Familial Risks of Heart Failure in Sweden

Lindgren, Magnus

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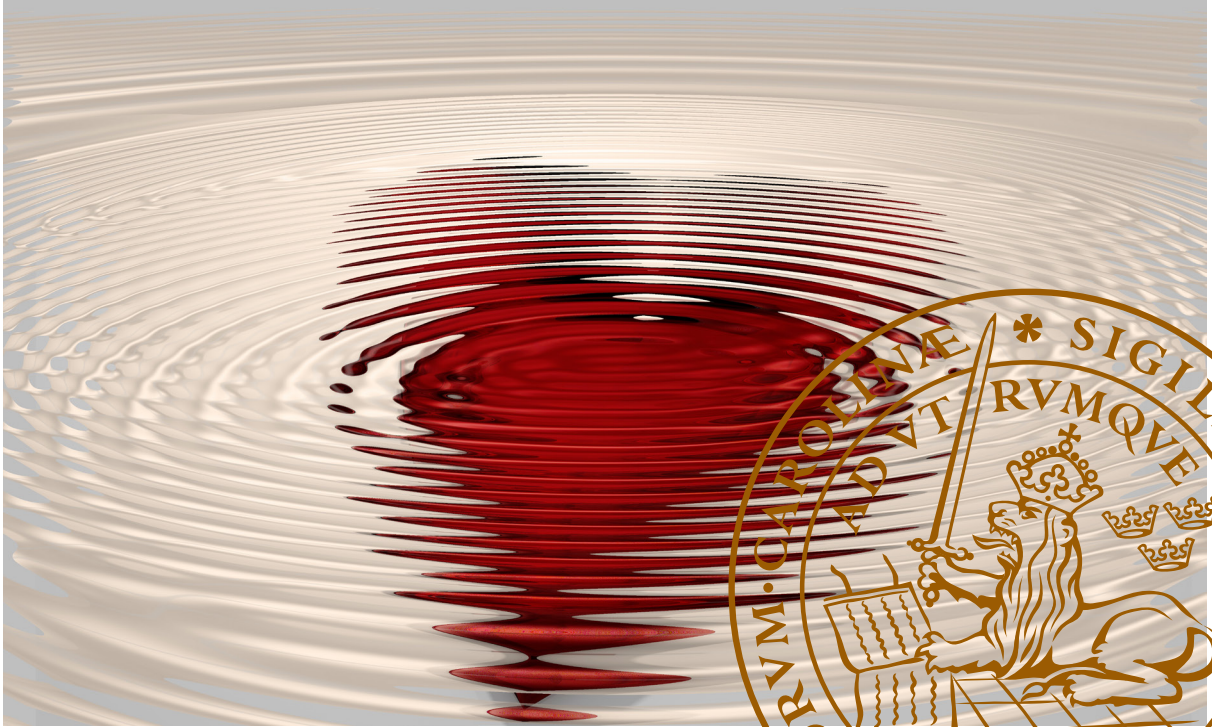

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DOCTORAL DISSERTATION

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Supervisor
Professor Bengt Zöller, Lund University, Sweden

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Professor Carl Johan Östgren, Linköping University, Sweden

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Familial risks of heart failure in Sweden

Introduction: Despite major advances, the incidence rate and mortality of heart failure (HF) remains high, with a five-year survival of approximately 50%. At the time of inception of this thesis the familial risks of HF, including the aspects of mortality, were largely underdetermined. This thesis is composed of four papers with the main aims as follows:

To determine the risk of hospitalization of HF associated with having affected siblings, and the ages at which this hypothesized risk apply (Paper I). To investigate the heritability (h2) of HF and the risk of HF in adoptees as determined by HF in biological and adoptive parents (Paper II). To determine if HF survival time is associated among affected siblings (Paper III). To investigate if mortality risks are increased in subjects with a sibling affected with HF (Paper IV).

Methods All studies were based on Swedish nationwide interlinked registry data including the National Patient Register and the Multi-Generation Register to retrieve information of, e.g. family relationships, hospital discharge diagnoses and, in some instances, also hospital outpatient data. Adjustments were made for common HF comorbidities, age, sex and (with the exception of Paper III) aspects of socioeconomic data. Standardized incidence ratios (SIRs) of HF hospitalization were calculated for individuals with siblings hospitalized with HF compared with those whose siblings were not (Paper I). In a cohort study design using unconditional logistic regression, the odds ratios (ORs) of HF hospitalization were calculated in adoptees as determined by adoptive and biological parental hospitalization for HF, respectively. Heritability was estimated by using the Falconer regression method (Paper II). Using Cox regression, mortality hazard ratios (HRs) after first hospitalization for HF was calculated as determined by the survival of a sibling previously hospitalized first time for HF (Paper III). Mortality HRs were calculated for siblings of individuals who had been diagnosed with HF compared with siblings of individuals unaffected by HF as the reference group (Paper IV).

Results: The SIR of HF hospitalization was 1.62 (95% CI 1.54–1.70) for subjects with one affected sibling and 15.46 (12.82–18.50) for subjects with two affected siblings. SIRs were highest among the youngest stratum of subjects under the age of 50 years and decreased with age (Paper I). The adoptee OR for HF hospitalization with an affected biological parent was 1.45 (95% CI, 1.04-2.03), whereas no significant association was found with an affected adoptive parent. Heritability of HF was 26% (SE, 14%) (Paper II).

The mortality HR after first HF hospitalization for subjects having a sibling with corresponding survival < 5 years was 2.02 (95% CI, 1.32–3.09) (Paper III). Subjects with a sibling affected with HF had a mortality HR of 1.21 (95% CI 1.18–1.25). This risk remained (HR=1.19, 95% CI 1.15–1.23) also among subjects without HF themselves (Paper IV).

Discussion: Family history, in the form of affected siblings or biological parents, is an important risk factor for HF. The moderate heritability level in relation to the magnitude of familial risk motivates further genetic studies. Sibling HF is also a risk factor for death. Familial factors may also be important for the prognosis of patients with HF. These results suggest the value of more studies to investigate the genomics influencing the risk of HF and the associated mortality risk. They also indicate that individuals with such a family history may be at increased risk and that clinical evaluation may be considered in select categories of patients.

Key words Heart failure, epidemiology, family history, genetics

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Dedicated to my beloved Louise, my father Bo, my mother Ingeborg and to my brothers

List of papers

This thesis is based on the following four papers referred to in the text by Roman numerals.

I. Lindgren, M. P., Smith, J. G., Li, X., Sundquist, J., Sundquist, K., & Zoller, B. (2016). Sibling risk of hospitalization for heart failure - A nationwide study. Int J Cardiol, 223, 379-384.

II. Lindgren, M. P., PirouziFard, M., Smith, J. G., Sundquist, J., Sundquist, K., & Zoller, B. (2018). A Swedish Nationwide Adoption Study of the Heritability of Heart Failure. JAMA Cardiol.

III. Lindgren, M. P., Smith, J. G., Li, X., Sundquist, J., Sundquist, K., & Zoller, B. (2018). Familial Mortality Risks in Patients With Heart Failure-A Swedish Sibling Study. J Am Heart Assoc, 7(24), e010181.

IV. Lindgren, M. P., Ji, J., Smith, J. G., Sundquist, J., Sundquist, K., & Zoller, B. (2019). Mortality risks associated with sibling heart failure. Int J Cardiol.

Abbreviations

ACC/AHA/HFSA - the American College of Cardiology Foundation/the American Heart Association/the Heart Failure Society of America

ACE - Angiotensin converting enzyme

ACEI - Angiotensin converting enzyme inhibitor

ARB - Angiotensin 2 type 1 receptor-blocker

ARNI - Angiotensin receptor neprilysin inhibitor

BB – Beta blocker

BNP - B-type natriuretic peptide

CHD - Coronary heart disease

DCM - Dilated cardiomyopathy

ESC - European Society of Cardiology

GWAS – Genome wide association study

HCM – Hypertrophic cardiomyopathy

HF - Heart failure

HFrEF - Heart failure with reduced ejection fraction

HFmEF - Heart failure with midrange ejection fraction

HFpEF - Heart failure with preserved ejection fraction

HR – Hazard ratio

ICD – International Classification of Diseases

ISFC - International Society and Federation of Cardiology

LVEF - Left ventricular ejection fraction

MRA - Mineralocorticoid receptor antagonist

NT-proBNP - N-terminal pro-BNP

NYHA - New York Heart Association functional gradation

OR – Odds ratio

RAAS - Renin-angiotensin-aldosterone system

SIR – Standardized incidence ratio

SNP - Single nucleotide polymorphism

WHF - World Heart Federation

WHO - World Health Organization

Abstract

Introduction

Despite major advances, the incidence rate and mortality of heart failure (HF) remains high, with a five-year survival of approximately 50%. At the time of inception of this thesis the familial risks of HF, including the aspects of mortality, were largely underdetermined. This thesis is composed of four papers with the main aims as follows:

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All studies were based on Swedish nationwide interlinked registry data including the National Patient Register and the Multi-Generation Register to retrieve information of, e.g. family relationships, hospital discharge diagnoses and, in some instances, also hospital outpatient data. Adjustments were made for common HF comorbidities, age, sex and (with the exception of Paper III) aspects of socioeconomic data. Standardized incidence ratios (SIRs) of HF hospitalization were calculated for individuals with siblings hospitalized with HF compared with those whose siblings were not (Paper I). In a cohort study design using unconditional logistic regression, the odds ratios (ORs) of HF hospitalization were calculated in adoptees as determined by adoptive and biological parental hospitalization for HF, respectively. Heritability was estimated by using the Falconer regression method (Paper II). Using Cox regression, mortality hazard ratios (HRs) after first hospitalization for HF was calculated as determined by the survival of a sibling previously hospitalized first time for HF (Paper III). Mortality HRs were calculated for siblings of individuals who had been diagnosed with HF compared with siblings of individuals unaffected by HF as the reference group (Paper IV).

Results

The SIR of HF hospitalization was 1.62 (95% CI 1.54–1.70) for subjects with one affected sibling and 15.46 (12.82–18.50) for subjects with two affected siblings. SIRs were highest among the youngest stratum of subjects under the age of 50 years and decreased with age (Paper I). The adoptee OR for HF hospitalization with an affected biological parent was 1.45 (95% CI, 1.04-2.03), whereas no significant association was found with an affected adoptive parent. Heritability of HF was 26% (SE, 14%) (Paper II).

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Discussion

Family history, in the form of affected siblings or biological parents, is an important risk factor for HF. The moderate heritability level in relation to the magnitude of familial risk motivates further genetic studies. Sibling HF is also a risk factor for death. Familial factors may also be important for the prognosis of patients with HF. These results suggest the value of more studies to investigate the genomics influencing the risk of HF and the associated mortality risk. They also indicate that individuals with such a family history may be at increased risk and that clinical evaluation may be considered in select categories of patients.

Table of Contents

Chapter 1. Introduction

Despite continual advances in the management of heart failure (HF), this syndrome remains one of the most ubiquitous clinical features in modern health care with a resulting stupendous toll of morbidity and mortality. This text herein, which is based on four studies, discusses various aspects of the effect of family history of HF on mortality and on the risk of HF.

1.1 Definition of HF and common terminology

HF denotes a clinical syndrome characterized by manifestations of insufficient cardiac function, owing to impaired ventricular filling or ejection of blood, to provide ample blood distribution to meet peripheral tissue metabolic demands. This current definition is contingent on the occurrence of concurrent present or previous symptoms of HF (e.g. fatigue, orthopnea, dyspnea or decreased exercise capacity, or peripheral edema) to which additional clinical signs indicative of HF may be present.(Authors/Task Force et al., 2016; Yancy et al., 2013) To reflect HF being an often progressive condition, American College of Cardiology/American Heart Association (ACC/AHA/HFSA) classifies the progression of HF into four stages, of which stage A and B represents asymptomatic patients with risk factors of HF where the latter, stage B patients, have progressed to also exhibit structural changes e.g. left ventricular hypertrophy, dilation or impaired function. Stage C includes patients presenting with or previously suffering from symptoms of HF whereas stage D designates refractory or end stage disease.(Hunt et al., 2009; Yancy et al., 2013) With reference to the definition of HF, only the symptomatic stages C and D in this classification are thus to be regarded as evolved into HF. Numerous terminologies and conventions have been utilized to describe and classify the current clinical phenotype of HF. With the commonly used New York Heart Association (NYHA) functional gradation of symptoms ranging from NYHA class I (no current symptoms) to class IV (symptoms in resting state)(Yancy et al., 2013) it follows that a patient also classified with NYHA class I must have previously been suffering from symptoms related to HF. With reference to left ventricular ejection fraction (LVEF), HF can be divided into HF with reduced ejection fraction (HFrEF, LVEF $\leq$ 40%), HF with midrange ejection fraction (HFmEF, LVEF 41-49%) and HF with preserved ejection fraction (HFpEF LVEF $\geq$50%), respectively, as referred

to by the European Society of Cardiology (ESC).(Authors/Task Force & Document, 2016)

The term cardiomyopathy has included a variety of conditions since the 1950s.(Mayosi, 2014) The 1980 World Health Organization (WHO)/International Society and Federation of Cardiology (ISFC), the latter now called World Heart Federation (WHF), definition differentiated idiopathic heart muscle diseases from heart muscle diseases specifically caused by congenital heart disease, coronary heart disease (CHD), systemic or pulmonary hypertension, or valvular heart disease. Many phenotypic functional and structural classifications, including hypertrophic, restrictive, and dilated cardiomyopathy were also introduced at that time.(WHO/ISFC, 1980) In the WHO/ISFC 1995 revision,(WHO/ISFC, 1996) this distinction between causalities was removed and greatly expanded upon the term cardiomyopathy to potentially include, e.g. heart muscle disease of ischemic ("ischemic cardiomyopathy"), hypertensive ("hypertensive cardiomyopathy") cause etc. In 2006 the AHA classified cardiomyopathies as heart muscle diseases of a mainly genetic basis, among which primary cardiomyopathies pertained to diseases with a phenotype predominantly localized to the myocardium alone, whereas for secondary cardiomyopathies the disease process also involved other organs.(Maron et al., 2006)

ESC defined cardiomyopathy in 2008, and in this recognized the disparities in relation to the recent AHA definition, as either familial or nonfamilial, structural and functional heart muscle disease not caused by congenital heart disease, CHD, hypertension, or valvular heart disease.(Elliott et al., 2008) In 2013, WHF presented the MOGE(S) system to more systematically categorize cardiomyopathies according to morphofunctional phenotype (M), organ involve¬ment (O), genetic inheritance pattern (G), etiological annotation (E), and functional status (S).(Arbustini et al., 2014)

1.2 Etiology and epidemiology of HF

Industrial world data indicate that the age-adjusted incidence rates of HF have declined during the last 60 years.(Ziaeian et al., 2016) This is also congruent with Swedish data, including both patients in primary care and those requiring specialist care, from the Stockholm region where a 24% decrease of the age-adjusted incidence rate of HF was reported between 2006 and 2010. In this study, the overall incidence and the mean age at diagnosis in 2010 were 3.7 cases per 1000 person-years and 80 years for females, and 3.9 cases per 1000 person-years and 74 years for males, respectively.(Zarrinkoub et al., 2013) Worth noting in this regard is that in 2009, the Swedish primary care diagnostic procedures were shown to differ from ESC diagnostic criteria.(Dahlstrom et al., 2009) Another Swedish population study

demonstrated a trend of increased incidence of HF hospitalization among younger adults, aged 18 to 44 years. (Barasa et al., 2014) In the UK, based on hospital records, the incidence rate of HF, standardized by age and sex, decreased for men and women between 2002 and 2014, from 3.58 to 3.32 per 1000 person-years.(Conrad et al., 2018) The incidence of HF is highly correlated with age and there has been a trend of steadily increasing prevalence in recent decades, which is expected to persist, in part due to an aging population and to improved survival after myocardial infarction. (Barasa et al., 2014; Benjamin et al., 2018; Levy et al., 2002; Lloyd-Jones et al., 2002).

The prevalence of HF is approximately 1-2% in industrial world countries for which the lifetime risk of developing HF is estimated to be 20% for both men and women.(Benjamin et al., 2018; Bleumink et al., 2004; Zarrinkoub et al., 2013) A meta-analysis of data from 11 cohort studies, the majority American, found that among asymptomatic patients with reduced LVEF and among patients with diastolic dysfunction, the incidence rates of HF were approximately 84 and 28 cases per 1000 person-years respectively. As a reference, the incidence rate of HF for individuals without evident ventricular dysfunction was 10.4 cases per 1000 person-years in these cohorts. (Echouffo-Tcheugui et al., 2016)

The most common comorbidities prevalent in patients diagnosed with HF in the UK material were hypertension 67%, CHD 49%, osteoarthritis, atrial fibrillation, dyslipidemia 28%, anemia 26%, cancer 25%, chronic kidney disease 24%, asthma 23%, diabetes mellitus 22%, depression 22%, chronic obstructive pulmonary disorder 19%, and stroke 19%. CHD was more common among males (55%) than females (42%).(Conrad et al., 2018) In the Stockholm area in Sweden, 73% and 43% of female, and 69% and 48% of male HF patients were registered with a diagnosis of hypertension and atrial fibrillation/flutter, respectively in 2010. Corresponding numbers for CHD were 47% among females and 56% among males. For both sexes combined, the prevalence of CHD among HF patients decreased between 2006 and 2010 by approx¬imately 7–8%.(Zarrinkoub et al., 2013) Between 44% and 72% of all HF cases have been estimated to be HFpEF. The most important risk factors for HFpEF are hypertension, age, female sex, diabetes and atrial fibrillation.(Ziaeian & Fonarow, 2016) Patients with HFrEF are more often younger, male and have a history of myocardial infarction.(Authors/Task Force & Document, 2016). Data from Olmstead County in Minnesota, United States, estimated CHD, hypertension, diabetes mellitus, obesity, and smoking to be responsible for 52% of incident HF (regardless of LVEF) cases.(Benjamin et al., 2018)

Studies have demonstrated a genetic predisposition for several common risk factors for HF, with numerous gene variants associated with the risk of CHD,(Khera et al., 2017; Roberts et al., 2019) hypertension,(Russo et al., 2018) type 2 diabetes,(Hivert et al., 2014; Scott et al., 2017) atrial fibrillation,(Kalsto et al., 2019) mitral valve prolapse,(Le Tourneau et al., 2018), and aortic valve stenosis.(Fulmer et al., 2019; Helgadottir et al., 2018)

1.3 Principal pathophysiology of HF

A common principal model offering to at least partially explain the development of HF is a process where the heart is initially triggered by one or several impeding factors, resulting in a sudden (e.g. myocardial infarction) or more gradual detrimental impact (e.g. hypertension, or chronic valvular disease) on the cardiovascular system. Compensatory mechanisms activated in order to short-term preserve cardiac output result in long-term partially more maladaptive effects which precipitates the progression of HF. These complex mechanisms may include elements of inflammation, activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system in accordance with the neurohormonal hypothesis(Grossman et al., 1975; Normand et al., 2019) with increased systemic vascular resistance, endothelial dysfunction, cardiac remodeling altered renal hemodynamics, and impaired cardiac output.(Normand et al., 2019) With reference to this model, both the frequency and severity of the trigger factor, as well as the long-term cardiovascular coping mechanisms could consequently be important for the risk of developing HF.

1.4 HF prognosis

Despite the trend of improving mortality rates for this highly age dependent outcome, industrial world data indicate a 30 day, 1-year, and 5-year risk of death after first hospitalization to be approximately 10%, 25%, and 50%, respectively.(Barasa et al., 2014; Benjamin et al., 2018; Levy et al., 2002) When adjusted for age, sex, and comorbidities, the risk of death for patients with HFpEF has been found to be only slightly lower than for patients with HFrEF, 121 deaths and 141 deaths per 1 000 patient-years, respectively.(Meta-analysis Global Group in Chronic Heart, 2012) After hospitalization for HF, patients with HFrEF were more likely to be readmitted for HF and cardiovascular causes in general, whereas HFpEF patients were at higher risk of all-cause readmission.(Cheng et al., 2014)

1.5 Principal methods for diagnosis and treatment with a brief historical overview

The contemporary procedure for HF diagnosis, although still principally relying upon clinical evaluation of the evidence of symptoms and signs (e.g. pulmonary rales, pleural effusion, elevated jugular venous pressure, and peripheral edema) disparately associated with HF, has been aided predominately by the development of cardiac imaging techniques, primarily transthoracic echocardiography, and

biomarkers.(Authors/Task Force & Document, 2016) Since the 1960s, the understanding of HF and the availability of methods for diagnosing HF, as well as means of treatment thereof have greatly expanded, as outlined below. The evolvement of the most fundamental methods for diagnosing and treating CHD are also briefly mentioned due to the high likelihood of it being applicable to HF patients. However, the progression in the fields of other comorbidities to HF are not covered in this text.

1.5.1 Measures to prevent or delay the onset of HFrEF

In patients with stable CHD free of HF and with normal LVEF, the addition of an angiotensin converting enzyme inhibitor (ACEI) was demonstrated to decrease the risk of HF, myocardial infarction, and death.(Dagenais et al., 2006) Furthermore, preventive studies of patients with elevated levels of B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) free of HF but with other cardiovascular risk factors treated with an ACEI or angiotensin 2 type 1 receptor-blocker (ARB), mineralocorticoid receptor antagonist (MRA) and/or beta blockers (BBs) have shown favorable outcomes.(Huelsmann et al., 2013; Ledwidge et al., 2013) ESC guidelines recommend ACEIs to be considered in patients with stable CHD normal LVEF, and recognize the potential value of BB and renin–angiotensin system antagonists for patients with elevated levels of these natriuretic peptides.(Authors/Task Force & Document, 2016)

Enalapril was demonstrated to decrease the risk of death and HF in asymptomatic patients with LVEF ≤ 35% not receiving treatment for HF, n.b. the majority of these patients suffered from CHD.(Investigators et al., 1992; Jong et al., 2003) In another trial, for patients with myocardial infarction and LVEF ≤40% at baseline, captopril reduced mortality and the risk of hospitalization for HF.(Pfeffer et al., 1992) ESC and ACC/AHA/HFSA recommended ACEI for all patients with reduced LVEF to prevent progression to symptomatic HF, (Authors/Task Force & Document, 2016; Yancy et al., 2013) whereas the latter guidelines also recommend BBs for these patients.(Yancy et al., 2017; Yancy et al., 2013) As for patients with CHD, although BBs have been considered beneficial for patients with myocardial infarction even before the advent of thrombolysis and ACEI, carvedilol was, in relation to placebo, also shown to reduce cardiovascular death and overall mortality in these patients with LVEF ≤ 40%.(Dargie, 2001) Furthermore, along with ACEIs and BB, the early addition of MRAs in patients with myocardial infarction (Montalescot et al., 2014; Pitt et al., 2003), especially in cases with concomitant reduced LVEF, is also recommended in ESC guidelines.(Authors/Task Force & Document, 2016) Statins, which have been shown to also decrease the risk of HF in patients with myocardial infarction, are recommended to patients with CAD or at high risk thereof.(Afilalo et al., 2007; Authors/Task Force & Document, 2016; Kjekshus et al., 1997; Scirica et al., 2006; Yancy et al., 2013)

A central part of preventing development of HF is taking preventive measures of and treating potential underlying risk factors. Patients with hypertension ≥ 75 years of age or at high risk of cardiovascular events are recommended intensive hypertensive treatment with a target of systolic blood-pressure < 120 mm Hg, as opposed to < 140 Hg, which was seen result in a decreased risk of HF hospitalization and death.(Authors/Task Force & Document, 2016; S. R. Group et al., 2015) Other measures, e.g. to prescribe certain sodium-glucose cotransporter-2 inhibitors (e.g. dabagliflozin, empagliflozin) to patients with diabetes, smoking cessation, and physical exercise are also recommended and/or found favorable.(Authors/Task Force & Document, 2016; J. J. V. McMurray et al., 2019; Yancy et al., 2013)

1.5.2 Prevention and Treatment of HFpEF and HFmEF

No treatment has been proven effective to generally reduce mortality or HF hospitalizations in patients with HFpEF. Diuretics are used to relieve symptoms. Measures of prevention and treatment revolves around risk factors.(Authors/Task Force & Document, 2016; Tomasoni et al., 2019) The characteristics of patients with HFmEF are more similar to those with HFrEF albeit with a moderately more favorable prognosis and retrospective analyses of previous trials suggest patients with HFmEF may benefit from the same treatments.(Tomasoni et al., 2019)

1.5.3 Core concept of current guidelines for long-term treatment of HFrEF

Current ESC and ACC/AHA/HFSA guidelines for treatment of the chronic aspect of HFrEF principally recommend treatment with a BB (metoprolol succinate, carvedilol, or bisoprolol), and an ACEI (considered a class-effect), ARB (candesartan, valsartan, or losartan which is however less documented) or angiotensin receptor neprilysin inhibitor (ARNI) (sacubitril/valsartan). Both ESC and ACC/AHA/HFSA recommend ACEIs in preference to ARBs. ESC recommends the addition of a MRA (spironolacton or eplerenone) to still symptomatic patients with LVEF ≤ 35% whereas ACC/AHA/HFSA now recommends the addition of MRA to all symptomatic HFrEF patients. As regards ARNIs, ACC/AHA/HFSA now primarily recommends initiating treatment with an ACEI or ARB but in patients in NYHA class II or III tolerating such a treatment then replacing it with ARNI. In the American guidelines, the addition of MRA is not considered mandatory prior to changing a patient to ARNI. In the current ESC guidelines however, the role of AVRIs is to replace ACEIs or ARBs in still symptomatic patients with LVEF ≤ 35% despite receiving optimized treatment including also a BB and a MRA. The ESC and ACC/AHA/HFSA criteria for the addition of Ivabradine and the indication for implantation of a cardioverter-defibrillator or cardiac resynchronization therapy are principally

similar.(Authors/Task Force & Document, 2016; van der Meer et al., 2019; Yancy et al., 2018; Yancy et al., 2017; Yancy et al., 2013) The evolution of treatment options for HFrEF has progressed quickly in recent decades and the foundation of some of the most important aspects thereof is briefly summarized below.

1.5.4 Evolvement of treatment options

The era prior to the 1980s is often considered the pre-treatment period as regards HF, with very few beneficial treatment possibilities available. In the beginning of the 1960s, the main drug treatments were limited to prescription of thiazide diuretics in order to alleviate symptoms of fluid overload(Davis et al., 2000) and digitalis.(Ferrari et al., 2016) During this decade loop diuretics were introduced,(Dettli et al., 1966) offering complementary means of reducing fluid overload.(Dettli & Spring, 1966; Jentzer et al., 2010) Diuretics may, besides improving symptoms, decrease the risk of death and HF hospitalization.(Authors/Task Force & Document, 2016; Faris et al., 2012)

Back in 1961 the first pump leading blood from the left atrium through a cannula to the femoral artery was implemented in a human and the further development of left ventricular assist devices during the 1960s. The first heart transplant operation was conducted in 1967 in Cape Town, South Africa.(Dennis et al., 1962; Ferrari et al., 2016; Frazier et al., 1994) During the 1970s and 1980s numerous studies of the effect of inotropic agents on patients with HF, mainly HFrEF, were performed. However, beta-receptor agonists and phosphodiesterase 3 inhibitors showed negative effects on long term survival.(Felker et al., 2001; Packer, 1988; Packer et al., 1991) Worth noting in this regard is that for Levosimedian, which exerts its inotropic effect via Troponin C calcium sensitization, data have not shown indications of aggravated survival.(Bouchez et al., 2018) Digoxin was repeatedly shown to improve symptoms with increasing exercise tolerance and reduce the risk for hospitalization although with no ameliorating effect on survival.(Digitalis Investigation, 1997; Packer, 1988) Since the 1990s the view on digoxin as an innocuous drug in the treatment of HF has come into question concerning both patients with atrial fibrillation and patients with sinus rhythm, including the combination with BBs.(Authors/Task Force & Document, 2016; Vamos et al., 2015; Ziff et al., 2015)

Major advancements in the treatment of heart failure took place in the middle of the 1980s. The Veterans Administration Vasodilator Heart Failure Trial (V-HeFT) suggested that hydralazine in combination with isosorbide dinitrate, although poorly tolerated, given in addition to diuretics and digoxin, conferred both increased exercise capacity and reduced mortality and improved LVEF.(Cohn et al., 1986; Packer, 1988) Long-term treatment with an ACEI was found to improve symptoms, hemodynamics, and survival.(Cleland et al., 1985; Ferrari et al., 2016; C. T. S. Group, 1987; Pfeffer et al., 1992; Sharpe et al., 1984) Although the ACEI enalapril

showed a survival benefit in relation to the combination of isosorbide mononitrate and hydralazine,(Cohn et al., 1991) the latter showed more benefit in patients with African ancestry.(Carson et al., 1999; Taylor et al., 2004)

In the late 1990s, several studies on the addition of a BB to ACEI showed incremental survival benefits and reduced risk for hospitalization for HF(Committees, 1999; M.-H. S. Group, 1999; Hjalmarson et al., 2000; Packer et al., 1996) and BBs and ACEIs are considered complementary.(Authors/Task Force & Document, 2016) Essentially concurrent with the new millennia, the ARB candesartan given to patients intolerant of ACEIs was found to reduce the risk of HF hospitalization and cardiovascular death.(Granger et al., 2003) Studies of patients with NYHA class ≥ II and LVEF ≤ 35% with conventional therapy at the time receiving the MRA spironolactone(Pitt et al., 1999) and in later studies eplerenone,(Zannad et al., 2011) respectively, both reduced the risk of hospitalization and death. More recent data on the non-steroidal MRA finerenone, with a higher selectivity and stronger affinity towards the mineralocorticoid receptor than spironolactone and eplerenone, respectively, have pointed toward more beneficial outcomes as regards hospitalization and death.(Filippatos et al., 2016; Yang et al., 2019)

Ivabradine reduces the depolarization rate in sinus note via inhibition of the If channel. In 2010, the addition of ivabradine, to conventional treatment, including BBs, in patients with LVEF ≤ 35% in sinus rhythm with a heart rate ≥ 70 beats per minute showed a reduced risk of the composite endpoint of cardiovascular death and HF hospitalization.(Swedberg et al., 2010) In 2013, a subgroup analysis found improved survival among patients with an initial heart rate ≥ 75 beats per minute.(Bohm et al., 2013) Ivabradine is indicated in ESC guidelines as an additional therapeutic option among these patients with symptoms and a resting sinus rhythm heart rate ≥ 70 beats per minute.(Authors/Task Force & Document, 2016)

In 2014 results from the PARADIGM-HF trial showed that the ARNI combination of valsartan and sacubitril decreased the risk of death, cardiovascular death and HF hospitalization in comparison with enalapril (McMurray et al., 2014; Packer et al., 2015). Sacubitril is an inhibitor of the enzyme neprilysin, which in turn degrades several vasoactive peptides, including natriuretic peptides, bradykinin, adrenomedullin(McMurray et al., 2014). As regards current ESC and ACC/AHA/HFSA guidelines for the use of ARNIs, see the previous section.(Authors/Task Force & Document, 2016; Yancy et al., 2018; Yancy et al., 2017)

Sodium-glucose cotransporter-2 inhibitors have been found to decrease the risk of hospitalization for HF in patients with type 2 diabetes. Recently, dapagliflozin was found to reduce the risk of hospitalization for HF and of death, also among patients without type 2 diabetes.(John J.V. McMurray et al., 2019) In the beginning of the

2000s ventricular arrythmias were recognized as a common cause of sudden death in HF patients and the option of implantable cardioverter-defibrillators was introduced for select patients. This was followed by the introduction of cardiac resynchronization therapy.(Authors/Task Force & Document, 2016; Ferrari et al., 2016) Iron deficiency has been associated with worse prognosis in HFrEF and administration of ferric carboxymaltose has been demonstrated to reduce the risk of hospitalization for HF and risk of death.(Anker et al., 2018; McDonagh et al., 2018) Iron replacement therapy is recommended for these patients in the latest ESC and ACC/AHA/HFSA guidelines.(Authors/Task Force & Document, 2016; Yancy et al., 2017)

1.5.5 Introduction of heart catherization and revascularization

In addition to electrocardiography and the preexistent use of chest X-ray, the latter which although it may be indicative of mainly acute exacerbated HF, is mostly helpful to identify differential diagnoses,(Authors/Task Force & Document, 2016) right heart catherization was clinically introduced in the 1950s. This enabled hemodynamic measurements of inter alia cardiac output, right atrial pressure, pulmonary artery pressure, and pulmonary wedge pressure.(Cournand, 1975; Katz, 2008; Mehta et al., 2002; Nossaman et al., 2010) With arterial access greatly facilitated with the Seldinger technique introduced in 1953,(Seldinger, 1953) the ventriculograms of the 1960s offered the opportunity for estimation of left ventricular volume and function.(Ryan, 2002) The latter half of the 1960s also saw the introduction of coronary angiography and the development of the coronary artery bypass graft operation primarily utilizing the saphenous vein, which quickly became a common surgical procedure by the early 1970s with progressively evolved techniques since then, including the more extensive use of the internal thoracic artery.(Ryan, 2002) In the late 1970s and early 1980s studies were conducted treating patients with myocardial infarction with streptokinase initiated thrombolysis as a means of treatment for these patients.(Ryan, 2002; Van de Werf, 2014) This also contributed to establishing the view that ST-segment-elevation myocardial infarction generally is the result of a proximate acute coronary thrombotic occlusion and that early intervention for preserving LVEF and survival is crucial.(Van de Werf, 2014) At the end of the 1980s, aspirin was confirmed as being beneficial for patients with CHD, both concomitant to thrombolysis and as an adjuvant and secondary preventative measure. This was quickly followed by studies demonstrating the value of early administration of heparin to patients with myocardial infarction and a further evolution of newer anticoagulant and antiplatelet drugs.(Van de Werf, 2014) In 1979 Andreas Grüntzig et al described a method called percutaneous transluminal coronary angioplasty by which a stenotic coronary artery in stable patients could be dilated by controlled inflation of a distensible balloon via a catheter system.(Gruntzig et al., 1979; Ryan, 2002; Smilowitz et al., 2016). Soon thereafter, Geoffrey Hartzler, applied angioplasty in the treatment of

patients with acute myocardial infarction.(Smilowitz & Feit, 2016) Bare metal coronary stents were introduced in the middle of the 1990s followed by the advent of drug-eluting stents approximately a decade later.(Smilowitz & Feit, 2016)

1.5.6 Development of echocardiography

The ultrasound technique applied to the heart was introduced piecemeal during the 1950s and 1960s and great advances to this technique, powered with improvements to the underlying technology, were made in the 1970s and 1980s. In 1953 cardiologist, Inge Edler, at the University Hospital in Lund, Sweden, in collaboration with physicist, Hellmuth Hertz, started to explore the use of one-dimensional ultrasonography and quickly also noticed the value of recording how reflecting interfaces may change position over time, denominated Motion Mode (M-mode).(Edler et al., 2004; Singh et al., 2007) Echocardiography was routinely used in Lund 1955 to identify patients with pericardial effusion and patients with mitral stenosis that also had significant concurrent mitral regurgitation and were therefore not suitable for closed mitral commissurotomy; the only surgical procedure available for this condition at the time.(Edler & Lindstrom, 2004) Although techniques based on this technology were developed to estimate the thickness, the inner dimensions and the stroke volume of the left ventricle, evaluation of mitral valve disease remained the main application of echocardiography during the 1960s.(Edler & Lindstrom, 2004)

Following an adequate technique of two-dimensional echocardiography was developed and successfully demonstrated to produce clinically useful moving cross-sectional images 1972-1973;(Edler & Lindstrom, 2004; Kloster et al., 1973) this technology was rapidly applied to the fields of cardiology and gynecology and for abdominal assessments during the latter half of the 1970s. The Doppler technique was introduced during the first half of the 1980s.(Edler & Lindstrom, 2004)

1.5.7 Cardiac magnetic resonance

Although several other imaging techniques have evolved to be of assistance in the context of some HF patients, e.g. cardiac computed tomography and techniques based on the use of gamma cameras, echocardiography remains the most frequently used contemporary imaging technique.(Authors/Task Force & Document, 2016) However, cardiac magnetic resonance, introduced in clinical settings during the latter part of the 1980s, often functions as a clinically adjunct method and is considered the gold standard for assessing biventricular function, mass and ejection fraction.(Authors/Task Force & Document, 2016; Pohost, 2008) In addition to evaluating cardiac function and structure based on the principle of tissue proton relaxation properties, currently mainly via evolved native T1 mapping techniques, this modality has also been valuable for detecting myocardial tissue characteristics

indicative of pathologies such as inflammation and edema, cardiac amyloidosis, hemochromatosis, diffuse fibrosis and cardiomyopathies. The gradual clinical introduction of gadolinium based contrast substances during the 1990s, mainly gadolinium-diethylenetriamine pentaacetic acid,(Pohost, 2008; Salerno et al., 2017) which besides offering a complementary modality in the aspect of angiography, also, with its slower dissipation to healthy tissue not crossing cellular membranes, offered an aid for detection of ischemia and inflammation and fibrosis.(Pohost, 2008; Salerno et al., 2017) Cardiac magnetic resonance is still a quickly evolving arena, e.g. newly developed T2 mapping techniques have increased the diagnostic accuracy of myocardial edema in patients with myocardial infarction and myocarditis, respectively.(Salerno et al., 2017)

1.5.8 Biomarkers

In the early 2000s BNP(Maisel et al., 2002) followed by NT-proBNP (Januzzi et al., 2005) was demonstrated as having a high negative predictive value for acute HF at low concentrations. Since then these biomarkers have also been recognized as a valuable tool to rule out non-acute HF. However, the positive predictive value is low.(Authors/Task Force & Document, 2016; Gaggin et al., 2018; Yancy et al., 2013) Moreover, for patients with a LVEF > 40% current ESC guidelines requires an increased concentration of BNP or NT-proBNP together with measurements indicative of diastolic dysfunction, or of left ventricular hypertrophy or left atrial enlargement.(Authors/Task Force & Document, 2016)

1.6 Genomics of HF

The contribution of genetic and possibly interrelated environmental factors to the development, progression and prognosis of HF, per se, to already established risk factors e.g. as mentioned above, is not fully understood. With the exception of studies on cardiomyopathies, at the onset of this thesis the Framingham heart study was the sole population study to have investigated the familial risk of HF. Most genetic studies of HF had been candidate gene studies accompanied by a small number of GWAS studies with sparse results. In recent years expanded GWAS and post-GWAS functional studies have generated new knowledge into polygenetic aspects of HF, as expanded upon below.

1.6.1 Monogenic HF - familial cardiomyopathy

The most prevalent cardiomyopathies, namely hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM), classically demonstrate in familial cases a predominantly Mendelian inheritance pattern and are mainly regarded as monogenetic autosomal dominant conditions predominantly relating to genes coding for sarcomere proteins.(Reza et al., 2019) Arrhythmogenic right ventricular cardiomyopathy also displays a dominant inheritance pattern for which an explanatory mutation can be found in approximately 60% of cases with desmosomal dysfunction being the dominating cause. In relation to DCM and HCM, arrhythmogenic right ventricular cardiomyopathy has a much lower prevalence, estimated to be 1 in 5000 individuals, and usually these patients present with ventricular arrhythmias, whereas HF is an uncommon and late manifestation and this condition(Calkins et al., 2017) is therefore not further expanded upon in this text. Likewise, left ventricular non-compaction cardiomyopathy and peripartum cardiomyopathy are not discussed in this text. Genetic counselling is currently recommended for patients with arrhythmogenic right ventricular cardiomyopathy, HCM and idiopathic DCM.(Authors/Task Force & Document, 2016; Sen-Chowdhry et al., 2016)

1.6.2 Familial HCM

Approximately half of the cases recognized as familial HCM come from alleles of the genes MYH7 (encodes for the beta-myosin heavy chain protein) and MYBPC3 (cardiac myosin binding protein 3). In addition, a sizeable portion of sarcomere thin filament gene variants in, e.g. TNNT2 (cardiac troponin T), TNNI3 (cardiac troponin I), TPM1 (tropomyosin 1), and ACTC (actin alpha cardiac muscle 1) have been found. (Reza et al., 2019; Sen-Chowdhry et al., 2016) No causal allele is found in around 40% of HCM patients, mostly in cases of sporadic HCM and in small families. It's been estimated that 1 in 200 individuals is likely a carrier of at least one sarcomere gene variant pathogenic for HCM, however, the prevalence of HCM has long been considered to be around 1 in 500 in the general population. This phenomenon could be indicative of either HCM being an underdiagnosed condition or gene variants of markedly reduced penetrance and expressivity.(Sen-Chowdhry et al., 2016) To this, studies have identified disease modifying genes.(Kumar et al., 2018; Sen-Chowdhry et al., 2016) Mutations in FHOD3 (encoding the formin protein formin homology 2 domain containing 3) which plays a role in sarcomere organization and its contractile function, have recently been confirmed to be implicated in familial HCM.(Ochoa et al., 2018) Variants of FHOD3 has also been associated with cases of sporadic DCM (see below)

1.6.3 Familial DCM

Recent studies point to DCM being more common than previously expected and may very well be equally prevalent to HCM. 20-50% of all DCM cases are classified as familial, in which 30-40% of the families present an identified genetic plausible cause.(Bondue et al., 2018; McNally et al., 2017; Reza et al., 2019) In all, more than 60 genes have been implicated in DCM with gene variants of TTN (coding for titin) in studies were listed responsible for 12% to 25% of all DCM cases.(McNally & Mestroni, 2017) Other common mutated genes found in DCM are LMNA (lamin-A/C intermediate filament proteins of the nuclear envelope), MYH6 and MYH7 (cardiac alpha-myosin heavy chain), SCN5A (encoding for the sodium channel protein type 5 subunit alpha), MYBPC3, FLNC (filamin C), TNNT2, and RBM20 (RNA motif binding protein, a regulator of mRNA splicing).(Bondue et al., 2018; McNally & Mestroni, 2017) Phenotypic characteristics may be influenced by the affected gene, eg., mutations in LMNA, PLN (phospholamban binds to and thereby inactivates sarcoplasmatic reticulum Ca2+- ATPase), RB20, and some TTN-truncating variants are associated with more arrhythmogenetic DCMs.(Bondue et al., 2018) There is also a phenotypic overlap to include other cardiomyopathies and channelopathies, e.g. mutations in MYH7 and MYBPC3 are also considered to be the most common known causes of left ventricular noncompaction cardiomyopathy, (van Waning et al., 2019) desmosomal mutations are also often found in arrhythmogenic right ventricular cardiomyopathy,(Bondue et al., 2018) mutations of SCN5A have been found in e.g. long QT syndrome type 3 (LQT3) and Brugada syndrome.(Bondue et al., 2018; Remme, 2013) Variants of BAG3 (see below) have also been implicated in familial DCM.(Franaszczyk et al., 2014)

1.6.4 Genetics of non-monogenetic HF, familial clustering

The rest of this section on HF genomics refers to studies with an outset of predominantly investigating HF as a non-monogenic condition.

In 2006 the Framingham Heart study investigated the familial risk of HF among 2214 offspring with a baseline examination ranging from 1978 to 1998 and continual evaluations up to 2004. Offspring mean age was 44 years at baseline and a mean follow-up of 20 years. Parents were evaluated from 1948 to 2004. HF was diagnosed based on the Framingham Heart Failure Criteria (Table A).(Lee et al., 2006) These epidemiological criteria have been validated to have a sensitivity of 70% and a specificity of 77%.(Svetlichnaya et al., 2013) Offspring relative risk of HF was 1.70 with one parent and 1.92 with both parents affected with HF respectively.(Lee et al., 2006)

However, in general, the majority of new HF events are found among the elderly population, with increasing incidence rates beyond 65 years of age. (Benjamin et al., 2018)

Table A. Framingham Heart Failure Criteria*

Major criteria
Paroxysmal nocturnal dyspnea
Orthopnea
Jugular venous distention
Hepatojugular reflux
Pulmonary rales
Radiographic evidence of cardiomegaly
Acute pulmonary edema
Third heart sound
Central venous pressure >16 cm of water
Weight loss >4.5 kg during first 5 days of treatment for suspected heart failure
Minor criteria
Bilateral ankle edema
Nocturnal cough
Dyspnea on ordinary exertion
Hepatomegaly
Pleural effusion
Heart rate >120 beats per minute

* Heart failure was considered to be present if two major or one major plus two minor criteria were present in the absence of an alternative explanation for the symptoms and signs

1.6.5 Candidate gene studies

Early studies on polygenetic risk factors for HF focused on candidate genes, which on a pathophysiological rationale, could have the potential to influence the risk for HF or the outcome hereof.

The insertion/deletion polymorphism of a 287 base-pair Alu sequence within intron 16 of the angiotensin-converting enzyme (ACE) gene accounting for half of the inter-individual variation of ACE serum levels,(Rigat et al., 1990), has for a long time been a presumptive genotype risk factor candidate of HF. Homozygous carriers having two shorter deletion alleles (ACE DD), with a prevalence of 27% in the American population,(Arnett et al., 2005) are predisposed to have the highest ACE levels.(Danser et al., 1995) Although not an identified independent risk factor of HF,(Andersson et al., 1996; Bai et al., 2012) ACE DD have been in several, still small and disparate studies however, reproducibly linked to decreased transplant-free HF survival(Andersson et al., 1999; Andersson & Sylven, 1996; McNamara et al., 2001; McNamara et al., 2004; Palmer et al., 2003) and aggravated disease progression.(Huang et al., 2004) HF patients with the ACE DD genotype have also been suggested to specifically benefit, as regards survival, from ACEI and BB therapy(McNamara et al., 2001; McNamara et al., 2004) although the former effect was later refuted.(Harrap et al., 2003) A more accepted association to this ACE polymorphism is that of left ventricular hypertrophy (Iwai et al., 1994; Sadoshima et al., 1993; Schunkert et al., 1994) including exercise induced left ventricular hypertrophy.(Montgomery et al., 1997; Myerson et al., 2001) In a smaller case-

control study of patients with hypertension and HFpEF, ACE DD was also associated with left ventricular hypertrophy.(Bahramali et al., 2016) Similarly, a meta-analysis found an association of the ACE D allele with the risk of HCM.(Yuan et al., 2017) The ACE DD allele has been associated with reduced coronary collateral circulation in patients with CHD as well as higher blood pressure.(Ceyhan et al., 2012; Dorn, 2011; Nakano et al., 1998; O'Donnell et al., 1998).

The Arg389Gly single nucleotide polymorphism (SNP) located in the fourth intracellular loop of the beta-1-adrenergic receptor, for which in the case of wild type amino acid arginine (Arg389) is substituted at position 389 with glycine (Gly389) renders diminished adenylyl cyclase signaling.(Dorn, 2010) Studies have shown Gly389 homozygous HF patients to have reduced peak oxygen consumption and exercise performance (Sandilands et al., 2005; Wagoner et al., 2002). For HF patients homozygous for Arg389, BB treatment has shown greater improvement in left ventricular EF and volume(Terra et al., 2005) but studies have shown mixed results as regards differences in effect on survival in BB naïve patients and no difference has been found in BB treated patients. However, patients homologous for the Arg389 allele might require higher doses of BB to attain a full survival benefit.(Fiuzat et al., 2013)".(Cresci et al., 2009; White et al., 2003) The Arg389Gly polymorphism does not seem to significantly affect the risk of CHD.(White et al., 2002)

For adrenergic receptors, G-protein Coupled Receptor Kinases (GRK) functions to phosphorylate and thereby desensitize them after their initial agonist bound activation. GRK2 and GRK5 are predominantly expressed in cardiomyocytes. The Gln41Leu SNP of GRK5, in which wild type glutamine has been replaced by leucine at position 41, is common among individuals of African descent with an allele frequency of 0.20(Liggett et al., 2008). The Leu41 allele uncouples intracellular adrenergic responses more effectively(Liggett et al., 2008; Wang et al., 2008) and hence implies an inherent reduction of beta-receptor signal transduction. BB naive HF patients homozygous and heterozygous for the Leu41 GRK5 allele have been shown to have better transplant-free survival(Cresci et al., 2009; Liggett et al., 2008). Moreover, for patients with hypertension this allele has analogously also been favorably associated with lower mortality rates and decreased risk for myocardial infarction and stroke.(Lobmeyer et al., 2011) However, in BB treated patients, survival in those homologous for the wild type Gln41 allele was not decreased in relation to patients with the Leu41 allele.(Cresci et al., 2009; Liggett et al., 2008)

1.6.6 Genome wide association studies

A Genome wide association study (GWAS) from the Framingham heart study cohort found one SNP, in gene KIAA1598, also known as SHTN1 (protein shootin-1, coding for a protein involved in neuronal actin filament retrograde flow) that showed a possible, unconfirmed association with HF.(Larson et al., 2007)

A GWAS of four cohorts based in the USA and the Netherlands, as part of the Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE) consortium, found two confirmed gene associations with HF; Among subjects with European ancestry, one SNP was found 58.8 kb from the USP3 gene encoding a ubiquitin-specific protease, and conferring a 53% increased risk of HF per allele. Among individuals of African ancestry, there was an association with a SNP located 6.3 kb from LRIG3,(N. L. Smith et al., 2010) a gene encoding for the protein leucine-rich repeats and immunoglobulin-like domains 3 possibly functioning as a regulator of growth factor signaling.(Mao et al., 2017)

A SNP of the CLCNKA gene, encoding the renal protein chloride voltage-gated channel Ka, in which the wild type arginine at position 83 is replaced by glycine, was found to increase risk of HF with an odds ratio (OR) of 1.27 per allele. In vitro the glycine 83 variant was found to render an approximately 50% reduction of channel current and hypothetically this could predispose for a lowered threshold for activation of the RAAS. (Cappola et al., 2011; Dorn, 2011).

Specifically taking into consideration LVEF, a GWAS in 2017 of HFpEF found nine significant SNP associations. However most of these were only significant in the absence of a common risk factor of HF. The most notable SNP was an intron variant of the gene TGFBR3, encoding the protein transforming growth factor-beta receptor 3, which has been implicated in both myocardial hypertrophy and fibrosis.(Kao et al., 2017)

In a GWAS of breast cancer patients who had been treated with anthracycline, an SNP rs28714259 was associated with HF and LVEF < 45%.(Schneider et al., 2017)

As for sporadic DCM, a case-control study using a sub-genome essay of around 2000 putative genes mutually prioritized with respect to their presumptive risk of cardiovascular disease, several SNPs of the HSPB7 gene was associated with sporadic DCM.(Cappola et al., 2010) In a following GWAS, HSPB7 and also BAG3 were associated with DCM.(Villard et al., 2011) HSPB7 encodes a small heat shock protein which binds to and stabilizes sarcomeric proteins in cardiac and skeletal muscle which was also linked to HF.(Cappola et al., 2010) BAG3 (Bcl-2–associated athanogene 3 protein), encodes for a co-chaperone protein predominantly expressed in skeletal muscle cells and cardiomyocytes with to it attributed pleotropic effects; It has been suggested to improve the quality of and stabilize contractile proteins, to be involved in beta-1 andrenergic receptor signaling to augment myocardial contraction and to increase L-type Ca2+ current over the sarcolemma and t-tubules,(Feldman et al., 2016) to inhibit apoptosis in response to metabolic or myocardial stress,(Franaszczyk et al., 2014) and to be involved in autophagic protein degradation in aging cells.(van der Ende et al., 2018) Furthermore, reduced BAG3 concentration prolongs cardiomyocyte action potential and interestingly, end stage HF has been associated with decreased levels of BAG3.(Knezevic et al., 2015)

A GWAS conducted in 2014 found and separately replicated an association of sporadic DCM with a SNP within a noncoding region within gene HCG22. This SNP was found to function as an expression quantitative trait locus for nearby genes encoding class I and class II major histocompatibility complex heavy chain receptors.(Meder et al., 2014) An exome wide association study (EWAS) genetic study of DCM conducted in 2017 from six populations of European ancestry found six novel common SNPs associated with sporadic DCM. This included mutations in TTN, BAG3, FLNC and FHOD3, previously known to be associated with familial cardiomyopathies, as mentioned above.(Esslinger et al., 2017)

In a GWAS from the UK Biobank, patients diagnosed with HF or cardiomyopathy but were free of CHD or HCM were linked to suggestive loci previously implicated in DCM or HF, namely BAG3 and CLCNKA-ZBTB17.(Aragam et al., 2018)

In the United States, African Americans have the highest prevalence of sporadic DCM. A GWAS of individuals of African American ancestry found an association with an intronic locus in the CACNB4 gene, which encodes for an L-type calcium-channel subunit.(Xu et al., 2018)

Recently, a meta-analysis GWAS of 26 cohorts of European ancestry found 12 variants at 11 loci associated with HF and for eight of these variants ≥ 50% of this effect remained after taking into account the risk factor trait associations. Among these loci, BAG3, CDKN1A (encoding for the protein p21, a cell cycle inhibitor), KLHL3 (encoding the kelch-like 3 protein, involved in the down regulation of the SLC12A3 thiazide sensitive sodium-chloride cotransporter), SYNPO2L/AGAP5 (associated with the expression of two cardiac proteins binding actin to the Z-disk) had no association with CHD and the latter two were associated with atrial fibrillation. Interestingly, Mendelian randomization analysis showed no CHD-independent causal relationship between diabetes and HF.(Shah et al., 2020)

1.6.7 Endophenotypes of HF and genetic associations

Despite the relatively sparse results of positive associations of common polymorphism and HF, associations with endophenotypes related to HF has been more ubiquitous. This includes genes associated with LV dimension, hypertrophy and mass, and levels of natriuretic peptides.(van der Ende et al., 2018; Writing Committee et al., 2016)

1.7 HF Mortality, genetic aspects

Genetic aspects on the prognosis for patients with HF has been sparsely studied. Results from candidate gene studies as regards HF survival are described separately in that dedicated section. A GWAS found a still not replicated association of an intronic SNP of the CMTM7 gene with the mortality rate in patients with HF of European ancestry.(Morrison et al., 2010). In another GWAS, a gene variant on chromosome 5q22 likely to influense an enhancer region associated with the expression of the gene TSLP (thymic stromal lymphoprotein, a cytokine involved in immunological responses actions) was associated with increased risk of death in HF.(J. G. Smith et al., 2016) Recently, a common polymorphism in the promoter region of RIP3 (Receptor-interacting protein kinase 3) was associated with increased risk of cardiovascular death and cardiac transplantation.(Hu et al., 2019) Also, among DCM and HCM different monogenetic variants influence phenotype as well as mortality.(Bondue et al., 2018; Sen-Chowdhry et al., 2016)

In African Americans with a DCM phenotype classified as having either non-ischemic or ischemic causes, four variants of BAG3 were found to increase the risk of HF hospitalization or death in both these strata.(Myers et al., 2018)

Alternatively spliced SCN5A transcript isoforms have been associated with mortality from arrhythmias in patients with HF.(Gao et al., 2013) A synonymous SNP was found facilitating binding of Micro-RNA-24 to SCN5A transcripts and suppressing translation, which has been speculated to increase concentration of reactive oxygen species and influence also non-arrhythmic death.(Zhang et al., 2018)

1.8 Environmental factors and epigenetics of HF

Several GWASs identifying SNPs located in introns may be an indication of a possible effect on gene expression levels. Epigenetic aspects, also in the form of e.g. DNA methylation and histone acetylation are likely important factors in the development and prognosis of HF. The contribution of epigenetics on the net phenotype may also be more complex taking into account the possibility of many epigenetic changes having the potential to dynamically interact with environmental factors.(Dorn, 2011; van der Ende et al., 2018).

1.9 Family studies of HF

At the outset of the work for this thesis, the extent of possible effects of genomics and environmental factors as part of a family history (FH) of HF per se, to already

established risk factors e.g. as mentioned above, on the development, progression and prognosis of HF had not been fully ascertained.

Familial risks derived from population-based studies could be of clinical use in identifying individuals with an increased risk of HF since family studies give the opportunity to estimate the net effect of genomic and environmental factors. In addition, estimating phenotypic aggregation in families can be helpful in the planning of genetic studies but is also an important prerequisite in order for genetic studies to be worthwhile.(Burton et al., 2005)

The familial risk of HF was studied in the Framingham Offspring Cohort for relatively young indiduals.(Lee et al., 2006) However, as most patients with HF are found among the elderly and most healthy individuals are not regularly assessed by health care professionals (Benjamin et al., 2018) this cohort can be argued to be not fully coherent with the majority of the HF population. No other population studies investigating familial aspects of HF had been performed at the onset of this thesis.

1.10 Aims

All four population studies presented in this thesis had the purpose of investigating different aspects of familial aggregation of HF. With HF remaining a common condition with a poor prognosis, we aimed at studying different outcomes of HF and mortality as determined by such phenotypic characteristics in family members. More specifically, our objective was to study the effects of first degree biological relative (sibling and parental) HF on the risk of HF and death, as well as to determine if there could be an association between the prognosis of HF in siblings. Since we also sought to discern indications of biological and environmental risks, analyses of risks in relation to non-biological family (spouse and adoptive parents, respectively) were also performed. The specific aims of each study herein is outlined below:

Paper I: To study the familial risk of hospitalization for HF in terms of having an affected full sibling also admitted for HF during the follow-up period. We also wanted to further investigate the effect of sibling HF as regards sex, age of onset, and multiplex family settings.

Paper II: To investigate the risk of HF in adoptees as determined by HF in biological and adoptive parents, respectively. We also sought to determine the heritability of HF.

Paper III: To determine if HF survival time is associated among affected siblings.

Paper IV: To investigate if mortality risks were increased in subjects with a sibling affected with HF.

Chapter 2. Methods

2.1 Ethics

All studies were approved by the Ethics Committee of Lund University, Sweden.

2.2 Nationwide Registers

All four studies in this thesis were based on data derived from Swedish nationwide registers provided by the National Board of Health and Welfare and Statistics Sweden. Data were interlinked via the Swedish personal identification number system, a ten-digit unique number assigned to all individuals upon birth in Sweden or permanent immigration to Sweden since its introduction in 1947.(Ludvigsson et al., 2009) These identification numbers were anonymized in the resulting merged data-set before its utilization.

2.2.1 The Swedish Multi-Generation Register

This register holds data on family relationships (97% maternal and 95% paternal coverage), including adoptions, from 1961 for individuals born in 1932 who had not emigrated or died during the period 1932-1960.(Ekbom, 2011) Sibling data were derived from information on parenthood in the Multi-Generation Register.

2.2.2 The Swedish National Patient Register

The Swedish National Patient Register includes data on inpatients and hospital-based outpatients. The Inpatient Register (also called the Hospital Discharge Register) contains all hospital diagnoses for residents in Sweden from 1964 and has had nationwide coverage since 1987. The Outpatient Register contains information on diagnoses of all hospital-based outpatients in Sweden from 2001. The ninth revision of ICD-9 (ICD-9) was in use from 1987 to 1996, after which it has been superseded by the 10th revision (ICD-10).(Ludvigsson et al., 2011) The Hospital Discharge Register generally has a positive predictive value between 85-95%. The validity of many cardiovascular diseases, e.g. myocardial infarction, angina pectoris

and atrial fibrillation is higher with a positive predictive value ranging from 90% to 95%. A main diagnosis is available for more than 99% of all discharged patients and this figure has increased further since the 2000s.(Ludvigsson et al., 2011) Since the purpose of all papers was to investigate HF as the main cause of hospitalization, we only used HF registered as a main diagnosis; this has been found to carry a positive predictive value of more than 95%.(Ingelsson et al., 2005; Ludvigsson et al., 2011; Nilsson et al., 1994)

2.2.3 The Cause of Death Register

The Cause of Death Register holds information on the underlying cause of death of Swedish citizens, and data can be electronically retrieved as far back as 1952 for the use of register-based research. The cause of death is missing in 0.9% of cases. The Cause of Death Register is often regarded as valid for the purpose of epidemiological studies of various diagnoses although it has been shown to be more accurate among cases of younger individuals.(Johansson et al., 2009; Johansson et al., 2000)

2.2.4 The Total Population Register

The Total Population Register started in 1968 and contains sociodemographic data on, e.g. address data, parish at birth, civil status, husband/wife, partner, biological and adoptive parents and children, education, etc. Information on 95% of immigrations and 91% of emigrations are recorded within 30 days.

2.3 Diagnose codes commonly used

In all studies, HF was defined as a main diagnose 428 (ICD-9) and I50 (ICD-10) as specified in the Swedish National Patient Register. For paper 2, codes 434.10, 434.20 (ICD-7, in use 1964-1968) and 427.00, 428.00 (ICD-8, in use 1969-1986) were registered. Cardiomyopathies were coded 425 (ICD-9); I42 and I43 (ICD-10), and for paper 2, 425 (ICD-8) was also used.

2.3.1 Covariates

Table B shows the diagnose codes used for covariates throughout these four papers, when applicable (see separate table for diagnoses used in paper 2):

Table B. Covariate Diagnose Codes *

Diagnose	ICD-9	ICD-10
Alcoholism	291,303,305A,357F, 535D,571A,B,C,D, V79B	E24.4, F10,G31.2, G62.1,G72.1, K29.2, K70, K85.2, K86.0, Q86.0,Z50.2, Z71.4, Z72.1
Atrial fibrillation	427D	I48
CHD	410-414	I20-I25
Cancer	140-208	C00-C99
Cerebrovascular disease	430-438	I60-I69
Chronic obstructive pulmonary disease	490-496	J40-J47
Chronic renal failure	585	N18
Dementia	290	F00-F03, G30
Diabetes	250	E10-E14
Hypertension	401-405	I10-I15
Hyperthyreosis	242	E05
Hypothyreosis	243, 244	E03
Myocarditis	422	I40, I41
Obesity	278A, 278B	E65, E66
Valvular heart disease	391, 394-398, 421,424	I05-I09, I33-I39
Non-rheumatic valvular disease (study 3 only)	424	I34-I37
Stroke	430, 431, 434-436, 438	I60-I64, I69

2.3.2 Exclusion criteria

Cases with a recorded main or secondary diagnosis of congenital heart disease, 745-747 (ICD-9) and Q20-Q28 (ICD-10) were excluded from all these studies.

2.4 Sibling risk of hospitalization for heart failure – a nationwide study (Paper I)

2.4.1 Outcome variable

This study aimed at estimating the risk of first time hospitalization for HF, hence the outcome variable was defined as first time registered main diagnose in the Inpatient Register, during the follow-up 1987-2010.

2.4.2 Predictor variable

The predictor variable was defined as records of having a sibling registered with a main diagnosis of HF in the Inpatient Register (ICD-9) and I50 (ICD-10) 1987 to 2010. Since this study aimed at estimating the relative risk of HF in individuals with sibling HF as compared to a reference group without sibling HF, subjects with no sibling alive in 1987 were excluded. In a separate analysis, the relative risk of HF as determined by spousal HF was calculated. Spouses were defined as individuals older than 25 years that have a common youngest child.

2.4.3 Adjusting variables

All calculations were adjusted for age, sex, and time period. Additionally, the following adjusting variables were used in the fully adjusted model; occupational category (Farmers, self-employed, blue collar workers, white collar workers, professionals, and others), geographic region (northern Sweden, southern Sweden, and larger cities consisting of Gothenburg, Malmö and Stockholm), and total number of siblings alive at the start of the follow-up. Additionally, the following comorbidities, including both main and secondary diagnoses coded in the Inpatient Register, recorded anytime between 1987 and 2010 were adjusted for: CHD, diabetes, hypertension, obesity, and valvular heart disease.

2.4.4 Statistical methods

Relative risks of HF was calculated as standardized incidence ratios (SIR). The incidence of HF (number of cases per total time at risk, i.e. person-years) for subjects with a sibling with HF was thus compared to that of a reference group during the follow-up from January 1 1987 or birth until the event at hand, i.e. hospitalization for HF, death, emigration or end of follow-up on 31 December 2010. The follow-up period and subject age was stratified into 5-year periods. Adjustments for covariates were made by creating cross-classified categories for

each combination of values of these adjusting variables O_1 to O_J for the "observed", O, study subjects (with sibling HF) in the numerator and for each cross-classified category register the number of cases and total time at risk. Indirect standardization accommodates (standardizes) the time at risk for each corresponding cross-classified category in the reference group, i.e. in the denominator, by for each reference category creating the "expected" corresponding number of HF cases had each reference category contained the time at risk equal to that in the numerator. This is accomplished by multiplying the time at risk for each "observed", E, reference category n_j with the incidence of HF for each corresponding reference category λ_j. The resulting ratio, SIR, is the total number of cases in the cross-classified categories in the numerator divided by the standardized corresponding cases in the categories in the denominator(Breslow et al., 1987)

$$SIR = \frac{\sum_{j=1}^{J} O_j}{\sum_{j=1}^{J} n_j \lambda_j} = \frac{O}{E}$$

The 95% confidence intervals (95% CIs) were calculated assuming a Poisson distribution.

In a family with two or more affected siblings, each affected individual is regarded as an eligible case of HF. Consequently, a family with two affected siblings will contribute with two observations, although only one independent event is present, resulting in an augmented variance of the relative risk. Therefore, the true variance of the log (relative risk) was approximated by 1/(N-M), rather than by 1/N, where N is the total number of cases and M is the number of ascertained families as described by Hemminki et al.(Hemminki et al., 2001)

2.5 A Swedish Nationwide Adoption Study of the Heritability of Heart Failure (Paper II)

2.5.1 Outcome variable

This study aimed at determining the risk of HF, defined as registered with a main diagnosis of HF in the Swedish National Patient Register (hence both inpatients and outpatients were eligible) in adoptive children born 1942-1990, during follow-up 1964-2015. Among the exclusion criteria were adoptees who after adoption had at any time been registered as having lived somewhere other than with their adoptive parent. Estimating the narrow-sense heritability, i.e. the additive genetic contribution to population variance, of HF was another important target in this study.(D. Falconer et al., 1996)

2.5.2 Predictor variable

Main independent variables were registered as main diagnose of HF in the Swedish National Patient Register 1964-2015 for biological and adoptive parents, respectively.

2.5.3 Adjusting variables

Adjustments were made for comorbidities registered as a main and secondary diagnose in the National Patient register 1964-2015, as outlined in Table C.

Table C. International classification of Disease (ICD) codes used for studied comorbidities

Diagnosis	ICD 10	ICD 9	ICD 8	ICD 7
Coronary heart disease	I20-I25	410-414	410-414	420
Hypertension	I10-I15	401-405	400-404	440-447
Valvular heart disease	I05-I09, I33-I39	391, 394-398, 421, 424	391, 393, 394-398, 421, 424	401.10, 401.11, 410-414, 421, 430
Diabetes mellitus	E10-E14	250	250	260
Chronic obstructive pulmonary disease	J40-J47	490-496	490-493	241, 502, 527.10, 527.11

2.5.4 Statistical analysis

A case-control design was applied where each adoptee HF case was matched to five unaffected adoptees by sex, birth year, county of birth, and level of education. Odds ratios (ORs) for adoptee HF as regards the relative number of affected biologic and adoptive parents, respectively, was calculated using conditional logistic regression. In addition, we also applied a cohort study design using unconditional logistic regression to calculate adoptee ORs and Cox regression to calculate hazard ratios (HRs) for adoptee HF.(Thomas, 2004).

We also calculated the narrow-sense heritability, assuming a liability threshold model (D. S. Falconer, 1965) for HF. For this purpose, we used both tetrachoric correlation (D. Falconer & Mackay, 1996; Tenesa et al., 2013) and Falconer's regression methods.(D. S. Falconer, 1965)

2.6 Familial mortality risks in patients with heart failure – a Swedish sibling study (Paper III)

2.6.1 Outcome variable

The main outcome was death, secondary outcome cardiovascular death, among subjects first time registered with HF as a main diagnosis in the Inpatient Register 2000-2012.

2.6.2 Predictor variable

The predicting variable was the survival time of a previously admitted sibling (proband) since first-time hospitalization for HF 2000-2007. With data until 2012, to obtain a minimum of five year record, subjects with probands hospitalized for HF 2008 and onwards were excluded. Likewise, only families with two affected siblings were included. Sibling pairs in which any had records of HF in the Inpatient Register prior to 2000 were also excluded.

2.6.3 Adjusting variables

The variables subject sex, age and calendar year at onset (time of first recorded main diagnosis) of HF were included in all analyses. The following diagnoses (main and secondary) registered in the Inpatient Register from 1987 to the time of HF admission were adjusted for: CHD, diabetes, hypertension, non-rheumatic valvular disease, and stroke.

2.6.4 Statistical analysis

Cox regression (Vittinghoff et al., 2012) was used to calculate relative risk of death as HRs, both with proband survival as a continuous predictor and as a binary variable with survival dichotomized as less than five years (<5 years) or longer (≥5 years).

2.7 Mortality risks associated with sibling heart failure (Paper IV)

2.7.1 Outcome variable

The outcomes analysed were risk of death in terms of overall mortality, cardiovascular mortality (ICD-10 codes I00-I99 and ICD-9 codes 390-459), and death of unknown cause (ICD-10 codes R96, R98 and R99 and ICD-9 codes 798 [not 798A] and 799) during the period 1987-2012 among subjects with a sibling and a spouse, respectively, registered with a primary diagnosis of HF in the Inpatient Register during this period.

2.7.2 Predictor variable

Sibling pairs in families with exactly two siblings alive in 1987 in which the sibling (proband) was affected with HF were matched (both the subject and the probands) with five controls by birth year and sex. The probands of the control pairs were not registered with HF at the time of the index date, defined as the date when the affected proband was first diagnosed with HF. Pairs of spouses with an affected proband were analogously matched to control pairs for which probands were free of HF. Families with an individual (parent or sibling) registered with a main or secondary diagnosis of cardiomyopathy were excluded.

2.7.3 Adjusting variables

The following comorbidities were adjusted for (main or secondary diagnose in the Inpatient register): CHD, hypertension, valvular disease, atrial fibrillation, myocarditis, hypothyreosis, hyperthyreosis, diabetes, chronic obstructive pulmonary disease, alcoholism, chronic renal failure, cancer, cerebrovascular disease, and dementia. Other adjusting variables were educational level (years of education, categorized as 1–9 years, 10–11 years, and >= 12 years), and country of birth (Sweden versus abroad).

2.7.4 Statistical analysis

Cox proportional hazards regression was used to calculate the association between proband sibling (or spouse) HF and subject mortality, measured as hazard ratios (HR).(Vittinghoff et al., 2012) Comorbidities were included as time dependent variables. The follow-up ranged from 1987 to 2012 in the sibling analysis and from 1990 to 2012 in the spousal analysis.

Chapter 3. Results

3.1. Sibling risk of hospitalization for heart failure – a nationwide study (Paper I)

3.1.1 Characteristics of included patients hospitalized for HF

From a cohort of 6 100 243 individuals from 2 399 506 different families with at least one sibling alive on 1 January 1987, a total of 23 212 patients were admitted for HF during the follow-up 1987-2010. 7155 of these patients were females. The oldest subjects were 78 years old at the end of follow-up in 2010. 9598 patients were between 60 and 69 years old, while only 4111 patients were 70 years or older at the time of hospitalization for HF. 11 547 and 7297 patients were recorded with CHD and diabetes, respectively.

3.1.2 Risk of heart failure by number of affected siblings

In the fully adjusted model, having a single sibling with HF was associated with a SIR of 1.65 (95% CI 1.55-1.75) and 1.56 (95% CI 1.43-1.70) for male and female subjects being hospitalized for HF respectively (Table D). Subjects with two siblings hospitalized for HF resulted in very high risks with a SIR of 13.78 (95% 10.74-17.42) for males and a SIR of 18.65 (95% CI 13.84-24.60) for females, rendering a SIR of 15.46 (95% CI 12.82-18.50) for both sexes in total.

Table D. Familial risks, standardized incidence ratios (SIR), of hospitalization for heart failure according to number of affected siblings*, fully adjusted model†. Individuals without at least one sibling alive in 1987 excluded.

	Males				Females				All			
Multiplex	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
One sibling	1043	**1.65**	**1.55**	**1.75**	513	**1.56**	**1.43**	**1.70**	1556	**1.62**	**1.54**	**1.70**
Two siblings	70	**13.78**	**10.74**	**17.42**	50	**18.65**	**13.84**	**24.60**	120	**15.46**	**12.82**	**18.50**
Three or more siblings	8	**27.26**	**11.64**	**53.97**	4	**63.09**	**16.41**	**163.14**	12	**33.62**	**17.29**	**58.92**
All	1121	**1.76**	**1.65**	**1.86**	567	**1.71**	**1.57**	**1.86**	1688	**1.74**	**1.66**	**1.83**

Bold type: 95% CI does not include 1.00.

O: observed number of cases of heart failure with a specified number of affected siblings; SIR: standardized incidence ratios; CI: confidence interval.

*Siblings defined as individuals born of the same mother and father; †Adjusted for age, family size, region of residence, sex, socioeconomic status, time period, coronary heart disease, diabetes, hypertension, obesity and valvular heart disease.

3.1.3 Age-dependent sibling risks of heart failure

Figure A depicts the highly age-dependent incidence rates in both males and females. Incidence rates of HF hospitalization applied to the European Standard Population, as determined by sibling history of HF.

Table E shows the fully adjusted age-stratified familial SIRs of HF. The relative risks associated with sibling HF were highest in younger subjects under the age of 50 years (SIR=2.67, 95% CI 2.24-3.16) and decreased with age. For individuals aged between 70-78 years of age, the familial risk was 1.54 (95% CI 1.38-1.71).

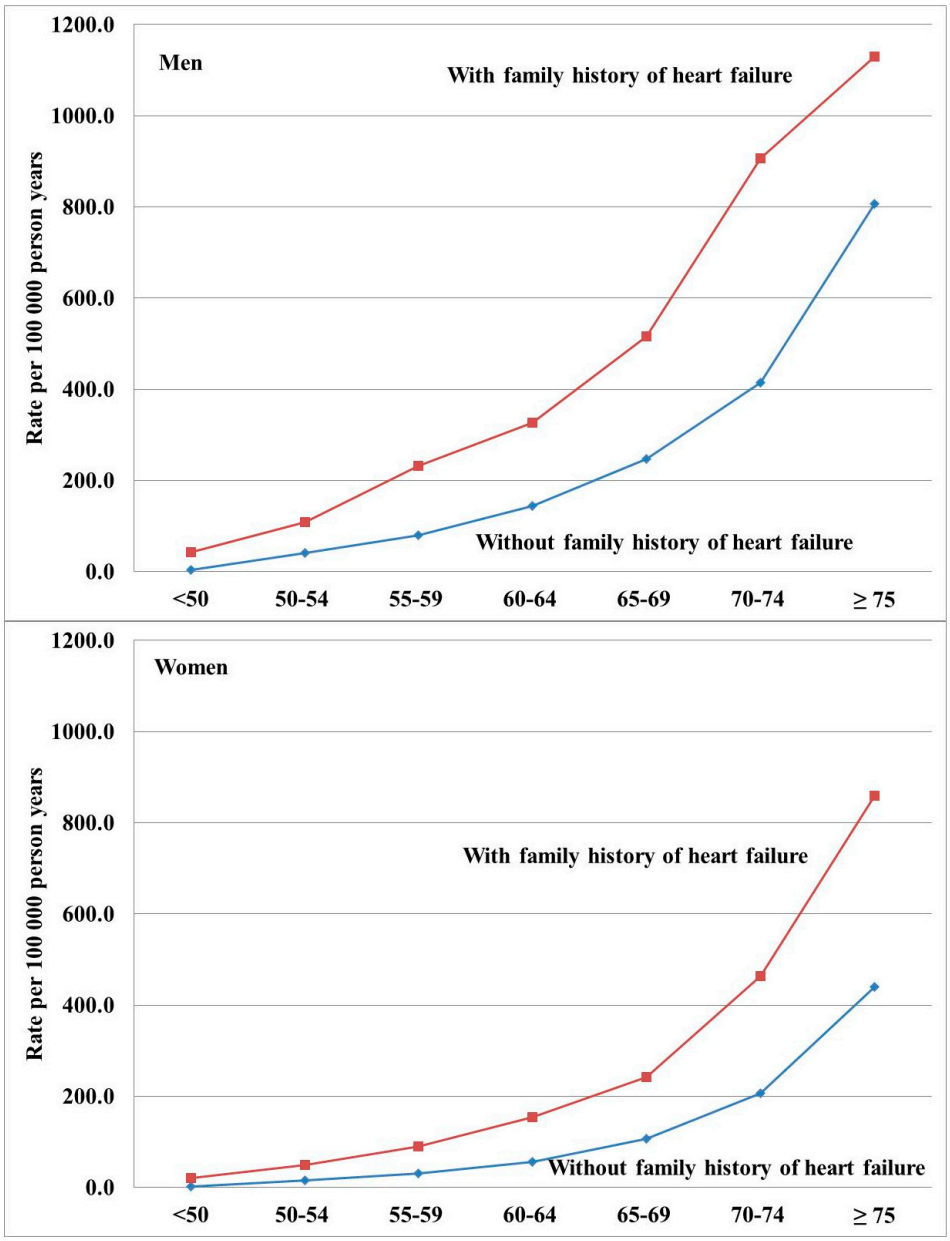

Figure A. Age and sex-specific incidence rates of hospitalized heart failure, with and without at least one affected sibling

Table E. Age-dependent familial risks, standardized incidence ratios (SIR), of hospitalization for heart failure with having at least one affected sibling*, fully adjusted model†. Individuals without at least one sibling alive in 1987 excluded.

	Males				Females				All			
Age at diagnosis in (years)	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
< 50	93	**2.58**	**2.08**	**3.16**	44	**2.88**	**2.09**	**3.87**	137	**2.67**	**2.24**	**3.16**
50-59	338	**1.96**	**1.76**	**2.18**	141	**1.82**	**1.53**	**2.15**	479	**1.92**	**1.75**	**2.10**
60-69	486	**1.67**	**1.53**	**1.83**	248	**1.56**	**1.37**	**1.77**	734	**1.63**	**1.52**	**1.76**
70-78	204	**1.46**	**1.27**	**1.67**	134	**1.68**	**1.41**	**1.99**	338	**1.54**	**1.38**	**1.71**
All	1121	**1.76**	**1.65**	**1.86**	567	**1.71**	**1.57**	**1.86**	1688	**1.74**	**1.66**	**1.83**

Bold type: 95% CI does not include 1.00.

O: observed cases of heart failure with at least one affected sibling; SIR: standardized incidence ratios; CI: confidence intervals.

*Siblings defined as individuals born of the same mother and father; †Adjusted for age, family size, region of residence, sex, socioeconomic status, time period, coronary heart disease, diabetes, hypertension, obesity and valvular heart disease

3.2 A Swedish Nationwide Adoption Study of the Heritability of Heart Failure (Paper II)

3.2.1 Characteristics of adoptees and parents

The study population consisted of 21 643 adoptees in the cohort study and could be linked to 35 016 adoptive parents and 43 286 biological parents. A total of 7823 cases of HF were found, of which 194 were adoptees, 3972 were adoptive parents and 3657 were biological parents. Descriptive statistics of adoptees and their adoptive and biological parents is outlined in **Table F**. There was an overrepresentation of comorbidities in cases of HF in all these three groups. The higher prevalence of HF among adoptive parents in relation to biological parents was statistically significant (p-value < 0.001).

Table F. Descriptive statistics of adoptees born 1942-1990 and their adoptive and biological parents.

	Adoptees (n = 21 643)	Adoptive parents (n = 35 016)	Biological parents (n = 43 286)
Female, No. (%)	10 626 (49.10)	14 872 (42.47)	21 643 (50.00)
High education level (12 years or more), No. (%)	6 206 (28.67)	5 587 (15.96)	3 980 (9.19)
NDI High socioeconomic status,a No. (%)	5 375 (24.83)	6 238 (17.81)	5 814 (13.43)
Occupational positionb, No. (%)	3 412 (15.76)	1 346 (3.84)	1 051 (2.43)
Median age (yrs.) at end of study period (interquartile range)	52 (45 – 58)	77 (68 – 84)	70 (62 – 77)
Median birth year (interquartile range)	1963 (1955-1968)	1928 (1919-1940)	1938 (1929 -1945)
Birth year (range)	1942-1990	1886-1972	1877-1974
Birth year (mean, SDc)	1963 (10)	1929 (14)	1937 (12)
Heart failure patients			
Heart Failure, No. (%)	194 (0.90)	3 972d (11.34)	3 657e (8.45)
Female, No. (%)	59 (0.27)	1 700 (4.9)	1 482 (3.42)
Median age (yrs.) at diagnosis (interquartile range)	55 (47 – 61)	79 (73 – 85)	72 (65 – 79)
Cardiomyopathy patients			
Cardiomyopathy, No. (%)	118 (0.55)	386 (1.10)	526 (1.22)
Female, No. (%)	33 (0.15)	119 (0.35%)	176 (0.41)
Median age at diagnosis (interquartile range)	50 (43 – 57)	69 (61 – 77)	63 (55 – 70)

a neighborhood Deprivation Index. b Manager position or occupation with a requirement for in-depth university competence according to the Swedish Standard Classification of Occupations 2012 (SSYK 2012) by Statistics Sweden (https://www.scb.se). c SD=standard deviation. d 216 families with both adoptive parents affected. e 206 families with both biological parents affected.

3.2.2 Adoptee risk of HF as determined by affected parents

Calculations were performed both with and without the inclusion of patients with cardiomyopathy. For both the cohort study and case-control study design, with and without cardiomyopathies, the ORs for HF in adoptees with at least one affected biological parent were significantly increased in all models. No such association was found between HF in adoptees and adoptive parents. For the cohort study, the fully adjusted model (**Table G**) conferred biological familial ORs of 1.45 (95% CI, 1.04-2.03) and 1.58 (95% CI 1.03-2.42), with cardiomyopathies included and excluded, respectively. Similarly, in the case-control study HF in the adoptees was significantly associated with HF in biological parents rendering an OR of 1.49 (95% CI, 1.05-2.12) with cardiomyopathies included and an OR of 1.64 (95 % CI, 1.05 – 2.56) with cardiomyopathies excluded.

3.2.3 Sex-specific risks

More males than females were affected by HF among adoptees as well as among adoptive and biological parents. In **Table H**, the risks of sex-specific biological familial transmission of HF are described. Only maternal HF was significantly associated with HF in adoptees in the adjusted models.

3.2.4 Heritability of HF

As for calculations of heritability with also cardiomyopathies included, with Falconer's regression the heritability was determined to 26 ± 14 %. The method of tetrachoric correlation, which is dependent on the population prevalence, the heritability varied from 14% ±6 (standard error) in a population with 0.1% prevalence to a heritability of 25% ±10 in a population with 12% prevalence. With a prevalence of 7.8%, as found in this study, the heritability was estimated to be 24% ±10%. Heritability was also analogously calculated with cardiomyopathies excluded. Falconer's regression yielded a heritability of 34 ± 18 %. With the method of tetrachoric correlation, the heritability ranged from 18% ±8 (standard error) with a prevalence of 0.1% prevalence to a heritability of 32% ±14 in a population with 12% prevalence. With an assumed prevalence of 7.3%, as observed in the present study population without cardiomyopathies, the heritability determined by tetrachoric correlation was calculated to 29% ±12%.

Table G. Odds ratio[a] of heart failure in adoptees as determined by affected parent (cohort study)

	No biological parental heart failure	Biological parental heart failure	No adoptive parental heart failure	Adoptive parental heart failure
Cardiomyopathies included				
Person-years at risk	844 228	167 010	828 375	182 863
Cases/persons at risk	135/18192	59/3451	155/17887	39/3756
Incidence rate per 1000 person years	0.16 (0.13-0.19)	0.35 (0.27-0.46)	0.19 (0.16-0.22)	0.21 (0.15-0.29)
Incidence ratio	1[b]	2.21 (1.62-2.99)	1[b]	1.14 (0.79-1.61)
	Odds ratio (95% CI)		*Odds ratio (95% CI)*	
Model 1	1[b]	2.33 (1.71-3.17)	1[b]	1.20 (0.84-1.71)
Model 2	1[b]	1.51 (1.10-2.08)	1[b]	1.19 (0.83-1.70)
Model 3	1[b]	1.45 (1.04-2.03)	1[b]	0.83 (0.57-1.20)
Cardiomyopathies excluded[c]				
Person-years at risk	825 608	150 032	807 625	168 015
Cases/persons at risk	79/17796	37/3092	93/17444	23/3444
Incidence rate per 1000 person years	0.10 (0.076-0.12)	0.25 (0.17-0.34)	0.12 (0.093-0.14)	0.14 (0.087-0.21)
Incidence ratio	1[b]	2.58 (1.73-3.79)	1[b]	1.19 (0.74-1.85)
	Odds ratio (95% CI)		*Odds ratio (95% CI)*	
Model 1	1[b]	2.72 (1.84-4.02)	1[b]	1.26 (0.79-1.98)
Model 2	1[b]	1.62 (1.09-2.43)	1[b]	0.82 (0.52-1.31)
Model 3	1[b]	1.58 (1.03-2.42)	1[b]	0.79 (0.49-1.29)

Abbreviations: CI, confidence interval. Model 1=univariate model; Model 2=adjusted for adoptee birth year, sex, county, and education; Model 3=adjusted for adoptee birth year, sex, county, education, coronary heart disease, hypertension, valvular heart disease, diabetes mellitus, and chronic obstructive pulmonary disease. [a] Risks are presented as odds ratios (95 % confidence interval) derived from unconditional logistic regression. [b] Reference group. [c] All adoptees diagnosed with cardiomyopathy, or that had a biological or adoptee parent diagnosed with cardiomyopathy, were excluded.

Table H. Odds ratio[a] of heart failure (HF) in adoptees as determined by affected biological parents (cohort design), stratified by sex. Individuals with cardiomyopathies included.

	No Biological Parental HF	Biological paternal HF	Biological maternal HF
All adoptees	*Odds ratio (95% CI)*		
Model 1	1[b]	1.65 (1.07–2.55)	3.11 (2.07–4.67)
Model 2	1[b]	1.20 (0.77–1.87)	1.81 (1.19 – 2.74)
Model 3	1[b]	1.14 (0.71–1.81)	1.77 (1.14 – 2.77)
Male adoptees	*Odds ratio (95% CI)*		
Model 1	1[b]	1.67 (1.04-2.67)	2.15 (1.30-3.55)
Model 2	1[b]	1.25 (0.78-2.01)	1.29 (0.77-2.15)
Model 3	1[b]	1.03 (0.62-1.71)	1.11 (063-1.95)
Female adoptees	*Odds ratio (95% CI)*		
Model 1	1[b]	1.56 (0.77-3.18)	5.31 (3.02-9.32)
Model 2	1[b]	1.10 (0.54-2.25)	3.08 (1.72-5.51)
Model 3	1[b]	1.45 (0.68-3.06)	3.65 (1.97-6.77)

Abbreviations: HF, heart failure; CI, confidence interval. Model 1=univariate model; Model 2=adjusted for adoptee birth year, sex, county, and education; Model 3=adjusted for adoptee birth year, sex, county, education, coronary heart disease, hypertension, valvular heart disease, diabetes mellitus, and chronic obstructive pulmonary disease. [a] Risks are presented as odds ratios (95 % confidence interval) derived from unconditional logistic regression. [b] Reference group.

3.3 Familial mortality risks in patients with heart failure – a Swedish sibling study (Paper III)

3.3.1 Descriptive statistics

A total of 96 deaths occurred among 373 eligible study subjects found in 372 families. Total follow-up time was 1196 years with an overall mortality incidence ratio of 80.27 (65.71-98.06, 95% CI) per 1000 person-years. The subject mean and median follow-up time was 3.21 years and 2.59 years respectively. A total of 131 of these 372 families had a member registered with a diagnosis of cardiomyopathy.

3.3.2 Overall HF mortality risk as determined by affected sibling survival

Survival of subjects hospitalized for HF was poorer among those with an affected proband that survived less than five years, see **Figure B**.

With reference to proband HF survival five years or longer, a shorter proband HF survival was associated with an increased fully adjusted risk of overall mortality (HR 2.02, 1.32-3.09, 95% CI), see **Table I**, and cardiovascular death (HR 2.35, 1.38-4.03, 95% CI) in patients with HF. After excluding families with any case of cardiomyopathy, also in the fully adjusted models, short proband survival less than five years was still similarly associated with an increased relative risk of subject overall mortality (HR 2.22, 1.33-3.71, 95% CI) and cardiovascular mortality (HR 2.30, 1.19-4.45, 95% CI).

Subjects were stratified (cardiomyopathies included), inter alia, by occurrence of a previous or at time of HF hospitalization registered diagnose of CHD. Fully adjusted overall mortality remained increased both among subjects without CHD (HR 2.35, 1.18-4.67, 95% CI) and among subjects with CHD (HR 1.84, 1.05-3.23, 95% CI)

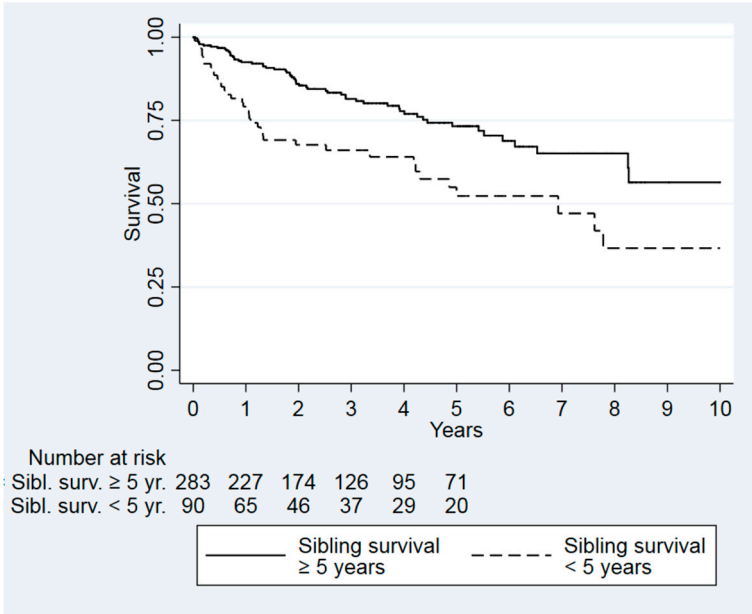

Figure B. Unadjusted Kaplan-Meier survival functions with regard to overall mortality from first hospitalization for heart failure 2000-2012 as determined by sibling heart failure survival

Table I. Overall mortality of subjects* first time hospitalized for heart failure (HF), as determined by survival of previously affected sibling (proband)

	Small model, HR† (95% confidence interval, CI)	P value	Fully adjusted model, HR† (95% CI)	P value
Proband HF survival < 5 yr. (yes/no)‡	1.98 (1.31-3.00)	0.001	2.02 (1.32-3.09)	0.001
Study person characteristics:				
sex (female/male)	0.92 (0.60-1.41)	0.69	0.98 (0.63-1.51)	0.91
age at onset§	2.14 (1.52-3.02)	< 0.001	2.11 (1.44-3.08)	< 0.001
year of onset§			0.97 (0.88-1.06)	0.46
CHD|| (yes/no)			0.90 (0.58-1.42)	0.66
Diabetes (yes/no)			2.68 (1.73-4.16)	< 0.001
Hypertension (yes/no)			0.80 (0.53-1.20)	0.30
Stroke (yes/no)			2.18 (1.40-3.39)	0.001
VHD# (yes/no)			1.75 (1.01-3.00)	0.044

*: Only families with two cases of HF and no case of congenital heart disease included. †: Cox regression hazard ratio, adjustments as specified below. ‡: 37 deaths among 90 subjects with proband survival <5 yr., from a total of 96 deaths among 373 subjects at risk. §: age at onset and year of onset presented as per 10 yr. and 1 yr. deviation from mean, respectively. ||: Coronary heart disease. #:Valvular heart disease.

3.4 Mortality risks associated with sibling heart failure (Paper IV)

3.4.1 Descriptive statistics

Among a total of 62 475 sibling pairs with a proband sibling affected with HF, 30 907 (49.5%) study subjects and 20 748 (33.2%) probands were females. In total, 11 754 study subjects (18.8%) died during the follow–up (mean follow–up 23.2 years).

3.4.2 Mortality Risks Conferred by Sibling HF

Having a sibling affected with HF during the follow-up was associated with an increased overall mortality both in the crude (HR=1.35, 95% CI 1.33-1.38) and the adjusted model (HR 1.21, 95% CI 1.18-1.25), as shown in **Table J**. The adjusted HRs for cardiovascular mortality and death of unknown cause were 1.39 (95% CI 1.32-1.45) and 1.58 (95% CI 1.29-1.95), respectively. When explicitly excluding subjects (2454 cases of HF) and controls (5836 cases) recorded with a diagnosis of HF (main or secondary diagnose recorded in the Inpatient or outpatient Register) during the follow-up, a sibling HF was still associated with an approximately 20% increased relative risk of death in the fully adjusted model (HR 1.19, 95% CI 1.15-1.23). The mortality risk associations with spousal HF were all minimal, with an overall mortality HR of 1.02 (1.01-1.02). Early sibling age of onset of HF < 50 years was associated with higher HRs for overall mortality, cardiovascular mortality and death of unknown cause, 1.33 (1.27-1.41), 1.54 (1.40-168) and 1.84 (1.27-2.67), respectively.

Table J. Overall mortality as determined by occurrence of sibling heart failure[a]

				Overall mortality					
				Crude model			Adjusted model[b]		
	No. of individuals	No. of deaths	%	HR	95%CI		HR	95%CI	
Sibling with heart failure									
No	312 303	45 457	14.6						
Yes	62 475	11 754	18.8	1.35	1.33	1.38	1.21	1.18	1.25
Country of birth									
Sweden	368 304	56 426	15.3						
Abroad	6474	785	12.1				1.02	0.93	1.13
Education, yr.									
1-9	130 655	27 619	21.1						
10-11	151 965	19 634	12.9				0.77	0.75	0.79
12+	92 158	9958	10.8				0.72	0.70	0.74
CHD									
No	331 131	45 226	13.7						
Yes	43 647	11 985	27.5				1.81	1.75	1.88
Hypertension									
No	303 549	42 330	13.9						
Yes	71 229	14 891	20.9				1.13	1.09	1.17
Valvular disease									
No	368 169	54 989	14.9						
Yes	6609	2222	33.6				2.10	1.94	2.28
Atrial fibrillation									
No	351 083	50 458	14.4						
Yes	23 695	6753	28.5				1.73	1.65	1.81
Myocarditis									
No	374 409	57 123	15.3						
Yes	369	88	23.8				2.33	1.60	3.39
Hypothyreosis									
No	366 579	55 483	15.1						
Yes	8199	1728	21.1				1.47	1.35	1.60

Hyperthyreosis						
No	372 918	56 815	15.2			
Yes	1860	396	21.3	1.21	1.02	1.43
Diabetes mellitus						
No	346 453	47 665	13.8			
Yes	28 325	9546	33.7	2.24	2.15	2.33
COPD						
No	354 183	49 846	14.1			
Yes	20 595	7365	35.8	3.13	2.99	3.28
Alcoholism						
No	360 004	50 121	13.9			
Yes	14 774	7090	48.0	5.96	5.70	6.23
Chronic renal failure						
No	370 655	54 807	14.8			
Yes	4123	2404	58.3	4.48	4.05	4.96
Cancer						
No	323 404	32 065	9.9			
Yes	51 374	25 146	48.9	13.86	13.46	14.27
Cerebrovascular disease						
No	349 959	48 299	13.8			
Yes	24 819	8912	35.9	3.08	2.96	3.21
Dementia						
No	370 909	54 932	14.8			
Yes	3869	2279	58.9	10.88	9.92	11.92

[a] Controls matched for age and sex.

[b] Adjusted model entails adjustments for all subject characteristics with resulting concurrent HRs outlined

Abbreviations: HR=hazard ratio; CI=confidence interval; CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease.

Chapter 4. Discussion

4.1. Sibling risk of hospitalization For Heart Failure – a nationwide study (Paper I)

This (Paper I) was the first population study to determine the familial risk of HF hospitalization. The fully adjusted risk, in the form of incidence rate, of hospitalization for HF was approximately 60% higher among subjects with one affected sibling during the follow-up as compared to the reference group with no familial aggregation. Having two and three affected siblings was associated with a much more augmented risk, approximately 15 and 33 times, respectively. Although the incidence ratios were higher among younger subjects, the increasing incidence of hospitalization for HF with age caused the majority of cases attributable to familial aggregation to be found among the elderly population. There was no marked difference in risk as regards sex of subjects.

The spousal association of HF hospitalization was very low, which may indicate that adult shared environment is not a major contributing risk factor.(Cheraskin, 1990)

The risk of hospitalization for HF associated with one affected sibling in this study was very similar to the risk of HF in offspring having one affected parent in the Framingham Heart Study (HR 1.70).(Lee et al., 2006) Notwithstanding the continually increased knowledge amassed from genetic studies during the time of this study and thesis, these results still quantify the net risk of HF from the contribution of the genome and epigenetic and environmental factors associated with family history of HF.(Dorn, 2011; J. G. Smith, 2017) Although these risks may speculatively still be related to a correlating environmental exposure during childhood, the recurrence-risk ratio of a trait in siblings has been found to vary mostly with the genotype relative risk and the frequency of this allele.(Rybicki et al., 2000) On the contrary, for environmental risk factors that confer a relative risk < 10, even a fully correlated exposure among siblings has been shown to generate low recurrence risks.(Khoury et al., 1988) Moreover, early phenotype onset is a common characteristic of many genetically caused traits(Burton et al., 2005) and this may be reflected by the higher risk association among younger subjects, which with time reasonably have the potential to be diluted by the increased incidence of HF correlated with age. Worth noting in this regard is that the material also includes

patients registered with cardiomyopathies. The risk of hospitalization for HF with having two or three affected siblings widely exceeded the risk of HF (HR 1.92) in offspring with both parents affected in the Framingham Heart Study.(Lee et al., 2006) This may be caused by recessive variants, epistasis or shared environmental factors in early life.(Hemminki et al., 2001; Risch, 1990) Familial aggregation of several strong genetic risk factors has also been shown to potentially have a more than additive effect on risk.(Zoller et al., 1995) In addition, the study subjects were not completely comparable as well. In the Framingham Heart Study, participants were regularly monitored and therefore reasonably offered an opportunity for early intervention (Lee et al., 2006) whereas our study calculated incidences of first hospitalization for HF in the general population.

4.1.1 Strengths and weaknesses

A strength of this study was the inclusion of older patients and analyzing a clinically related and important outcome. However, the follow-up ended with the oldest subjects being 78 years old, which still does not include the most elderly part of the population.(Bolmsjo et al., 2013)

An important limitation is the potential for disparate treatment for HF during the follow-up period, although the separately calculated sibling risks during the first half and second half of the follow-up were similar. Subjects may have had siblings admitted for HF and died prior to the start of follow-up in 1987, which underestimates the HF burden in the family including erroneously rendering these individuals as eligible controls. This may in turn thus underestimate the familial risks. Cardiomyopathies were not accounted for (see subsection below). Entries of comorbidities were regarded as eligible also after the occurrence of HF, which may overestimate the influence of these parameters.

4.2 A Swedish Nationwide Adoption Study of the Heritability of Heart Failure (Paper II)

This study (Paper II) of adoptees was performed in an attempt to differentiate the familial risks of HF caused by genetic and environmental factors, respectively. The risk of HF, defined as a primary diagnose in the hospital inpatient or outpatient register, was increased in adoptees with at least one biological parent affected with HF, in magnitude comparable to the previous two population studies, i.e. paper 1(Lindgren et al., 2016) and the Framingham Heart Study.(Lee et al., 2006) However, adoptee risk was not influenced by HF in adoptive parents. The two methods used for estimating the narrow sense heritability for HF rendered a moderate heritability of approximately 25%.

The risk of HF and heritability increased when families with any member (an adoptee or a biological or adoptive parent) registered with cardiomyopathy were excluded. Speculatively, this may be due to sporadic cases of cardiomyopathy and HF caused by environmental factors, e.g. alcohol, pregnancy, or myocarditis. However, this could also be the result in cases where the primary diagnose is registered as cardiomyopathy and not HF. Furthermore, the changing definition of cardiomyopathy during the follow-up may also be an important factor influencing the results.

A moderate level of heritability for HF and the significant association found exclusively between HF in adoptees and their biological parents indicates that biological family history based on genetic factors is an important risk factor for HF. The net risk may, however, be the result of both shared genetics and to some extent early environmental exposure occurring before adoption. A support for the latter could be the fact that biological maternal HF (Table H) conferred a higher risk of HF. However, this is also a sign of the Carter effect, for which a positive phenotype of a complex trait in an individual of the sex that is less susceptible to the trait consequently carries a higher genetic burden for the trait at hand.(Carter et al., 1969) Although familial aggregation of a complex trait is often characterized with an earlier age of onset,(Lander et al., 1994) the different follow-up periods of this study allowed for a discrepancy in the age of onset between adoptees (mean age of diagnosis 55 years) and biological parents (mean age of diagnosis of 72 years). Familial and genetic factors may thus be important in the development of HF also in older patients. It is important to note in this regard that a significant heritability of HF does not imply specific genetic underlying mechanisms for the development of HF and although adjustments were made for comorbidities in the cohort analysis the determined familial risk of HF may still be related to the comorbidities at hand.

4.2.1 Strengths and weaknesses

An important limitation in this study was the lack of information regarding at which age the child was adopted and consequently how long the child may have been subjected to a shared environmental exposure with the biological parent or parents. Data from previous studies has indicated that the majority of children were adopted before they were 12 months old.(Bohman, 1972; Nordlöf, 2001) The period of intrauterine development is of course also an important period of shared environment.

The number of HF cases among adoptees were few and the total number of cases registered with cardiomyopathy in relation to this was considerable, which may influence the result (see subsection below). By excluding patients with cardiomyopathy the risk of HF associated with an affected biological parent and the heritability increased.

4.3 Familial mortality risks in patients with heart failure – A Swedish sibling study (Paper III)

Paper III studied the relationship of survival after first hospitalization for HF in pairs of siblings both hospitalized for HF. There was an approximately two-fold overall mortality risk in subjects with a previously admitted proband sibling who survived less than five years from discharge. This was also true for the risk of cardiovascular death. Excluding sibling pairs belonging to families with any sibling diagnosed with cardiomyopathy did not fundamentally change these results. Subject risk of death decreased with each year of proband survival. No difference in mortality was found between the sexes.

The results suggest that familial factors influence survival in patients with HF and that information on family history in this regard is a valuable clinical instrument in assessing the prognosis. Subject overall mortality was not affected by adjusting for the incidence ratio of death of siblings not affected with HF in the family, which indicates a familial association of HF survival per se.

Speculatively, this familial risk of mortality in HF may stem from a more rapid progression rate or elevated risk of arrhythmia, or be a result of familial susceptibility for more severe comorbidities, or perhaps a combination of these factors. As previously mentioned, especially in recent years, various gene variants (Hu et al., 2019; Myers et al., 2018; J. G. Smith et al., 2016) along with known mutations of monogenetic DCM and HCM,(Bondue et al., 2018; Sen-Chowdhry et al., 2016) and epigenetic factors(Gao & Dudley, 2013; Zhang et al., 2018) have been found to influence the survival of HF. Interestingly, adjusting for HF comorbidities in subjects and, in an additional analysis, adjusting for the burden of CHD in the family of siblings did not significantly alter the mortality risks. Although conjectural, the remaining pronounced risk after adjustments could indicate that familial factors relating to survival in HF may not be completely caused by the effects of its comorbidities. The continuous inverse relationship between subject mortality risk and proband survival is suggestive of phenotype potentially influenced by many different loci as for a polygenetic trait, although environmental effects may also be such a cause.

4.3.1 Strengths and weaknesses

Among the strengths of this study was the more contemporary follow-up period, the earliest of which commenced at first event of hospitalization for HF past the millennium. At this time BB had been shown to improve survival in patients with HFrEF and ARBs and MRAs were introduced. Analyses were performed with and without families with cardiomyopathies but rendered similar results.

The short subject follow-up time with a mean of only 3.21 years is an important limitation. In addition, the number of eligible sibling pairs was small and consequently also the number of adjusting variables, including comorbidities, was limited. Furthermore, only comorbidities registered before the event of hospitalization for HF were adjusted for.

4.4 Mortality risks associated with sibling heart failure (Paper IV)

The risk of death (overall mortality) was found to be approximately 20% higher in subjects who had a proband sibling hospitalized for HF during the follow-up as compared to matched control pairs of siblings for which the proband was not registered with HF at time of inclusion. Adjustments were made for common risk factors of HF and death. The corresponding risks of cardiovascular death and death of unknown causes were markedly higher. Mortality risks were not affected by subject or proband sex but were more increased in subjects for which the proband had been registered with HF before 50 years of age. The overall mortality risk remained fundamentally the same when exclusively studying subjects free of HF themselves. Mortality risks for subjects as determined by spousal HF were minute, suggesting a limited influence of a shared adult environment.(Risch, 2001)

The results of this study suggest that genetic factors and early shared environment may influence the risk of HF and, as well as mortality risks, and that sibling HF is an important risk factor for death, also in individuals not diagnosed with HF. With previous studies having determined the existence of familial aggregation of HF(Lee et al., 2006; Lindgren et al., 2016) including those founded exclusively on biological relationships(Lindgren et al., 2018), the increased mortality risks associated with sibling HF in this study may be the cause of unrecognized heart disease. Speculatively, the underlying mechanism may also be pleiotropic genetic effects resulting in an increased risk for HF as well as malignant arrhythmia. The modality of death for which sibling HF conferred the highest relative risk was death of unknown causes, especially in younger patients. The majority of these younger patients would have been likely autopsied and with no found cause of death during this procedure may point towards a high proportion of malignant arrhythmias. The higher relative risks of death in individuals with a proband with early-onset HF is also consistent with a more likely genetic involvement.(Burton et al., 2005) Individuals with a family history of early-onset HF may benefit from clinical evaluation and screening for heart disease.

4.4.1 Strengths and weaknesses

A strength of this study is the large number of sibling and spousal pairs included and the possibility of the registers to find matched pairs. Moreover, few exclusion criteria were used and the results of the study pertain to a large portion of the Swedish population.

In addition to the complete coverage of inpatients and the Swedish public low barrier to entry health care system, the low HF hospitalization association between spouses is also an indication of a low risk of selection bias due to socioeconomic factors or family per se.

Among the limitations is the possibility of events occurring before the start of the follow-up in 1987. Furthermore, probands of the control pairs were considered eligible as regards hospitalization for HF as long as this event did not occur before that of proband of the study subjects. For that reason the effect of sibling HF on survival may be underestimated. Moreover, the follow-up did not include outpatient data. The Swedish Cause of Death Register and also death registers from other countries are often regarded as valid for the purpose of epidemiological studies of various diagnoses, including CHD.(de Faire et al., 1976; Johansson & Westerling, 2000; Mahonen et al., 2013; Merry et al., 2009). However, the overall accuracy of the Swedish Cause of Death Register has been found to exceed 91% for individuals who died before the age of 65 years.(Johansson et al., 2009) The risks for the three modalities of death in this study were reasonably congruent between younger individuals below the age of 50 years of age and older individuals.

The category of heart disease not pertaining to CHD as a cause of death has also been found to have a lower accuracy in an evaluation of the Swedish Cause of Death Register,(Johansson et al., 2009) and due to the unknown accuracy of deaths caused by HF within this category the absence of association with HF mortality may not be correct.

4.5 Strengths and limitations common to all four papers

4.5.1 Strengths

Among the general strengths were that all four studies were based on data derived from nationwide registers with the central part being the Inpatient Register that has nearly complete coverage of the Swedish population since 1987. The Inpatient Register carries a positive predictive value of 90-95% for most cardiovascular diseases. HF also bears high validity as a primary diagnosis (Ingelsson et al., 2005; Ludvigsson et al., 2011; Nilsson et al., 1994) as it was employed in these studies as an outcome or predictor variable. Diagnoses in the Inpatient Register are recorded

at time of hospital discharge allowing for attentive assessment of the patient's condition.(Ingelsson et al., 2005; Ludvigsson et al., 2011) The Swedish healthcare system is a low-cost public system funded by tax revenues and therefore both accessible to the entire population and is intended to offer the same care to the entire population. As a result, the risk for selection bias and differences in outcomes relating to care is relatively low. Another strength inherent to these registers is the lack of recall and selection bias, including the potential of female under-representation.(Pressler, 2016)

Additionally, the design with analyzing predicting and outcome variables in siblings as in most of the studies (Paper I, III and IV) as opposed to analyzes of data separated by generations, reduces the influence of different time-dependent environmental settings.

4.5.2 Weaknesses

Concerning general limitations inherent to all four studies were the use of register-based data and the lack of additional case-specific clinical information and details beyond the specific ICD-code at hand. This also pertains to the diagnosis of HF and further important details of, e.g. LVEF, NYHA class, medications, etc. However, although the number of adjusting comorbidities differed among the studies, CHD is the most common cause of HFrEF and was also frequently used as a variable for stratification. There is an absence of other specific clinical parameters in the register data, e.g. physical activity, BMI, weight, smoking, and laboratory tests although several are correlated to available covariates that were adjusted for in several of the studies, e.g. common comorbidities and measures of socioeconomic class or education. Another limitation concerns the diagnosis of cardiomyopathy, which, if repeatedly recorded as the main diagnosis reasonably decreases the probability of such patients to be recorded as diagnosed with HF. Although the number of cardiomyopathies in relation to HF of other causes is relatively low in the general population, this aspect may play a more important role among younger patients. However, analyses were stratified by the occurrence of a diagnosis of cardiomyopathy in the subject (Paper II) or in the family (Paper III and IV) and although the inclusion of cardiomyopathies rendered lower risks and heritability, the results of the corresponding analyses were congruent. An alternative approximate approach to this problem could have been to equate a primary diagnose of cardiomyopathy with HF. In all, residual confounding is to be expected. No data from primary care were used.

4.6 Conclusions

Papers I and II of this thesis conclude and confirm that family history, in the form of affected siblings or biological parents, are important risk factors for HF. This tendency for familial aggregation of HF impacts the incidence and total number of cases in all ages but the relative risk imparted is more pronounced in younger ages (Paper I). The heritability of HF was estimated to be approximately 25%, which amounts to a moderate level and in relation to the magnitude of familial risk motivates further genetic studies (Paper II).

The results from Paper III suggest that shared familial factors influence the survival of patients with HF. Poor sibling survival in HF may be an important risk factor for death in patients with HF.

Paper IV shows that sibling history of HF is associated with increased mortality risk, also in patients not diagnosed with HF.

Papers I, II and IV indicate that individuals with a family history of HF are at increased risk of HF and death, and that clinical evaluation may be considered in select categories of patients. In all these four papers, there was an absence or only slight association between the risk of HF or the risk of death and the variables included to reflect environmental exposure. Further genomic studies of HF are likely to be of great value both to determine molecular mechanisms influencing the risk of disease and prognostic aspects.

4.7 Future Aspects

Future genomic studies of disease-causing mechanisms affecting the risk of HF and mortality may also further focus on the effect potentiated by comorbidities and the possibility of pleiotropy as a potential cause of covariance. In the studies for this thesis, we principally adjusted for the main comorbidities of HF and thereby did not focus on this potential shared heritability. Further molecular studies of the risk of HF as contributed by specific risk factors, e.g. hypertension, obesity, CHD, etc. in order to form the basis for genetic risk scores is likely a valuable approach. However, with familial risk being the net result from a function of genetics and environment, further epidemiological studies may also be valuable in this regard. Moreover, from a clinical perspective, in light of the massive health burden that persists as a result of HF, the results in part from the studies of this thesis may have a potential for contribution in the present. Clinicians monitoring patients with common HF comorbidities have the opportunity to integrate the concept of family history of HF as a tool in evaluating patients at risk of HF and death.

Chapter 5. Svensk Sammanfattning

Hjärtsvikt betecknar ett syndrom som innebär att hjärtat har otillräcklig förmåga att försörja kroppen med blod. Detta kan antingen bero på att hjärtat inte kan fyllas med eller stöta ut tillräckligt med mängd blod. Patienter med hjärtsvikt har i allmänhet hög dödlighet, detta trots att stora framsteg har gjorts avseende behandlingen av hjärtsvikt, speciellt sedan 1980-talet. Femårsöverlevnaden för patienter efter att diagnostiserats med hjärtsvikt är bara ungefär 50 %.

Detta arbete och dess delarbeten tog sin utgångspunkt från de relativt sparsamma fynd genetiska studier resulterat i avseende risk för hjärtsvikt och relaterad till detta risk för död. I den vid denna tid enda genomförda familjestudien avseende ärftlighet och hjärtsvikt, the Framingham Heart Study, sågs att barn till en förälder med hjärtsvikt hade 70 % ökad risk för hjärtsvikt. Familjestudier kan ha ett stort värde för att bedöma sjukdomsrisk då de är ett mått på både arv och miljö.

Detta arbete består av fyra delarbeten, i form av registerbaserade familjestudier, som hade följande huvudmål; Vi ämnade dels att undersöka hur risken för hur första sjukhusinäggning för hjärtsvikt var sammankopplat med syskonanhopning av detta utfall (studie 1). Vi sökte också estimera heritabiliteten för hjärtsvikt samt beräkna hur hjärtsvikt hos biologiska respektive adoptivföräldrar påverkar risken för hjärtsvikt hos gällande adoptivbarn (studie 2). Vi avsåg vidare att undersöka om hjärtsviktsöverlevnad hos syskon är sammankopplade (studie 3). I den avslutande studien undersökte vi hur risken för död påverkas av att ha ett syskon som behövt inneliggande sjukhusvård på grund av hjärtsvikt (studie 4).

Samtliga dessa fyra studier var således registerstudier vars anonymiserade huvudsakligen rikstäckande information hade hämtats från Statistiska centralbyrån och Socialstyrelsen. Speciellt betydelsefulla register i alla dessa studier var Patientregistret och Flergenerationsregistret. Patientregistret innehåller bland annat information om sjukhusvårdade patienters diagnoskoder. I Flergenerationsregistret finns information om individers släktband till biologisk mor och far men även om adoptioner. I de statistiska analyser som genomfördes för dessa studier gjordes statistiska justeringar för den påverkan som kön, ålder, socioekonomiska faktorer (ej studie 3) samt viktiga sjukdomar kan ha för risken för hjärtsvikt eller död.

Studie 1 kunde baserat på 23212 hjärtsviktsfall under åren 1987-2010 konstatera att incidensen (antal fall per tidsenhet) av sjukhusinläggningar för hjärtsvikt var mer än 60 % högre hos dem som också hade ett syskon inlagt för hjärtsvikt denna period.

Denna incidenskvot var 15 gånger högre hos dem med två drabbade syskon. Denna relativa risk sammanhängandes med syskonpåverkan var högst hos unga individer under 50 års ålder.

I studie 2 följdes 21643 adoptivbarn födda 1942-1990 samt deras adoptivföräldrar samt biologiska föräldrar fram till och med 2015. Baserat 194 adoptivbarn inlagda för hjärtsvikt sågs att adoptivbarn med en drabbad biologisk förälder hade en statistiskt signifikant ökad oddskvot för sjukhusinläggning för hjärtsvikt. Ingen sådant samband fanns mellan adoptivbarn och deras adoptivföräldrar. I denna studie räknade vi också ut heritabiliteten, det vill säga den del av variationen i befolkningen som beror av genetiska faktorer, för sjukhusinläggning för hjärtsvikt. Heritabiliteten estimerades till ungefär 25 %.

Studie 3 undersökte risken för död bland 373 studiepersoner som inlagts på sjukhus med hjärtsvikt under åren 2000 till 2012. Dessa hade också tidigare ett syskon inlagt för hjärtsvikt mellan åren 2000 till 2007. Risken för död var fördubblad hos studiepersonerna med ett syskon som överlevt kortare tid än fem år efter första sjukhusinläggningen.

Studie 4 studerades risken för död under åren 1987-2012 hos 62475 studiepersoner hade som ett proband-syskon inlagd på sjukhus för hjärtsvikt denna tid. Studiepersonerna och dess syskon matchades i storleksrelation 1:5, båda för födelseår och kön, med syskonpar där korresponderande proband-syskon drabbades senare eller inte alls av sjukhusinläggning för hjärtsvikt. Studiepersonernas risk för död var ökad 20 % och detta gällde även om studiepersoner med hjärtsvikt under uppföljningstiden exkluderades.

Sammanfattningsvis sågs i dessa studier att hjärtsvikt hos syskon och biologisk förälder är kopplat till ökad risk för hjärtsvikt. Heritabiliteten för hjärtsvikt bestämdes till 25 % vilket brukar betecknas som måttlig och kan med hänsyn till risk motivera till vidare genetiska studier. Syskonhjärtsvikt sågs också vara en riskfaktor för död. Familjefaktorer, möjligen ärftliga, tycks också viktiga för prognosen hos patienter med hjärtsvikt. Förutom att detta arbete ger ökat stöd för värdet av fortsatt genetiska studier avseende risk för hjärtsvikt samt risken för död vid hjärtsvikt så kan dess resultat också vara värdefulla för att i den kliniska vardagen identifiera riskindivider.

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