching the endpoint. Hazard ratio (HR) is the ratio of two hazards also known as relative hazard and is interpreted in a similar way as relative risk. The ratio of two risks is known as relative risk, for example the risk of disease in a cluster of individuals exposed to some factor divided by the risk in unexposed individuals. The basic condition in the proportional hazard regression model is that the relative hazard is constant over time. One or more explanatory variables may be related to each other and to the outcome. Then it is difficult to assess the independent effect of one variable on the outcome. This is called confounding. There are different methods to adjust for confounding such as multi-variable Cox regression model for estimation of risk.

Conditional probability is the probability of an event, assumed that another event has happened. Life expectancy is defined with statistical methods as estimated average time an individual or group of people are expected to live, based on the year of birth, current age, also including other demographic factors such as gender, and is often presented in life expectancy tables. Life expectancy is expressed as average and an individual may die many years after or before the “expected” survival. Conditional survival is the life expectancy from a point in time for an individual who already survived a certain period after disease start. In other words, it is the survival probability calculated after a certain length of survival and takes only into account individuals that survived to that point. Consequently it might be looked on as an update of life expectancy.

THE RATIONALE OF THE THESIS

Paper I

Today we do not know whether the observed increase in cardiomyopathy diagnoses⁽¹⁷⁾ represents a real increase of the disease or whether the diagnosis setting is based on other reasons today compared to the late 1980s. Consequently, validating the diagnosis is an important step.

Paper II

With an aging population, advances in treatment and changes in risk factor profile⁽⁹⁸⁾, even potential changes in mortality trends in patients with HF over time are of interest. No study so far investigated the survival of patients with HF and explored possible changes of mortality risks compared to controls from the general population over time on the national level with emphasis on different age categories and in both sexes.

Paper III

Young patients were described in comparison to elderly patients in selected patient populations^(54, 55), or with data sets not reporting data on echocardiography results or prevalence of co-morbidity such as cardiomyopathy⁽⁴³⁾, or including subset of young patients with preserved EF only⁽⁹⁹⁾. Accordingly, a detailed and comprehensive description of the growing subset of young patients with HF in a less selected population is needed.

Paper IV

Sex differences in elderly patients with HF are well described⁽⁸⁰⁻⁸³⁾, while in young patients these are, to our knowledge, still to be addressed.

AIMS

Paper I

The aim of this study was to examine the accuracy of cardiomyopathy diagnoses and evaluate if there were changes in validity over time from 1987 to 2009, taking into consideration possible changes in the use of diagnostic methods and potential changes in prevalence of co-morbidities.

Paper II

This study aims to investigate short-term and long-term mortality in patients first time hospitalized for HF and compare survival in patients with HF with controls from the general population and to assess potential changes of the mortality risk over time in different age categories and in both sexes.

Paper III

The aim of the study is to compare clinical characteristics, treatment and outcomes of patients with HF <55 years and those ≥ 55 registered in the SwedeHF. In addition, to study survival of patients <55 years in comparison with matched controls from the general population and investigate the risk for all-cause mortality and life-years lost after being diagnosed with HF in young age.

Paper IV

This study aims to compare clinical characteristics, management and causes of death between sexes in patients with HF <55 years. Also, to compare mortality risks, and estimate potential loss of life-years in men and women with HF <55 years compared with those of matched controls. We also wanted to investigate the impact of baseline co-morbidities on mortality in young men and women with HF, respectively.

METHODS

Paper I

Patients from 1989-90, 1994-96, 1997-99, 2004 and 2009 with a cardiomyopathy diagnosis, irrespective of the diagnostic position, in both outpatient and inpatient settings were identified from the local hospital discharge registers with the use of the International Classification of Diseases (ICD) codes. From 1987 to 1996, ICD-9 was in use, and thereafter ICD-10. ICD codes for all hospital discharges are entered into the Swedish National Inpatient Register, mandatory on national level since 1987. Patient records were divided into three groups: dilated, hypertrophic, and other cardiomyopathies. Hypertrophic and hypertrophic obstructive cardiomyopathy formed one group. Due to few cases, cardiomyopathies such as peripartum, restrictive, arrhythmogenic right ventricular, left ventricular non-compaction and takotsubo cardiomyopathies were analyzed as one group labeled “other cardiomyopathies”. Diagnoses were then validated according criteria defined by the European Society of Cardiology from 2008⁽⁴⁶⁾. The accuracy of the diagnoses was categorized as definite, uncertain or miscoded. In undecided cases, two very experienced cardiologists read the records separately and then a joint decision was made. Also, 20 medical records were randomly selected, and two experienced cardiologists validated the cardiomyopathy diagnoses separately. Finally, 20 medical records with diagnostic code for HF (I50), but without a cardiomyopathy diagnoses, were studied for potential occurrence of cardiomyopathy as a co-morbidity. Accuracy rates of diagnosis including frequency of co-morbidities were examined using the Pearson χ^2 test for categorical variables. Student’s *t*-test was used for continuous variables. All *p* values are two sided, values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA).

Paper II

For the purposes of this study all patients ≥ 18 years with a first recorded hospitalization for HF and registered in NPR between January 1st, 1987 to December 31st, 2014 were included. With the use of personal identification number two controls per patient were selected from the Total Population Register. Controls were defined as individuals without HF and they were matched for age, sex and county. Information on time and cause of death were obtained from the Cause of Death Register.

HF and all co-morbidities were defined according to the ICD-9 and ICD-10 codes. Codes used to identify comorbidities and causes of death were ICD-9: 410–414, 250, 401–405, 431, 433, 434, 436, 394–397, 424, 427D, 425, 415B, 490–496, 140–208 and ICD-10: I20–I25, E10–E14, I10–I15, I61–I64, I05–I08, I34–I37, I48, I42, I43, I26, J44, J45, C00–C97. The Kaplan-Meier method was used to assess probability of survival with the cohort stratified into two groups: 18–64 years and >65 years, and the study period was split from 1987–2002 and from 2003–2014. Cox proportional hazard regression was used to assess differences in 1-year all-cause mortality between cases and controls and to estimate the relative risk of mortality between cases and

controls. All statistical analyses were performed with the statistical software SAS, version 9.4 (SAS Institute, Cary, NC) and all graphs were created using R version 3.1.3 (<http://R-project.org>).

Paper III and IV

All patients ≥ 18 years registered in the SwedeHF from 1st January 2003 to 31st December 2014 were included. All patients had a minimum follow of 2 years. The data set was merged with NPR and Cause of Death Registers with the use of the PIN. The population was divided into patients < 55 years, and ≥ 55 years. Patients with HF < 55 years were further subdivided into three age categories: 18-34, 35-44 and 45-54 years. For each patient with HF < 55 years, we identified 2 controls from the Total Population Register matched for age, sex and county. Controls were defined as individuals without a prior HF diagnosis. Co-morbidities were identified from the NPR with the use of ICD codes; ICD-9 codes from 1987 to 1996, and ICD-10 codes from 1997. ICD codes were also used to identify the underlying and first contributory cause of death from the Cause of Death Register. ICD-9 and ICD-10 codes used for the purposes of Paper III and IV are presented in Table 1. The latest update of the Cause of Death Register in this study was 31st December 2015. All analyses were performed in men and women < 55 years with HF separately in Paper IV.

Table 1. International Classification of Diseases ICD-9 codes and ICD-10 codes used to identify co-morbidity in the National Patient Register

Category	ICD-9	ICD-10
Heart failure	428 A, 428B, 428X	I50
Other cardiovascular diagnoses	401-405, 410-414, 416A, 427D, 425, 425F, 425E, 425B, 674W, 391, 394-398, 421, 422, 424, 745-747	I10-I15, I20-I25, I27.0, I40- I41, I48, I42.0, I42.1, I42.2, O90.3 I05-I09, I33-I39, Q20 - Q28, Q87, Q89
Diabetes mellitus	250	E10-E14
Obesity	278A, 278B	E65-E66
Depression	296, 296B, 296D, 296W, 296X, 298A, 331	F32-F33
Kidney disease	583, 584, 585	N17-N19
Cancer	140-208	C00-C97

For comparison between continues variables the Student's *t* test and for categorical variables the Pearson chi-square test were used. The impact of age on different co-morbidities was tested with logistic regression with adjustment for sex. Compared with controls, for patients < 55 years the association between age at inclusion and risk for all-cause mortality was tested with Cox proportional , both univariate and multivariate models as purposed by Rawshani et al.⁽¹⁰⁰⁾.

The conditional survival was estimated for patients and presented as median. As reference to the life expectancy of controls, life expectancy tables from Statistics Sweden,¹² were used. These are available at the website: http://www.statistikdatabasen.scb.se/pxweb/sv/ssd/START_BE_BE0701/LivsUtbLan/. The conditional survival

for patients and conditional life expectancy for controls were estimated at 30, 35, 40 and 45 years of age. The difference between life expectancy and conditional survival for patients with HF was defined as life-years lost and is presented as median. All p values are two-sided and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS, Windows version 18.0 (SPSS Inc., Chicago, IL, USA), SAS 9.3 or in R 3.5.3. This study was approved by the Ethics Committee of the University of Gothenburg, Sweden.

RESULTS

Paper I

In total 611 medical records with cardiomyopathy diagnoses were validated. Mean age of the population was 58.9 (SD 15.5) years, 68.2% were male. The records were divided into those with dilated, hypertrophic and other cardiomyopathies with 85.5%, 87.5%, and 100% of accuracy, respectively. The accuracy of diagnosis DCM and HCM/HOCM by year are presented in Figure 1 and 2. The use of echocardiography

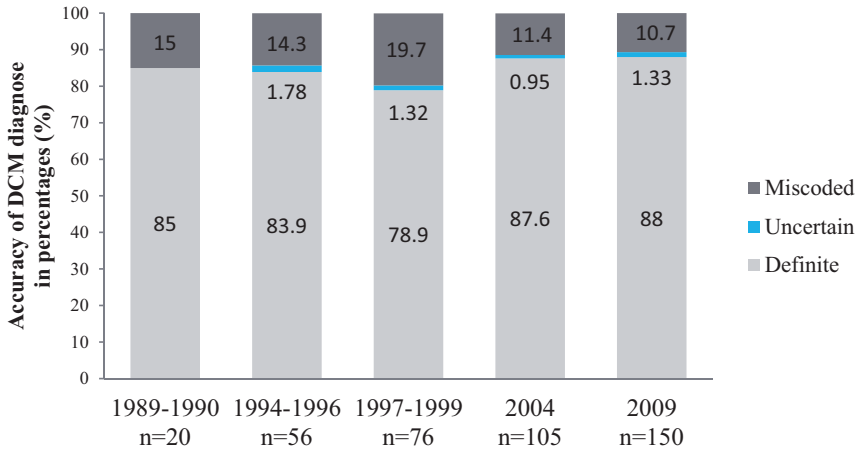


Figure 1. Accuracy of the dilated cardiomyopathy (DCM) diagnose by year.

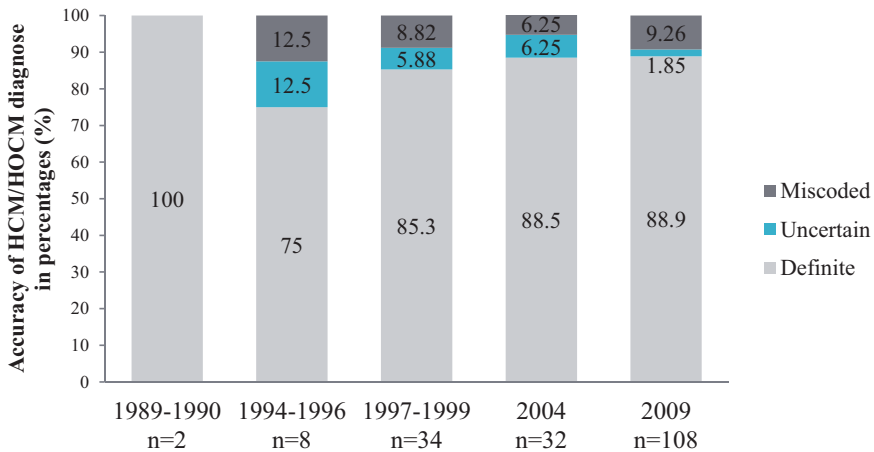


Figure 2. Accuracy of hypertrophic and/or hypertrophic obstructive cardiomyopathy (HCM/HOCM) diagnoses by year.

was high, performed in 99.7% of cases, of which 94.6% were complete reports (Figure 3). The use of echocardiography was consistently high during the study period and without significant difference between periods studied or between hospitals. The presence of co-morbidities, hypertension, coronary artery disease, diabetes mellitus, AF and alcohol and/or drug abuse, was also analyzed. During the study period there was no systematic variation of any co-morbidity, in the whole material, nor in the subset with the accurate cardiomyopathy diagnoses.

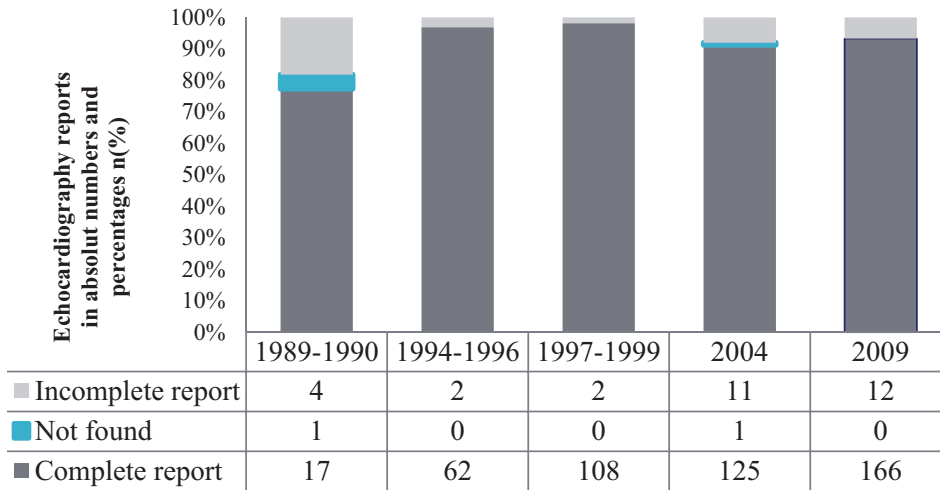


Figure 3. Use of echocardiography by year in the whole population studied.

Paper II

The total population comprised 702,485 patients with HF (49.8% men and 50.2% women) and 1,306,183 controls. In patients aged 18 to 65 years, both short-term (29 days to 6 months) and long-term (<11 years and >11 years) mortality rates decreased during the study period, but in patients ≥ 65 years the decrease in mortality rates was marginal (Figure 4 and 5). Compared to controls, HF patients aged <65 years had a relative mortality risk at 29 days to 6 months of 3.66 (95% CI 3.46-3.87) during 1987-2002, but the relative risk was considerably higher 2003-2014 with the HR 11.3, 95% CI 9.99-12.7. Also, long-term mortality (>11 years) increased from 3.16, 95% CI 3.07-3.24 in 1987-2002 to 4.11, 95% CI 3.49-4.85 in 2003-2014 (Figure 6 and 7). Similar, but less pronounced alterations between the two periods were seen in patients ≥ 65 years. The increase in mortality risk over time in both age groups mainly may be explained by the more marked improvement of survival in controls than in patients.

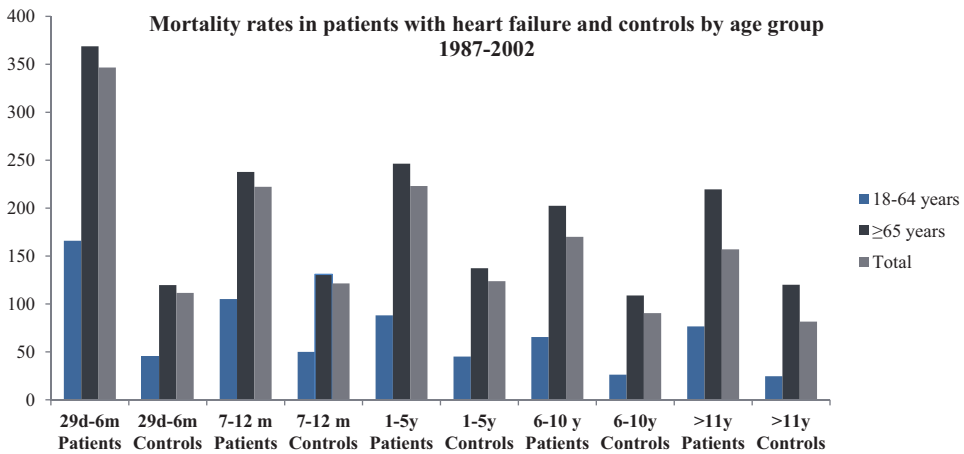


Figure 4. Mortality rates per 1000-person-years in the period 1987-2002 in patients with heart failure and controls by age group.

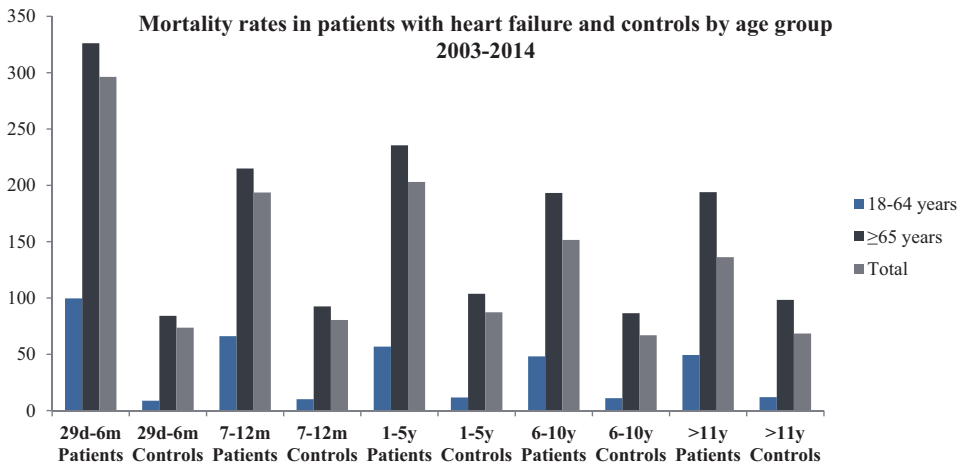


Figure 5. Mortality rates per 1000-person-years in the period 2003-2014 in patients with heart failure and controls by age group.

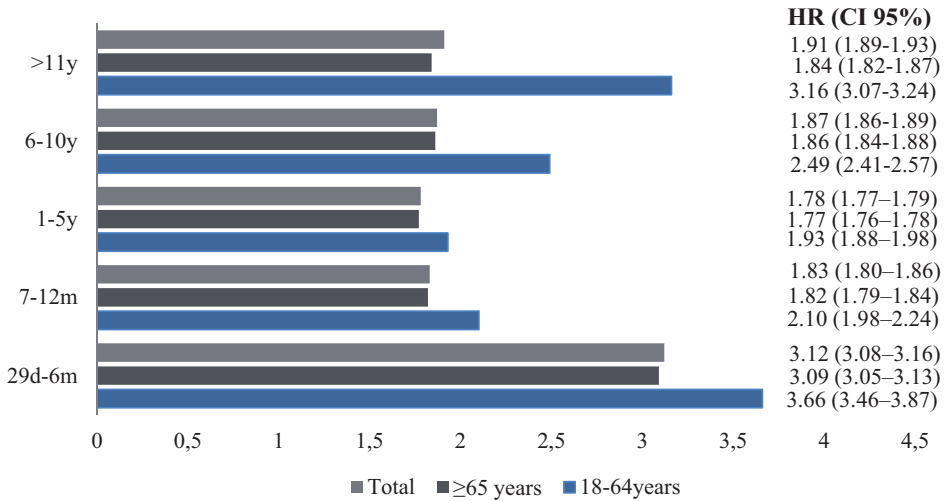


Figure 6. Relative risk of death in patients with heart failure compared to controls from the general population by age group between 1987 and 2002.

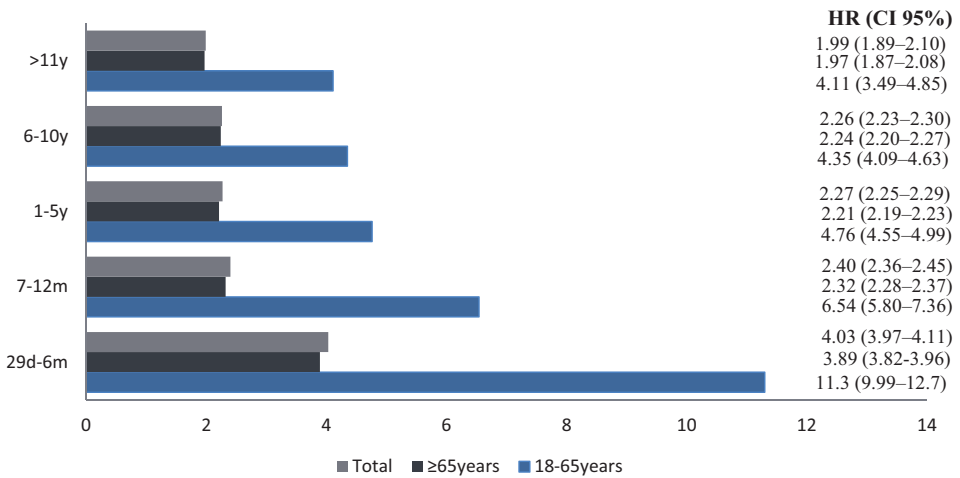


Figure 7. Relative risk of death between 2003 and 2014 in patients with heart failure compared to controls from the general population by age group.

Paper III and IV

In total, 60,962 patients were included. Out of those 3,752 (6.2%) were <55 years and they were compared to 7,425 controls. Among patients <55 years, 2781 (74.1%) were men and 971 (25.9%) were women, mean age 46.4 (7.3) and 44.9 (8.4) years, respectively. Patients <55 had more often obesity, dilated cardiomyopathy and congenital heart disease compared to patients ≥ 55 (Table 2). EF <40% was also more common in patients <55 years, 67.9% vs. 45.1% ($p < 0.001$) compared to patients ≥ 55 . Patients 18-34 years of age had more often HFpEF and HFmrEF than HFrEF. Hypertension, IHD and AF were more common in male patients <55 years while congenital heart disease and obesity were more often found in female patients (Table 2). Patients had significantly higher frequency of co-morbidities when compared to controls <55 years. There was no significant difference in treatment among young men and women with EF <40% (Figure 8).

Table 2. Frequency of co-morbidities in different age groups and by sex in patients with heart failure. Data originates from the Swedish Heart Failure and National Patient Registers

	All patients			Patients <55 years		
	Patients <55 years n=3752	Patients ≥ 55 years n=57210	p-value Patients <55 vs ≥ 55 years	Men n= 2781	Women n=971	p-value men vs. women
Obesity	367 (9.8)	2706 (4.7)	<0.001	245 (8.8)	122 (12.6)	0.001
Ischemic heart disease	972 (25.9)	31982 (55.9)	<0.001	768 (27.6)	204 (21.0)	<0.001
Atrial fibrillation	933 (24.9)	31364 (54.8)	<0.001	763 (27.4)	170 (17.5)	<0.001
Hypertension	1186 (31.6)	33197 (58)	<0.001	906 (32.6)	280 (28.8)	0.002
Diabetes mellitus	627 (16.7)	14975 (25.6)	<0.001	476 (17.1)	147 (15.1)	0.154
Valvular disease	467 (12.4)	11556 (20.2)	<0.001	333 (12.0)	134 (13.8)	0.138
Dilated cardiomyopathy	1020 (27.2)	3165 (5.5)	<0.001	967 (34.8)	338 (34.8)	0.983
Hypertrophic cardiomyopathy*	75 (2.0)	532 (0.9)	<0.001	45 (1.6)	30 (3.1)	0.005
Myocarditis	78 (2.1)	257 (0.4)	<0.001	55 (2.0)	23 (2.4)	0.462
Congenital heart disease	140 (3.7)	456 (0.8)	<0.001	75 (2.7)	65 (6.7)	<0.001
Cancer	320 (8.5)	14175 (24.8)	<0.001	165 (5.9)	155 (16.0)	<0.001

Values are expressed as numbers (percentages) unless otherwise stated. *Hypertrophic cardiomyopathy - together with patients with hypertrophic obstructive cardiomyopathy

One-year all-cause mortality was highest in patients ≥ 55 years of age, 21.2% vs. 4.2% in those <55 years, and only 0.3% in controls (all $p < 0.001$). One-year all cause mortality in men and women <55 years was 16.5% and 14.8%, respectively. Total observation time was 12 years, median 4.87 years. In a multi-variable Cox regression model adjusted for age, sex, duration of HF, IHD, diabetes mellitus, dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy/hypertrophic obstructive cardiomyopathy (HCM/HOCM), and cancer patients <55 years compared with controls had five times higher mortality risk; HR 5.48 (4.45-6.74) with the highest relative risk among the youngest patients 18-34 years; HR 38.3 (8.69-168) (both $p < 0.001$). Cancer at baseline was associated with increased mortality risk almost three times in patients, HR 2.79

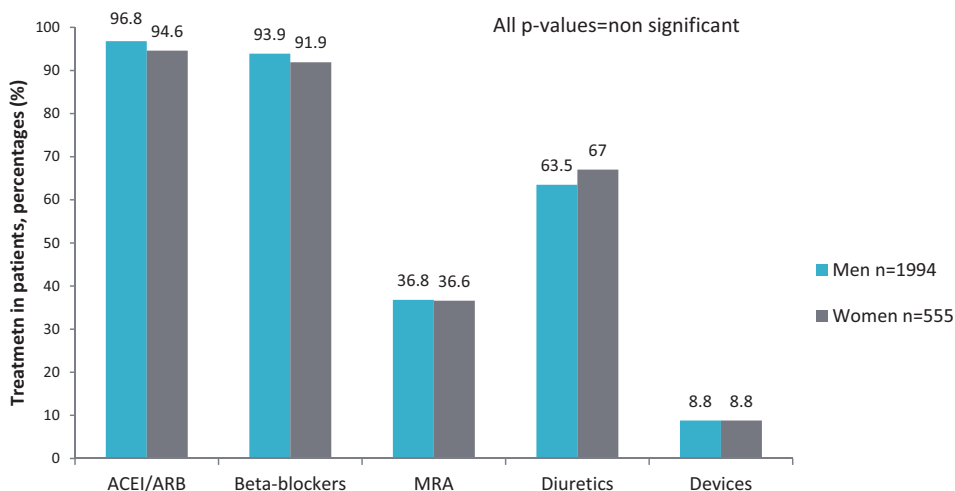


Figure 8. Treatment in men and women <55 years with ejection fraction <40%. Data originates from the Swedish Heart Failure Register.

(2.29-3.41) (Table 3). Compared to controls, patients lost 26.1, 23.5, 20.6 and 19.1 life-years when estimated at 30, 35, 40 and 45 years of age. Mortality risk and life-years lost declined with increasing age. In men and women with HF <55 the relative mortality risk was 4.29 (3.39-5.44) and 7.06 (4.33-11.5), respectively (p-value for interaction 0.1185). Women lost up to 2.9, 1.1 and 3.8 years more than men if HF at 35, 40 and 45 years of age. CVD was the most common cause of death, 58.9% vs 50.7% in male vs female patients <55 years, respectively. Cancer was the second most common cause of death, 9.1% vs. 22.2% in men and women, respectively (all $p < 0.001$).

Table 3. Impact of coexisting conditions at baseline on total mortality in patients with heart failure <55 years by sex. Data originates from the Swedish Heart Failure, National Patient and Cause of Death Registers.

	Men		Women	
	HR (CI 95%) **	p-value	HR (CI 95%) **	p-value
Age	1.02 (1.01-1.04)	0.0008	1.03 (1.01-1.05)	0.0165
Ischemic heart disease	1.28 (1.05-1.57)	0.0166	1.17 (0.80-1.71)	0.4191
Diabetes mellitus	1.74 (1.42-2.14)	<0.0001	1.67 (1.13-2.46)	0.0093
Dilated cardiomyopathy	1.10 (0.89-1.35)	0.3753	0.70 (0.46-1.06)	0.0947
Hypertrophic cardiomyopathy*	0.85 (0.37-1.94)	0.7004	2.46 (0.95-6.36)	0.0638
Congenital heart disease†	1.29 (1.01-1.65)	0.0404	1.73 (1.17-2.55)	0.0060
Pulmonary arterial hypertension	4.20 (1.85-3.13)	<0.0001	7.91 (2.87-21.86)	0.0001
Cancer	2.40 (1.85-3.13)	<0.0001	3.18 (2.27-4.46)	<0.0001
Kidney disease	1.68 (1.23-2.29)	0.0012	3.92 (2.31-6.64)	<0.0001
Duration of heart failure	1.08 (1.05-1.10)	<0.0001	1.03 (0.98-1.09)	0.2288

Abbreviations: HR, hazard ratio; CI, confidence interval. *Hypertrophic cardiomyopathy – together with hypertrophic obstructive cardiomyopathy. †Congenital heart disease – together with valve disease. **Adjusted for age, IHD, diabetes mellitus, dilated cardiomyopathy, hypertrophic cardiomyopathy/hypertrophic obstructive cardiomyopathy, pulmonary arterial hypertension, congenital heart disease, valve disease, cancer, kidney disease and duration of HF.

DISCUSSION

Heart failure is a serious syndrome with overall five-year survival of approximately 50%⁽¹⁶⁾. HF may occur in all age groups but the highest prevalence is among elderly⁽¹⁰¹⁾. There is always a cause to HF^(2, 26). Cardiomyopathies present an important etiological group, especially in young, where approximately 20% of hospitalized patients with HF are diagnosed with concomitant cardiomyopathy⁽¹⁷⁾. Recent studies showed an increase in hospitalization⁽¹⁷⁾ and prevalence⁽¹³⁾ of diagnosed HF among young patients since 1987, including increasing rates of incident diagnosis for cardiomyopathies⁽¹⁷⁾ which is worrying as it may include a very detrimental effect on young individuals. Thus, it is important to study etiology, survival trends and mortality risks more in detail in this aged group which was performed in the following parts of this thesis:

Validity of cardiomyopathy diagnoses

Since 1987 diagnoses of cardiomyopathies had more than doubled among young patients 18-44 years of age⁽¹⁷⁾. This is of considerable concern as it may imply that a real increase of cardiomyopathy disease may have occurred among young patients.

To our knowledge, this is the first time the validity of cardiomyopathy diagnoses has been studied. The accuracy of the diagnoses during a 20 year period (from 1989 to 2009) was high, >85% (Figure 1 and 2), without differences between the three hospitals or time periods analysed and where the use of echocardiography (Figure 3) over time was consistently high. The validations of the diagnoses were performed according to the most recent and most comprehensive classification criteria presented in an ESC position statement in 2008⁽⁴⁶⁾. According to these criteria presence of comorbidities eg. hypertension or coronary artery disease did not exclude cardiomyopathy if the extensions of the associated condition was insufficient to cause global impairment of cardiac function. Thus, we did not exclude cases from the early years, where in that period, cardiomyopathy diagnoses were mostly based on exclusion and presence of comorbidities could disqualify from the cardiomyopathy diagnosis⁽⁴⁸⁾. Also, use of a wider definition over time might have involved increasing trends of comorbidities over time, which we did not find in this study population.

Referring to the design of this study, a diagnosis was only considered accurate if ESC criteria were met and a complete echocardiography report containing all relevant data for decision making was presented in the medical record. Echocardiography was performed in 99.6% of cases, of which 94.5% were complete reports. We also took into consideration other data as cardiac markers, electrocardiograms, coronary angiography and cardiac magnetic resonance images, if performed.

Because echocardiography had the highest hierarchical order the diagnosis was defined as uncertain or wrong if relevant data was not found or if data contradicted the diagnosis. In those instances where a dilated cardiomyopathy diagnosis was found to be miscoded, this was mostly due to presence of IHD of such magnitude that global myocardial dysfunction might be a consequence and in the case of a diagnosis of hypertrophic cardiomyopathy, the presence of long term and/or inadequately treated hy-

pertension could make it impossible to distinguish between hypertrophic cardiomyopathy or hypertrophy caused by hypertension. There were only 20 cases of specific forms of cardiomyopathies; Takotsubo, peripartum, restrictive, arrhythmogenic right ventricular, left ventricular non-compaction cardiomyopathies, that were analyzed together as one category and defined as other cardiomyopathies. Due to very specific classification criteria⁽¹⁰²⁻¹⁰⁶⁾ the validity of this category was 100%, as expected. Diagnostic criteria for cardiomyopathies changed over time which might have affected diagnostics^(7, 48). Therefore, the validation was performed according to the latest and most wide diagnostic criteria⁽⁴⁶⁾. Consequently, cardiomyopathy diagnosis from earlier periods could have been defined as accurate even in presence of comorbidities. Even though diagnoses with cardiomyopathy increased over time the occurrence of comorbidities did not follow the same increase as expected with widened diagnostic criteria or increased recognition. Accordingly, this supports that a real increase of cardiomyopathy diseases might have taken place. Regardless, in the early period we detected only few cases. That remains unclear. Overall, this may mean a real increase of cardiomyopathy diagnosis but it is important to take into account that we may have missed early cases of cardiomyopathy because the diagnostic criteria were narrower then and we therefore might not be able to capture some patients who would have been diagnosed with cardiomyopathy at a later stage. Also, 20 medical records with the diagnosis of heart failure and without co-morbidities were searched thoroughly and in three cases cardiomyopathies were confirmed in subsequent years after total medical workout. This was not likely to affect the validation process but caution is needed when hospital discharge registers are used^(107, 108), as underestimation of the cardiomyopathy diagnoses might be the case.

Survival of patients with heart failure in Sweden

This nationwide study that included more than 700,000 patients with HF and 1,3 million controls showed that mortality in patients with HF remains high, although an overall decrease in mortality rates since 1987 to 2014 has been observed. The survival in patients <65 years improved during both periods studied (1987 to 2002 and 2003 to 2014), but in patients ≥65 years the survival improved only slightly (Figure 4 and 5). Overall, only marginal improvements in mortality have been seen in Sweden since 2003, consistent with the data from UK⁽²⁵⁾. The improvement in survival, to a great extent, reflected the initial period.

Short- and long-term mortality was markedly higher in patients than in matched controls from the general population. Additionally, survival improved more among controls than in patients. Consequently, over the two periods, the relative mortality risk in patients increased, mainly due to improved survival in the control group. Long term mortality risk did not increase to the same extent as the short-term mortality risk, mostly due to consistently high HR between 2003 and 2014 (Figure 6 and 7).

Mortality in patients ≥65 years remained high and one possible explanation might be that the majority of the patients were elderly. As previously described, the proportion of patients with HFpEF increased with increasing age, as well as the proportion of patients with multiple comorbidities^(29, 30, 109). Another explanation to the persistent high mortality among patients ≥65 years might also depend on current lack of treat-

ment modalities leading to mortality reduction in this patient group, as no study so far showed mortality benefit in patients with HFpEF^(32-35, 37), at the same time as there is a whole palette of recognized and lifesaving treatment available for patients with HFrEF⁽²⁾. Worryingly, as shown in other studies, many patients are still not offered treatment even though they fulfill criteria for specific treatments⁽¹¹⁰⁻¹¹⁴⁾, which also may have contributed to the observed mortality trends. Two retrospective studies that compared younger with older patients showed that the young more often had HFrEF^(54, 55) and thereby fulfilled requirements for being treated according to guidelines, with potential benefit with respect to prognosis. However, as presented in a CHARM subgroup analysis, young patients also had low treatment adherence, which could also contribute to explain persistent high mortality rates⁽⁵⁴⁾.

Description and survival of young patients with heart failure with emphasis on sex differences in the young

As mentioned above, a recent analysis showed an increase in hospitalization⁽¹⁷⁾ and prevalence⁽¹³⁾ among patients with HF <55 years. Thus, in part III and IV we focused in particular on patients <55 years with HF. Young patients were compared with elderly and with controls from the general population with detailed description of young patients in SwedeHF with emphasis on gender differences and outcomes compared to controls.

Patients <55 years vs. ≥55 years

Major differences were present in baseline characteristics, where younger patients more often had cardiomyopathies, congenital heart disease and myocarditis and those ≥55 years had hypertension, IHD and AF (Table 2), in line with previous studies^(54, 55). Current survival of patients with congenital heart disease into adulthood is 75% to 85%^(115, 116). They are at increased risk to develop ventricular dysfunction^(117, 118) and HF. The prevalence of cardiomyopathies in our study was in accordance with data previously published in a nationwide study from the NPR⁽¹⁷⁾, but was much lower compared to the CHARM subgroup⁽⁵⁴⁾ and the MAGGIC meta-analyses⁽⁵⁵⁾, most probably owing to different study designs. Besides, the CHARM study was included in the MAGGIC meta-analysis. Further, the prevalence of obesity was more common among the young, in line with other studies^(54, 119). Obesity is associated with increased risk for early HF⁽²¹⁾. Causal relationship between adiposity and HF has also been proposed⁽¹²⁰⁾. Recently, an association with obesity in young age and early development of cardiomyopathy and known cause of HF, has been suggested⁽²²⁾.

Young patients were more often treated with guideline recommended therapy⁽²⁾ than elderly patients, probably as they had more often reduced EF, and when indicated (EF <40%) young men and women with HF from this cohort were equally treated (Figure 8), which differs from other studies showing that women were less often offered this treatment. However, elderly patients more frequently had HFpEF and thereby lacked indication for this treatment. They also, as stated in previous studies, were more often less treated probably owing to contraindications and intolerance of medications as a reason why physicians may abstain from providing treatment^(110-112, 121).

Male vs. female patients <55 years

The majority of young patients with HF were men. The prevalence of IHD, hypertension and AF was higher in men, as these conditions are more prevalent in men in the general population^(122, 123). Also, the later onset of IHD in women compared to men⁽¹²⁴⁾, might explain the higher occurrence of IHD in men <55 years in this cohort. Accordingly, this might also have been reflected in echocardiography reports, showing a higher prevalence of reduced left ventricular EF in the young, particularly in men. Women <55 years more often had congenital heart disease and hypertrophic cardiomyopathy which might explain higher occurrence of HFmrEF and HFpEF in this group. Besides, young women with HF also had higher rates of cancer and obesity. Detailed analysis of subgroups of congenital heart disease and cancer were not performed due to small number of patients and this should be kept in mind when interpreting these results. Men and women with HF <55 years and EF <40% were equally treated with evidence-based lifesaving treatment⁽²⁾ which to some extent contradicts previous studies showing that women are likely to be less treated⁽⁸⁷⁾ (Figure 8).

Additionally, functional class between young men and women did not differ which might reflect why re-admission rates for HF did not differ either^(125, 126). Moreover, there was no difference in mortality rates between sexes.

Patients <55 years vs. controls

Compared to controls from the general population patients <55 years had higher occurrence of all coexisting conditions. The mortality rates were also significantly higher in patients, both men and women.

Strikingly, the highest relative mortality risk was among the youngest patients 18-34 years of age, which was up to 38 times higher than in controls. There might be a few explanations for that. First, there were more with HFmrEF and HFpEF among the youngest patients, and consequently lacking the indication for lifesaving treatment. Second, having comorbid cancer increased the mortality risk at most, up to three times in patients 18-34 years of age. Third, the lowest mortality rates were found among the youngest controls, resulting in the highest risk ratio for mortality.

In absolute numbers, mortality rates did not differ among sexes, but when compared to controls from the general population relative mortality risks were almost doubled in women than in men <55 years with HF but this difference was not significant and thereby congruent with previous data on patients with HF⁽⁹¹⁾. Female controls had lower mortality rates, thereby the HR for all-cause mortality were higher.

Moreover, when addressing prognosis comorbidities play an important role^(127, 128). Coexisting cancer and kidney disease at baseline were associated with increased mortality risk in both men and women. Furthermore, more young women died of non-cardiovascular causes compared to men. Cancer was registered as underlying cause of death in 22.2% of women and 9.1% of men.

The mortality risk was highest among the youngest patients and decreased with age, as was the case with life-years lost. The youngest patients lost up to 26 years when compared to the conditional life expectancy of controls. According to the estimated life expectancy in the general population, women are likely to live longer than men. In this cohort of patients with HF <55 years at the age of 30 years men and women lost approximately as many life-years. After the age of 30, women lost more life-years than young men with HF.

Strengths and limitations

In Paper I high validity of the cardiomyopathy diagnoses was found in an unselected population which included a review of 611 medical records of patients covering large parts of western Sweden. To our knowledge this is the first study to assess the validity of cardiomyopathy diagnoses. The study population was recruited from three different types of hospital and the use of echocardiography was constantly high over the whole study period. Even so, in a few instances complete echocardiography reports could not be found.

All records were analyzed by an experienced investigator. In doubtful cases two cardiologists separately investigated the cases. Moreover, 20 randomly selected medical records were independently evaluated by two cardiologists and with 100% conformity. In the early years 1989 to 1990 we only found a few cases of cardiomyopathy diagnoses, which remains unexplained but might hypothetically reflect a real increase of the cardiomyopathy diagnoses, something which has been shown previously in studies from our group⁽¹⁷⁾.

In Paper II, where a nationwide register with almost complete coverage throughout Sweden was used, a high number of patients and controls over a long time period were included. A previous study confirmed high validity of the HF diagnosis in the NPR and the external validation of the NPR also showed high validity for other diagnoses including heart disease^(94, 95). Underreporting hypertension was probably present but it is unlikely to influence mortality rates differently in different age groups. Also, data about time and cause of death was taken from the Cause of Death Register with a practically complete coverage⁽⁹⁶⁾. However, data on eg. cardiac biomarkers such as TNT or NT-proBNP as well as data on EF would have added value to this study.

In Paper III and IV the description of young patients with HF were based on a more contemporary cohort when compared to other studies. Besides, this study presents a comprehensive evaluation from a more unselected patient population than earlier studies^(43, 54, 55, 99) including patients within the whole range of EF, description of men and women separately and corresponding comparison with the general population. Furthermore, to our knowledge the estimation of life-years lost has not been performed previously in patients with HF. The population studied was selected from SwedeHF, a national quality register that includes a large number of patients throughout Sweden. The prevalence of cardiomyopathy in this cohort corresponded well to that of a previously published nationwide study on all hospitalized patients in Sweden

further confirming the representativity of the cohort⁽¹⁷⁾. However, involvement by hospitals and primary care clinics in the SwedeHF is optional and selection bias is thereby a potential limitation. Variables with incomplete data were excluded from statistical analysis and reduced the opportunity to use the register to its full potential. Due to the small number of patients with congenital heart disease specific subgroups were not analysed and data should be interpreted with caution. Also, specific forms of cancer were not studied which should be kept in mind when interpreting the results of the impact of cancer at baseline on mortality.

CONCLUSIONS

Paper I of this doctoral thesis reports high validity of the cardiomyopathy diagnoses and supports the hypothesis that a real increase of the disease might have taken place.

Paper II of this thesis demonstrates decreasing trends in mortality over time, mainly among patients with HF <65 years, while the mortality trends in patients aged ≥ 65 years improved only slightly. Mortality rates decreased even more in the general population. Consequently, both short- and long- term relative risk for all-cause mortality increased in patients, particularly in the younger age group.

Paper III and IV showed that young patients with HF had different characteristics than elderly and compared with the general population they had higher occurrence of all comorbidities. Patients <55 years had lower mortality rates and better survival compared to older patients but when compared with the age matched controls the relative mortality rates, mortality risk and life-years lost were markedly higher, this was especially obvious among the youngest patients. At the age of 30 years patients may lose up to 31.6% of the expected life time. The mortality risk and life-years lost decreased with increasing age. After the age of 30, women lost more life-years than men, as they were expected to live longer. Baseline comorbidities were of importance, while they had impact on the survival, especially cancer. Modifiable coexisting conditions should be recognized. Specific programs may be needed if presence of comorbidities, such as cancer, in young age to further optimize management and improve survival.

CLINICAL IMPLICATIONS

This project is well established clinically. Why the HF diagnosis is increasing among young patients is unclear and important to investigate due to its high morbidity and mortality. There is always an underlying cause to HF, and in this thesis, we primarily wanted to seek the causes of the increase in HF by studying co-morbidities. The almost three times increase of cardiomyopathy in young adults is extremely worrying. The different types of cardiomyopathies have different treatment strategies and different prognosis. Some types may also be prevented. In order to ensure that there is a real increase in the diagnosis, it is important to validate the diagnosis. The first Paper of this thesis confirms high validity of the cardiomyopathy diagnoses and supports the hypothesis that a real increase might have occurred. Thus, it is extremely important to gain more knowledge about the disease and the risks of developing it. Recently, an association between obesity and cardiomyopathy has been presented. As obesity is increasing in all age groups other etiological links are possible, for example sleep apnoea.

Knowledge about aetiology, patient characteristics and prognosis is needed for resource allocation in order to prevent modifiable factors, but also for direct treatment strategies, to relieving symptoms and improve prognosis for patients with established HF. As patients with HF in younger age are a growing patient group it is presumable they will have a high health care consumption. As shown in Paper II of this thesis, mortality improved only marginally since the beginning of the 21st century in patients ≥ 65 years. This group represents the majority of patients with HF. Also, even though the mortality rates decreased in patients < 65 years the mortality risk increased when compared to age matched counterparts. This suggests that better understanding of etiological factors, co-morbidities, treatment strategies and causes of death are thereby needed.

In Paper III and IV of this thesis we showed that young patients with HF have different coexisting conditions than the elderly. The distribution of those conditions differs among sexes. This knowledge is important as identifying and treating these conditions may have an impact on prognosis, eg. cancer, and special follow up programs may be needed in order to improve prognosis. The mortality risk was up to five times higher in the patients and it was almost double as high in women as in men. Besides, the impact on life longevity was also greater the younger the patients were when they got the HF diagnosis. By estimating mortality risks in patients compared with age and sex matched counterparts we are able to give patients more appropriate risk evaluation that may be more accurate than if compared with patients much older and with multiple co-morbidities.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Bakgrund: Syndromet hjärtsvikt uppstår då hjärtmuskeln inte kan uppfylla kroppens metabola krav. Tidigare arbete visade att både hospitaliseringar och förekomsten av diagnosen hjärtsvikt ökat bland unga patienter liksom kardiomyopati diagnoserna. Nyligen publicerade studier visade att mortaliteten hos patienter med hjärtsvikt fortfarande är hög.

Syfte: Validera kardiomyopati diagnoserna i Västra Götaland. Undersöka mortalitetstrender och risker för död över tid i olika åldersgrupper. Beskriva patienter <55 år avseende patientkaraktäristika, utfall och mortalitetsrisker med detaljerad beskrivning av könsskillnader.

Metoder och Resultat: I delarbete I validerades kardiomyopati diagnoserna i Västra Götaland genom granskning av medicinska journaler på tre sjukhus från 1989 till 2009. Validiteten av diagnoserna var hög (86%) liksom användning av ultraljud som undersöknings metod (99.7%). I delarbete II användes patientregistret, dödsorsaksregistret och populationsregistret. Vi fann överlag sjunkande mortalitet mellan tidsperioder 1987-2002 och 2003-2014, framförallt bland patienter <65år medan förbättringen hos äldre var minimal. Mortalitetsrisken ökade framförallt hos patienter <65 år i samma tidsperioder. I delarbete III och IV har vi använt data från Rikssviktsregistret samt samma register som i delarbete II. Patienter <55 år hade högre förekomst av all samsjuklighet och dödlighet jämfört med kontroller. Obesitas, kardiomyopati och kongenital hjärtsjukdom var vanligare hos patienter <55 år. Den högsta mortalitetsrisken hittades hos de allra yngsta patienterna som också förlorade flest levnadsår. Medianöverlevnaden vid till exempel 30 år var 56.3 år jämfört med kontrollernas 82.4 år vilket ger 26.1 förlorade levnadsår. Med åldern minskade mortalitetsrisken och de förlorade levnadsåren. Mortalitetsrisken hos patienterna jämfört med kontrollerna var nästan dubbelt så hög hos unga kvinnor som hos män. Förväntad livslängd hos kvinnor är högre än hos män varför kvinnor förlorade fler levnadsår än män. Komorbiditeter, speciellt cancer, var associerad med ökad mortalitetsrisk hos båda könen.

Slutsatser: Vi fann hög validitet av kardiomyopati diagnoserna, vilket stödjer hypotesen att ökning av sjukdomen möjligen har skett. Mortaliteten hos patienter med hjärtsvikt har förbättrats framförallt hos patienter <65 år, medan hos patienter som är äldre är förbättringen marginell. Jämfört med kontroller ses en ökning av mortalitetsrisken över tid, mest uttalad hos de yngsta patienterna. De allra yngsta patienterna hade högst mortalitetsrisk och förlorade levnadsår upp till 26 år i median, båda minskande med ökande ålder. Kvinnor med hjärtsvikt <55 år hade dubbel så hög mortalitetsrisk som män även om skillnaden inte var signifikant.

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