Neurological and psychiatric comorbidity in patients with heart failure: Risk and prognosis

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THESIS STRUCTURE

This dissertation is based on the following five papers, which are referred to by their Roman numerals (I–V) in the text.

I. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open 2016 Nov 18;6(11)*

II. Adelborg K, Sundbøll J, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiac examination, procedure, and surgery codes in the Danish National Patient Registry: a population-based validation study. *BMJ Open 2016* Dec *9;6 (12)*

III. Adelborg K, Schmidt M, Sundbøll J, Pedersen L, Videbech P, Bøtker HE, Egstrup K, Sørensen HT. Mortality Risk Among Heart Failure Patients With Depression: A Nationwide Population-Based Cohort Study. *J Am Heart Assoc. 2016 Sep 7;5(9)*

IV. Adelborg K, Horváth-Puhó E, Ording A, Pedersen L, Sørensen HT, Henderson VW. Heart failure and risk of dementia: a Danish nationwide population-based cohort study. *Eur J Heart Fail. 2017 Feb 19(2):253-260*

V. Adelborg K, Szépligeti S, Sundbøll J, Horváth-Puhó E, Henderson VW, Ording A, Pedersen L, Sørensen HT. Risk of Stroke in Patients With Heart Failure: A Population-Based 30-Year Cohort Study. *Stroke. 2017 Apr 4* [Epub ahead of print]

INTRODUCTION

Affecting more than 37 million people worldwide, heart failure constitutes a major and growing public health issue.[1,2] In the United States and Europe, the prevalence of heart failure in the adult population is around 1%-2%, increasing steeply with advancing age to above 10% in those older than 70 years.[1,3] The lifetime risk of developing heart failure is 20%–33%.[1,4] In a cross-sectional study of patients aged ≥65 years presenting with dyspnea in the primary health care sector, 16% had unrecognized heart failure, as determined by diagnostic criteria from an expert panel, indicating that the burden of heart failure is even greater than anticipated.[5]

In past decades, the incidence of heart failure was stable or slightly declining.[6-9] Due to increasing survival rates among heart failure patients, attributable to improvements in treatments,[10,11] along with aging of the Western population, the prevalence of heart failure is rising,[12,13] and the corresponding estimated health care expenditures are expected to increase three fold during the next 15–20 years.[14,15]

HEART FAILURE DEFINITION

Several different diagnostic criteria such as the Framingham criteria,[16] Boston criteria,[17] and Gothenburg criteria[18] have been used to ascertain heart failure. According to the most recent guidelines from the European Society of Cardiology,[3] heart failure is characterized by (1) symptoms (*e.g*. ankle swelling and breathlessness), (2) signs (*e.g.* pulmonary crackles and peripheral edema), and (3) structural abnormalities (*e.g*. systolic or diastolic dysfunction) (Table 1). Patients with heart failure can broadly be divided into those with reduced left ventricular ejection fraction (LVEF) and those with preserved LVEF (≥50%) (Table 1).[3] This terminology was introduced because the two types of heart failure may involve different etiologies, characteristics, treatment, and prognosis.[3,19,20]

HEART FAILURE RISK AND PROGNOSTIC FACTORS

The term *risk* relates to the probability of an event whereas exposures increasing the likelihood of an event are *risk factors*.[21] In contrast, *prognosis* is the prediction of a disease course whereas characteristics associated with disease outcome are referred to as *prognostic factors*.[21] Thus, *risk factors* and *prognostic factors* are analogous but represent different parts of the exposure–disease–outcome association.[21] For example, ischemic heart disease represents a risk factor for heart failure[3] but also is a prognostic factor for death following the diagnosis of heart failure.[22]

Table 1. Criteria for the diagnosis of heart failure with reduced left ventricular ejection fraction and for heart failure with preserved left ventricular ejection fraction. To be diagnosed with heart failure, all 3 criteria should be fulfilled (A–C). Modified from Ponikowski et al. Eur Heart J, 2016.[3]

Criteria	Reduced ejection fraction	Preserved ejection fraction
A.	Symptoms	Symptoms
B.	Signs	Signs
C.	Left ventricular ejection fraction <50%	Left ventricular ejection fraction ≥50% and 1. Elevated natriuretic peptides and 2. Relevant structural heart disease or diastolic dysfunction

The etiology of heart failure is often multifactorial, consisting of several cardiovascular and non-cardiovascular underlying risk factors that may induce heart failure.[3] Heart failure is the end stage of conditions involving diseased myocardium, such as ischemic heart disease, toxic damage, immune-mediated and inflammatory damage, infiltration, metabolic derangements, and genetic abnormalities. In addition, abnormal loading conditions such as valvular heart disease, hypertension, and pericardial pathologies, as well as volume overload and cardiac arrhythmias, may contribute to the development of heart failure.[3]

The prognosis following a diagnosis of heart failure is serious and, with a 50% mortality rate at 5 years, resembles that of many cancers.[1,3,7,20] Heart failure is one of the most frequent causes of hospitalization among people aged ≥65 years.[23] In the United States, the total number of heart failure–related hospitalizations was 3.9 million in 2001, increasing to 4.2 million in 2009.[23] This trend was driven by an increase in secondary heart failure hospitalization such as, *e.g.*, pneumonia or renal failure, while hospitalization with primary heart failure diagnoses declined during the study period.[23] Thus, in recent years, patients with heart failure are more likely to be admitted to the hospital for comorbidities rather than for worsening heart failure. Prognostic factors in heart failure include atrial fibrillation, anemia, chronic kidney disease, peripheral artery disease, and diabetes mellitus.[22]

HEART FAILURE PATHOPHYSIOLOGY

Heart failure is a chronic condition that often is irreversible; however, it may be transient due to conditions such as uncontrolled atrial fibrillation. The symptoms and signs in patients with heart failure arise from compensation in the early stages of the disease, adaptations to maintain cardiac output. Activation of the renin–angiotensin–aldosterone system and the sympathetic nervous system leads to vasoconstriction and sodium and water retention, which is beneficial in the short term, ensuring that blood is directed to vital organs,[24] and improves myocardial contractility and heart rate, restoring cardiac output.[24] On the other hand, these pathophysiological changes may have long-term deleterious effects, including ventricular remodeling and further decline in myocardial dysfunction.[24]

COMORBIDITY IN HEART FAILURE

Comorbidity is frequent in patients with heart failure.[23] Comorbidity can be defined as diseases present at the time of heart failure diagnosis or later but not being a direct consequence of heart failure.[25] In an analysis from the Nationwide Inpatient Sample database in the United States, hospitalized heart failure patients in 2009 had on average six comorbid conditions.[23] The heart failure patients had not only a high prevalence of various cardiovascular conditions but also a high prevalence of non-cardiac conditions such as diabetes mellitus (41%), mental illness (38%), renal failure (40%), chronic obstructive pulmonary disease (30%), and anemia (30%).[23] The presence of comorbid conditions may affect prognosis and choice of treatment (*e.g.* angiotensin-converting enzyme inhibitors and beta blockers are used with caution in patients with renal disease and chronic pulmonary disease, respectively).[3,20] Therefore, the European Society of Cardiology[26] and the American Heart Association/American College of Cardiology[20] stress several knowledge gaps in the treatment and outcome assessment of heart failure–associated comorbidities that should be prioritized in future research.

DEPRESSION IN HEART FAILURE

In a 2006 meta-analysis of 27 studies, the aggregated prevalence of depression among heart failure patients was 22%, equivalent to a 2–3-fold increased risk of depression relative to the general population.[27] The analysis also found that the prevalence of depression in patients with heart failure varies substantially (from 9% to 60%), which may reflect different depression assessment methods or depression definitions, discrepancies in heart failure severity classification, and variable inclusion criteria.[27] In the same meta-analysis, seven studies reported on rates of health care use and found a higher rate among those with depression than those without depression. In addition, eight studies investigated the association between depression and mortality and associated cardiac events, documenting a 2.1-fold higher rate [pooled adjusted risk ratio=2.10; 95% confidence interval (CI), 1.71−2.58] among those with depression compared to those without depression. Similarly, another meta-analysis from 2014 also provided evidence that depression was a predictor for all-cause mortality in patients with heart failure [overall adjusted hazard ratio (aHR)=1.51; 95% CI, 1.19−1.91].[28] Subgroup analysis revealed that major depression was associated with increased all-cause mortality (aHR=1.98; 95% CI, 1.23−3.19) but that mild depression was not (aHR=1.04; 95% CI, 0.75−1.45). Consistent with this result, a 2016 meta-analysis of 26 studies reported a pooled aHR for all-cause mortality of 1.40 (95% CI, 1.22−1.60).[29] Of note, the studies included in the meta-analyses were limited by small sample sizes, inclusion of selected patients, short follow-up period, inadequate adjustment for confounding factors, and the inability to stratify their analyses into subgroups of heart failure patients. The main focus of a majority of the studies was to assess the prognostic impact of depression diagnosed after the diagnosis of heart failure, and the impact on pre-admission depression was less explored. In addition, no previous studies included routinely collected hospital-based depression diagnoses from psychiatrists. The mechanisms of heart failure and depression share several overlapping features, which may contribute to the high mortality of heart failure patients with depression.[30,31] Depression is characterized by activation of the hypothalamic–pituitary–adrenal axis,[32] which may augment the neurohormonal activation inherent to heart failure. Patients with depression have higher levels of inflammatory markers such as interleukin 1,[33] interleukin 6,[34] tumor necrosis factor,[35] interferon gamma,[36] and acute-phase response,[37] which may worsen cardiac dysfunction. The threshold for developing ventricular arrhythmias may be lowered in those with depression relative to those without depression because of a depression-associated decrease in heart rate variability[38] and as a

side effect of antidepressants, particular tricyclic antidepressants.[39] Finally, depression has been linked to abnormal platelet function,[40] lower adherence to medication,[41] a more sedentary lifestyle, and a higher suicide rate compared to patients without depression.

Although several observational studies have suggested an association of depression with heart failure mortality, results from randomized controlled trials of heart failure patients treated with selective serotonin reuptake inhibitors have generally been neutral.[42,43] The SADHART-CHF study from the United States assessed outcomes of 12 weeks of sertraline treatment or placebo in 469 New York Heart Association (NYHA) class II–IV heart failure patients with depression and LVEF ≤45%.[42] Compared with placebo, sertraline did not decrease the depression score or the risk of a cardiovascular composite outcome.[42] In line with this finding, the MOOD-HF study, conducted in Germany, randomized 372 NYHA class II–IV heart failure patients with LVEF <45% to either 24 weeks of escitalopram or placebo and showed no difference in all-cause death or hospitalization rates and no improvement in depression.[43] Inclusion of a high proportion of patients with mild to moderate depression in these studies could partly explain the lack of positive findings; selective serotonin reuptake inhibitors are efficient in reducing depressive symptoms only in patients with very severe depression.[44] In addition, the SADHART-CHF study and the MOOD-HF study evaluated changes in depression symptoms using the Hamilton Depression Rating Scale and Montgomery-Åsberg Depression Rating Scale; however, the Hamilton Depression Rating Scale in particular appears to be inappropriate for assessing depression severity in elderly patients with medical conditions.[45] Furthermore, the discrepancy between the observational studies and the randomized studies indicates that the observational studies thus far have not sufficiently specified depression exposures and heart failure populations with enough detail to guide development of positive randomized controlled trials. Randomized studies also usually restrict inclusion to younger patients with a low prevalence of comorbidity whereas observational studies often involve entire patient populations without excluding older and frail patients. Finally, randomization limits confounding, but confounding is always a concern in observational studies, potentially explaining disparities in results between observational and randomized studies.[46]

NEUROLOGICAL COMPLICATIONS OF HEART FAILURE

Dementia and stroke are frequent neurological diseases, which to some extent share risk factors with heart failure.

Dementia

Dementia is a burdensome health condition primarily affecting the elderly.[47,48] It is characterized by a decline in cognition, with Alzheimer's disease being the most common form (about 50% of all cases), followed by vascular dementia (about 25%) and mixed Alzheimer's disease and vascular dementia.[47] In 2015, the prevalence of dementia was approximately 47 million people worldwide.[48] Owing to the aging of the Western population, a striking increase in the burden of dementia will occur in the coming decades, reaching 76 million in 2030 and 135 million in 2050.[48] Risk factors for dementia include age, lack of physical activity, smoking, obesity, low educational level, traumatic brain injury, alcohol abuse, atherosclerosis, diabetes mellitus, hypertension, depression, and genetic mutations.[49,50] There is, however, a critical need to identify other potentially modifiable risk factors for dementia.

Few studies have examined the risk of dementia among heart failure patients relative to the general population.[51,52] In two small cohort studies from Sweden and Finland, heart failure in late life was clearly associated with a 1.8–2.1-fold increased risk of all-cause dementia. More data on the association between heart failure and dementia are needed.

Heart failure is characterized by several risk factors, which *per se* also are linked to a higher dementia risk.[53] Low cardiac output may reduce cerebral blood flow, contributing to cerebral hypoperfusion, which in the long term could impair cerebral autoregulation and cause white matter injury.[54] Neurohormonal activation related to heart failure may trigger inflammation and cerebral microvascular dysfunction. These mechanisms could cause chronic cerebral hypoxia and contribute to dementia pathogenesis.[55]

Stroke

As for dementia, stroke is a leading cause of disability and death. In the United States, approximately 795,000 patients experience a stroke each year.[56] Of all strokes, 87% are ischemic in origin, 10% are intracerebral hemorrhages (ICHs), and 3% are subarachnoid hemorrhages (SAHs).[56] Risk factors for stroke include age, hypertension, hypercholesterolemia, myocardial infarction, smoking, diabetes, chronic kidney disease, atrial fibrillation, obesity, physical inactivity, and depression.[56] Accumulating evidence also suggests that heart failure is a risk factor for stroke,[57-59] but the evidence is less clear. Three studies have indicated that stroke risk among patients with heart failure is particularly high in the short term, but conclusions are conflicting regarding the long term and associations with hemorrhagic stroke.[57-59] In addition, these studies have been hampered by their short follow-up periods, small sample sizes that precluded stratification by or adjustment for atrial fibrillation, and the inability to separately assess ischemic and hemorrhagic stroke outcomes. Considering these inconsistencies, there is a need for more research on this issue.

The association between heart failure and stroke has been hypothesized to be related to several putative mechanisms.[60,61] One potential mechanism involves thrombus formation in the left ventricle and in the left atrium with subsequent embolization to the brain.[60,61] Moreover, shared cardiovascular risk factors and increased activity of procoagulant factors, aggregation of thrombocytes, and endothelial dysfunction among patients with heart failure are other potential explanatory pathways in the association between heart failure and stroke.[60,61] Also, with ischemic heart disease and atrial fibrillation or atrial flutter, heart failure patients often require treatment with antiplatelets and anticoagulants, which protects against ischemic stroke at the expense of an increased risk for hemorrhagic stroke. In contrast, heart failure is often accompanied by low blood pressure, which likely attenuates potential associations with stroke.

The association between heart failure and ischemic stroke has led to the hypothesis that heart failure patients in sinus rhythm, in addition to those with atrial fibrillation or atrial flutter, would benefit from anticoagulants, but the results from the HELAS,[62] WARCEF,[63] and WASH[64] trials have been neutral. A substudy analysis of the WARCEF trial, however, recently indicated that patients receiving high-quality anticoagulation with warfarin may benefit from the treatment.[65] Of importance, the role of direct-acting oral anticoagulants is unknown but is currently being investigated in the COMMANDER-HF study (with estimated study completion in May 2018),[66] assessing the effectiveness and safety of

rivaroxaban *vs*. placebo in reducing the risk of death, myocardial infarction, or stroke in patients with heart failure and coronary artery disease without atrial fibrillation.

DANISH HEALTH REGISTRIES

Worldwide, health care data are becoming increasingly available from sources such as disease registries, electronic medical record systems, epidemiological surveillance registries, and administrative registries.[67] These data sources facilitate cost-effective research to improve patient treatment and help decision- and policy-making in the health care system. As the use of health care data is increasing, evaluating the strengths and limitations of these data sources becomes imperative.[68] Thus, assessing the validity of data sources is essential.[46,69]

Validation studies may promote a positive feedback loop, motivating clinicians to improve coding in the registries because data from the registries are used to improve patient outcomes.[70] Results from validation studies can be used in bias analyses, evaluating the potential impact of misclassification on study results.[70]

The importance of validation studies has been highlighted in international guidelines,[71] epidemiological textbooks,[46] position papers from pharmacoepidemiological societies,[72] and editorials in *Epidemiology*[73] and *Clinical Epidemiology.*[70]

Denmark is unique worldwide for the richness of its population-level health care databases that offer the possibility of conducting longitudinal studies with long-term follow-up.[74] The cornerstone of Danish registries is the Civil Registration System, which enables cross-linkage of data from the registries.[75] The Danish National Patient Registry (DNPR)[76] has been used in many cardiovascular epidemiology studies.[76] Several validation studies of algorithms to identify cardiovascular diagnoses have been published,[76] but as documented in a recent review of the DNPR, many cardiovascular diagnoses remain to be validated.[76] The DNPR has been the data source to an even lesser extent in studies on cardiac interventions, which correspondingly mirrors a limited knowledge about the accuracy of these variables.[76] The diagnosis of heart failure in the DNPR has been evaluated in a few validation studies. Using information in the medical records or clinical examination applying heart failure criteria as the reference standard, the positive predictive value (PPV) has previously been estimated with large variations, ranging from 80% to 100%.[77-79] Thus, great uncertainty remains about whether the validity of the diagnosis of heart failure is moderate (around 80%) or high (above 90%).

Taken together, validation studies covering all major cardiovascular diagnoses, including heart failure, as well as cardiac interventions in the DNPR are needed and would provide a benchmark for future studies within cardiovascular epidemiology.

HYPOTHESES

Epidemiological studies relying on routinely collected health care data require valid coding to identify study cohorts such as patients with heart failure; therefore, we examined the PPV of major cardiovascular diagnoses (study I) and cardiac interventions (study II) in the DNPR. In addition, this thesis explores the following hypotheses:

- Depression is an adverse prognostic factor for all-cause mortality (study III) among patients with heart failure.
- Heart failure is a risk factor for dementia (study IV).
- Heart failure is a risk factor for stroke (study V).

METHODS

SETTING

In Denmark, all residents have free access to universal tax- and government-supported health care services at general practitioners and hospitals.[75] Upon birth or immigration, residents are assigned a unique and permanent identification number that allows unambiguous linkage of data from the various registries.[75] In Denmark, all patients who are suspected to have heart failure and those with heart failure in the primary care setting should be referred to a hospital department of cardiology to receive a relevant diagnostic work-up, including echocardiography, coronary angiogram, and blood samples, to ensure appropriate treatment. Heart failure patients are most often followed and treated in hospital outpatient clinics. In Denmark, dementia is typically diagnosed and treated both by general practitioners and in departments of neurology and psychiatry. Care for and treatment of stroke patients is also provided by public hospitals.

DATA SOURCES

The studies included in the dissertation are based on prospectively collected data from nationwide population-based registries, which are described below.

Danish Civil Registration System

This registry is updated electronically on a daily basis and has been used since 1968 to track demographic data and changes in vital status and migration for all Danish residents.[75]

Danish National Patient Registry

The DNPR holds data on all residents admitted since 1977 to Danish somatic hospitals and all visits since 1995 to hospital outpatient clinics and emergency room departments.[76] Each admission is registered by one primary diagnosis and one or more secondary diagnoses classified according to the *International Classification of Diseases, Eighth Revision* (ICD-8) until the end of 1993, and *Tenth Revision* (ICD-10) thereafter.

The Registry of Causes of Deaths

Since 1943, this registry has been used to record dates and immediate and underlying causes of death in Denmark.[80]

The Danish Heart Failure Registry

This registry, launched in February 2003, is a part of the Danish Clinical Registries,[81,82] which is a nationwide initiative aimed at monitoring and improving the quality of care for several patient groups, including patients with heart failure. All heart failure patients admitted to a cardiology department or outpatient heart failure clinic in Denmark are consecutively included in the Danish Heart Failure Registry.[83] In contrast to registration of heart failure in the DNPR, where patients are recorded based on ICD codes, only patients who meet one or more of the well-defined criteria, including symptoms/objective signs indicative of heart failure, and those with clinical response to treatment for heart failure are enrolled in the registry.

The Danish National Prescription Registry

Since 1995, this registry has held information on all redeemed prescriptions, including package size, strength, form and Anatomical Therapeutic Chemical code.[84]

DANISH PSYCHIATRIC CENTRAL RESEARCH REGISTER

All patients admitted to psychiatric hospitals and psychiatric wards in general hospitals in Denmark are included in this registry.[85] Since 1995, information on all psychiatric outpatient contacts has been included. Information on diagnoses is based on the ICD system.

Danish registers on personal labor market affiliation

Statistics Denmark administers an extensive number of registries, including nationwide registers of labor market affiliation. These registries contain information on highest completed education, employment, and personal income, with annual updates since 1980.[86]

STUDY DESIGNS

We conducted two validation studies and three cohort studies.

STUDY POPULATIONS

In all studies, the study populations were identified through the DNPR. For studies I-II, we randomly sampled patients with cardiovascular diagnoses, examinations, procedures, and surgeries in the study period using pre-specified algorithms defined in appendices I-II. For studies III–V, we included patients with a first-time hospitalization for

heart failure using primary and secondary diagnoses (*e.g.* heart failure secondary to myocardial infarction or atrial fibrillation). In study III, we also identified a subset of patients from the Danish Heart Failure Registry. In studies IV and V, we excluded patients with previous dementia and stroke or transient ischemic attack before the heart failure admission date, respectively, to examine first-time events only.

Depression exposure

In study III, the exposure was a history of depression any time before the heart failure admission date. Depression was defined as a hospital-based discharge diagnosis recorded in the DNPR or the Danish Psychiatric Central Research Register (DPCR). We categorized patients according to depression severity with ICD-10 codes for mild, moderate, and severe depression (where patients with more than one diagnosis were assigned the most severe depression group), and timing of depression in relation to the hospitalization for heart failure (depression diagnosed within 1, 2, and 3 years before heart failure admission date). Patients with depression treated exclusively by general practitioners are not captured in the Danish registries; thus, we expanded our exposure definition by including data on redeemed prescriptions for antidepressants as a proxy for depression to increase the sensitivity for depression. We defined patients with no depression diagnosis and less than one redeemed prescription for antidepressants as the reference group. In addition, we categorized patients as those with or without a depression diagnosis and further subdivided these patients into those with less than or more than one prescription for antidepressants. The ICD-10 code for a single depressive episode in the DPCR has been validated with an interview using the Schedules for Clinical Assessment in Neuropsychiatry as the reference standard. The overall PPV was 75%, representing PPVs of 83% for severe depression, 76% for moderate depression, and 65% for mild depression.[87] The PPV of depression in the DNPR is unknown.

OUTCOMES

REFERENCE STANDARD FOR CARDIOVASCULAR DIAGNOSES AND INTERVENTIONS

In studies I-II, the primary outcome was PPVs for the cardiovascular diagnoses and intervention recorded in the DNPR. Information in the medical record review was the reference standard.[88] Three physicians (K.A, J.S, and T.M.) reviewed and adjudicated all the medical records (unblinded) and determined whether the codes in the DNPR were correct.

Mortality

All-cause mortality ascertained from the Danish Civil Registration System was the primary outcome in study III.

Dementia

In study IV, the primary outcome was all-cause dementia recorded in the DNPR or DPCR. Secondary outcomes were Alzheimer's disease, vascular dementia, and other dementias. A validation study of 197 in- and outpatients with dementia recorded in the DNPR and the DPCR revealed a PPV of 86% for all-cause dementia and 81% for Alzheimer's disease, whereas the PPV was markedly lower for other specific dementia subtypes.[89]

Stroke

In study V, the primary outcome was stroke, specifically ischemic stroke, ICH, and SAH ascertained using the DNPR. In a validation study by Krarup *et al.*, first-time stroke diagnoses recorded in the DNPR diagnosed in 1998−1999 were validated using the World Health Organization stroke definition as the standard reference.[90] A total of 264 patients were identified as potential stroke cases with PPVs of 97% ischemic stroke, 74% for ICH, and 67% for SAH. They also reported that the unspecified stroke diagnosis was commonly used (44% of all stroke diagnoses in the study) and that a majority of these patients (approximately 60%) were truly patients with ischemic stroke. Therefore, we classified unspecified strokes as ischemic stroke in the main analyses.

GENERAL POPULATION COMPARISON COHORTS

To contribute to the understanding of heart failure as a risk factor for dementia and stroke in a population context, we took advantage of the unique opportunities of the Danish Civil Registration System,[75] forming two general population comparison cohorts (studies IV-V). We matched each heart failure patient with up to five individuals without a previous diagnosis of heart failure from the general population. Matching strategies include sampling with replacement (that is, individuals from the general population could serve as comparators for more than one heart failure patient) or sampling without replacement in random or chronological order.[91,92] We used matching with replacement for two reasons: it is assumed to be superior to matching without replacement in producing unbiased comparison cohorts, and no comparators were available for using matching without replacement for approximately 30% of our heart failure patients because of their advanced age.[91,92] If individuals from the general population comparison cohort developed heart failure during follow-up, they were maintained in the general population comparison cohort to avoid informative censoring (equivalent to the intention-to-treat principle in randomized controlled trials).[46]

COVARIABLES

We collated data from the DNPR on a number of covariables to characterize the study cohorts, to adjust our analyses for potential confounders, and to examine potential disparities in PPVs and risks across subgroups. In general, most of the discharge diagnoses of the covariables have high PPVs in the DNPR.[79] Lifestyle factors such as alcohol abuse and smoking are severely underreported in the DNPR,[93] indicating the necessity of also using other data sources for assessment of these covariables.

STATISTICAL ANALYSES

The statistical analyses used for the studies are described in detail for the individual studies in appendices I–V. For studies I-II, we applied the Wilson score method for CI calculation.[94] In all time-to-event analyses (studies III–V), we followed patients from admission date for heart failure until the date of the event, death, emigration, or end of follow-up, whichever came first. The Kaplan–Meier method was implemented, and we graphically illustrated survival curves for the depression exposure groups. For dementia and stroke outcomes, the cumulative incidence (risk) function was used to calculate absolute rates, accounting for death as a competing risk. In study III, we used Cox regression analyses, comparing heart failure patients with a history of depression to those without a history of depression. For the matched-cohort studies (studies IV-V), we used stratified Cox regression analysis[95] (that is, sustaining the age, sex, and calendar period matching in the analyses), comparing the risk of an event in heart failure patients with the general population cohorts. Moreover, we also calculated standardized incidence ratios as a measure of relative risks.[46] To account for confounding, we controlled for matching factors by study design, adjusted the analyses, and stratified the analyses by potential confounders.

In study III, we used data from the Danish Heart Failure Registry to adjust our analyses for smoking and alcohol abuse in a complete-case analysis and applied multiple imputation to handle missing data. Multiple imputation with chained equations was used to create 25 data sets with imputed values for smoking and alcohol, assuming that data were missing at random.[96] In the imputation model, we included the covariables from the main model, additional covariables as described in Appendix III, the outcome indicator, and the Nelson–Aalen cumulative baseline hazard.[96]

All statistical analyses were performed using Stata version 14.1 (Stata Corp, College Station, TX, USA) or SAS version 9.2 (SAS Institute, Cary, NC, USA). The individual studies were approved by the Danish Data Protection Agency. According to Danish legislation, informed consent from patients or ethics committee approval is not required for registry-based studies.

SENSITIVITY ANALYSES

A sensitivity analysis is a repetition of the analyses, introducing alternative methodological decisions to those made in the main analysis.[46] The purpose of sensitivity analyses is to ensure that findings are robust to the methodological decisions (Table 3). Shortcomings of our sensitivity analyses included the necessity of shortening the study periods due to limited data availability (*e.g.* in stratified analyses of intensive care admission, where data in the DNPR on intensive care unit admission are available from 2005 onwards only), and the basis of the analysis on complete cases only (*e.g.* in multivariable analysis, where education was included in the regression models).

RESULTS

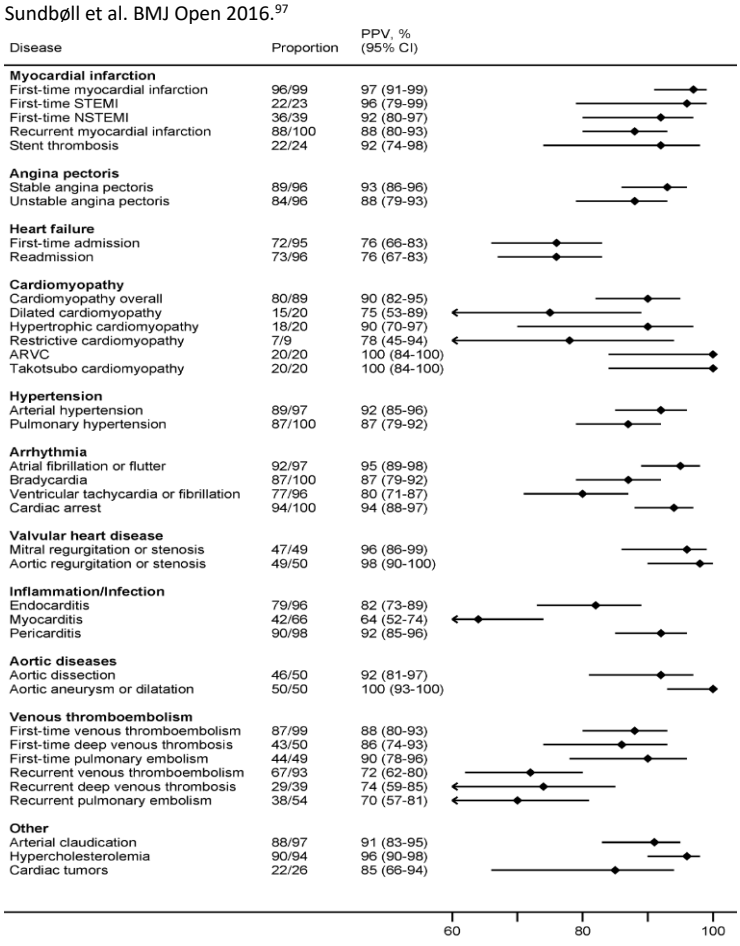
The main findings from studies I–V are presented in the following section and in detail in appendices I–V.

PPV OF CARDIOVASCULAR DIAGNOSES AND INTERVENTIONS IN THE DNPR (STUDIES I–II)

Of the total sample, 2153 medical records (97%) for patients with various cardiovascular diagnoses and 1333 medical records (98%) from patients who underwent cardiac interventions were available for review.

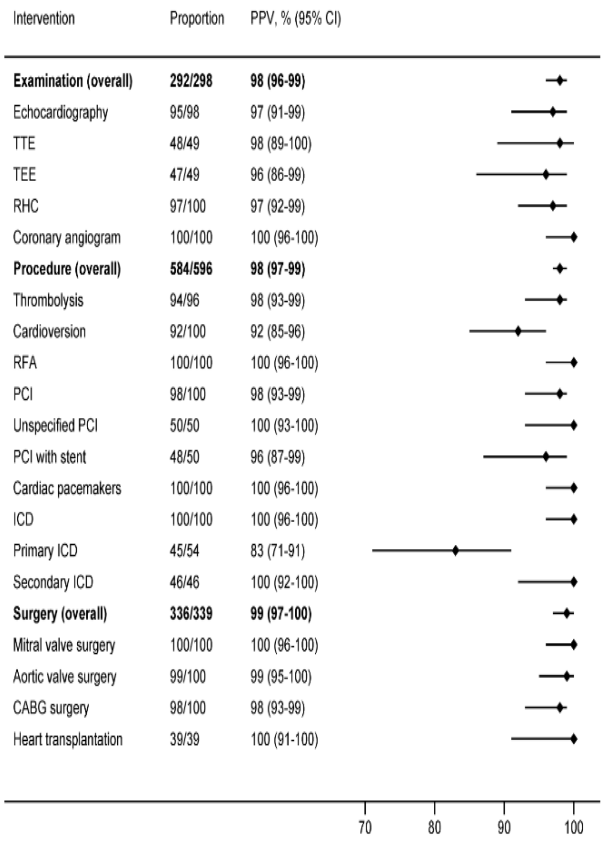
The PPVs ranged from 64% to 100% (Figures 1-2). For the cardiovascular diagnoses, a majority of the PPVs were above 85%, except for first-time and readmission for heart failure (76% for both), dilated cardiomyopathy (75%), restrictive cardiomyopathy (78%), ventricular tachycardia or fibrillation (80%), myocarditis (64%), and recurrent venous thromboembolism (72%) (Figure 1). For the cardiovascular examinations, procedures, and surgeries, all PPVs were above 85% except for primary implantable cardiac defibrillators (83%) (Figure 2). The PPVs varied, although not substantially, across age groups, sex, calendar year, hospital type (regional or university hospital), type of diagnosis (primary or secondary), and type of hospital contact (inpatient or outpatient clinic visit).

Figure 1. Positive predictive values for major cardiovascular diagnoses recorded in the Danish National Patient Registry, 2010−2012. Modified from Sundbøll et al. BMJ Open 2016.[97]



Abbreviations: ARVC, *arrhythmogenic right ventricular cardiomyopathy;* PPV, positive predictive value; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-STEMI

Figure 2. Positive predictive values for cardiac interventions recorded in the Danish National Patient Registry, 2010−2012. Modified from Adelborg et. al. BMJ Open 2016.[98]



Abbreviations: CABG, coronary artery bypass graft surgery; CI, confidence interval; ICD, implantable cardiac defibrillator; PCI, percutaneous coronary intervention; RFA, radiofrequency ablation; RHC, right heart catheterization; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography

PROGNOSTIC IMPACT OF DEPRESSION ON MORTALITY (STUDY III)

Patients with a history of depression diagnosis had higher absolute mortality rates than those without depression prior to heart failure (1-year, 36% *vs*. 33% and 5-year, 68% *vs*. 63%). This difference yielded a multivariable adjusted mortality rate ratio (MRR) of 1.03 (95% CI, 1.01−1.06) (Table 4) and similar MRRs for mild, moderate, and severe depression. The results remained consistent when the analysis was restricted to patients with recent depression diagnoses. The associations increased slightly when redefining depression using a combination of depression diagnoses and use of antidepressants (Table 4). Analysis of cause-specific deaths revealed that patients with previous depression (defined as either a depression diagnosis or at least one prescription of antidepressant) had a higher non-cardiovascular mortality (adjusted MRR, 1.19; 95% CI, 1.17−1.21) and a slightly higher cardiovascular mortality (adjusted MRR, 1.09; 95% CI, 1.06−1.11) than patients without previous depression. Specifically, the risk of dying from arrhythmia was only slightly higher among those with depression than those without depression (adjusted MRR, 1.08; 95% CI, 1.01−1.16).

In a subset of patients, the MRRs changed by LVEF, with adjusted MRRs of 1.17 (95% CI, 1.05−1.31) for LVEF ≤35%, 0.98 (95% CI, 0.81−1.18) for LVEF 36%–49%, and 0.96 (95% CI, 0.74−1.25) for LVEF ≥50% (Figure 3). The associations were broadly unchanged across age group and sex and in patients with different heart failure causes (Figure 3)

HEART FAILURE AND RISK OF DEMENTIA (STUDY IV)

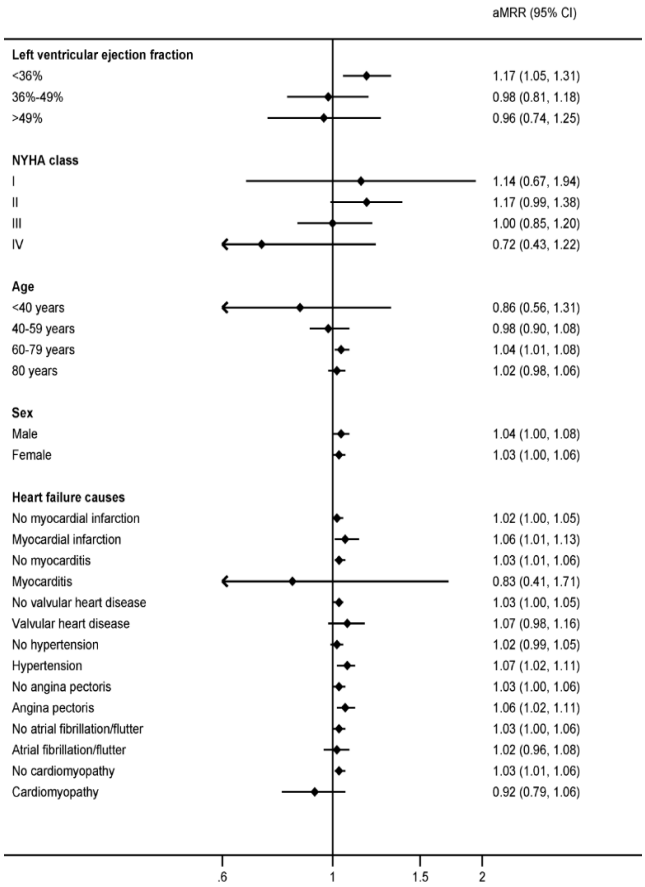
This study included 324,418 heart failure patients and 1,622,079 individuals from the general population (median age=77 years, 52% male). Relative to the general population comparison cohort, the all-cause dementia rate was increased among heart failure patients (aHR=1.21; 95% CI, 1.18−1.24) (Figure 4). This increase was mainly driven by higher risks for vascular dementia (aHR=1.49; 95% CI, 1.40−1.59) and other dementias (aHR=1.30; 95% CI, 1.26−1.34), while there was no association with Alzheimer's disease (aHR=1.00; 95% CI, 0.96−1.04). The associations were stronger in men than in women and in heart failure patients under age 70 than in those ≥70 years. The standardized incidence ratio estimates were comparable to the unadjusted HRs.

Table 4. The association between depression and all-cause mortality, by depression diagnoses and use of antidepressant as proxy for depression. Adapted from Adelborg K et al. JAHA 2016.[99]

Depression diagnosis	Use of antidepressants	Unadjusted MRR (95% CI)	Adjusted MRR (95% CI)
No depression	N/A	Reference	Reference
Depression (n=9636)	N/A	1.14 (1.12–1.17)	1.03 (1.01–1.06)
Mild (n=1379)	N/A	1.27 (1.20–1.35)	1.06 (1.00–1.13)
Moderate (n=2914)	N/A	1.16 (1.11–1.21)	1.03 (0.99–1.08)
Severe (n=1305)	N/A	1.05 (0.99–1.12)	1.02 (0.96–1.09)
	Non-use (n=156,168)	Reference	Reference
No depression	Former use (n=16,457)	1.08 (1.06–1.10)	1.07 (1.05–1.09)
	Current use (n=22,262)	1.37 (1.34–1.39)	1.21 (1.19–1.23)
	Non-use (n=1912)	1.07 (1.02–1.13)	1.00 (0.95–1.06)
Depression	Former use (n=2007)	1.07 (1.01–1.13)	1.00 (0.95–1.06)
	Current use (n=5717)	1.28 (1.25–1.32)	1.10 (1.06–1.13)

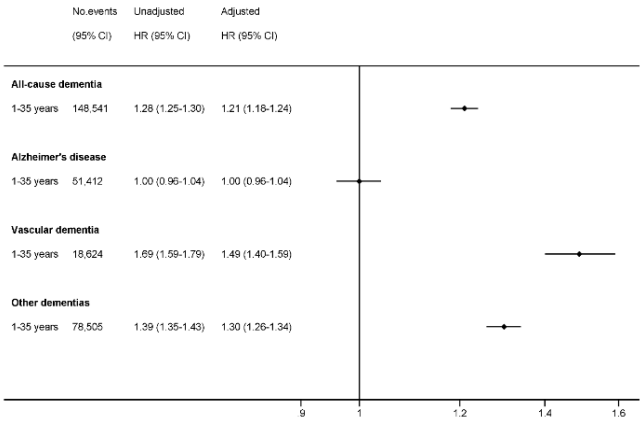
Abbreviations: CI, confidence interval; MRR: mortality rate ratio

Figure 3. Association between a history of depression and all-cause mortality in subgroups of heart failure patients. Modified from Adelborg et al. JAHA 2016.[99]



Abbreviations: aMRR, adjusted mortality rate ratio; CI, confidence interval; NYHA class, New York Heart Association functional class

Figure 4. Rates of dementia in the heart failure and general population comparison cohorts during 1–35 years of follow-up. Modified from Adelborg et al. Eur J Heart Fail 2017.[100]

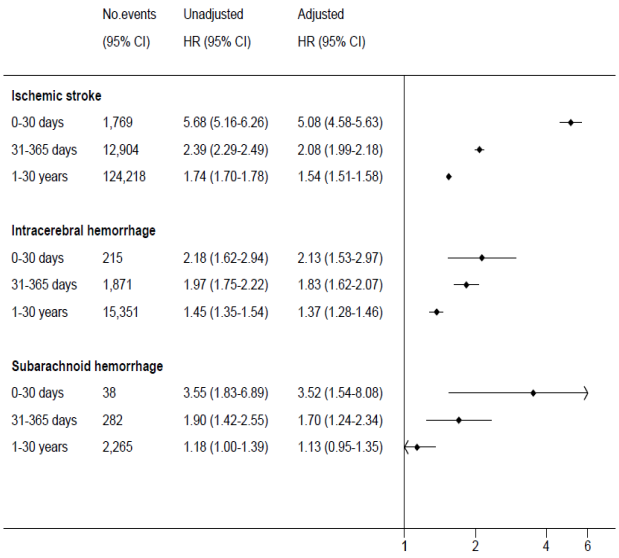


Abbreviations: CI: confidence interval; HR: hazard ratio

HEART FAILURE AND RISK OF STROKE (STUDY V)

In study V, we identified and followed 289,353 patients with heart failure and 1,446,765 individuals from the general population matched for age, sex, and calendar year. The one-year rates among heart failure patients were 1.4% for ischemic stroke, 0.2% for ICH, and 0.03% for SAH. The 30-day adjusted stroke rate ratio (aSRR) was 5.08; 95% CI, 4.58−5.63 for ischemic stroke, 2.13; 95% CI, 1.53−2.97 for ICH, as well as 3.52; 95% CI, 1.54−8.08 for SAH (Figure 5). Between 31 days and 30 years, heart failure remained positively associated with all stroke subtypes (1.5- to 2.1-fold for ischemic stroke, 1.4- to 1.8-fold for ICH, and 1.1- to 1.7-fold for SAH) relative to the general population comparison cohort.

Figure 5. Rates of stroke in the heart failure and general population comparison cohorts.
Modified from Adelborg et al. Stroke 2017.[101]



Abbreviations: CI: confidence interval; HR: hazard ratio

The associations with all stroke outcomes were largely the same for men and women while the aSRR increased with decreasing age. In analyses restricted to those without atrial fibrillation or atrial flutter, heart failure was still associated with ischemic stroke (30 days: aSRR=5.49; 95% CI, 4.95−6.10; 31–365 days: aSRR=2.18; 95% CI, 2.09−2.28; and 1–30 years: aSRR=1.52; 95% CI, 1.49−1.55). When using intensive care unit stay and length of hospital stay as proxies for heart failure severity, the association between heart failure and one-year risk of ischemic stroke was higher for patients admitted than for those not admitted to the intensive care unit, and for those with length of stay >7 days than for ≤7 days.

DISCUSSION

MAIN FINDINGS

This dissertation using population-based Danish medical databases provides the following insights. First, codes for the vast majority of cardiovascular diagnoses and cardiac interventions had high PPVs in the DNPR during 2010−2012, while the PPVs for conditions that included recurrent events, heart failure, and myocarditis were somewhat lower. Second, among patients with heart failure, prior depression diagnoses were not associated with all-cause mortality; however, in subgroups of heart failure patients with LVEF≤35% and when extending the depression definition combining depression diagnosis with at least one redeemed prescription for antidepressants, those with a history of depression had a higher all-cause mortality rate than those without a history

of depression. Third, as compared with general population comparison cohorts matched for age, sex, and calendar year, heart failure was associated with increased rates of all-cause dementia, as well as with markedly increased short-term and long-term rates of ischemic and hemorrhagic stroke.

Comparison with existing literature

Below, we discuss our findings in the context of the literature.

PPV of cardiovascular diseases and cardiac interventions in the DNPR

Our results confirm previous validation studies, using the DNPR as a data source, on myocardial infarction (PPV∼92%–100%),[102,103] arterial hypertension (PPV∼88%),[104] atrial fibrillation or atrial flutter (PPV∼93%–99%),[105,106] and first-time venous thromboembolism (PPV∼75%–90%).[107,108] In line with a previous study, our PPV for recurrent venous thromboembolism was lower than for first-time venous thromboembolism,[108] indicating that differentiation is challenging between true recurrent events and previous events based on ICD codes in the DNPR.

The PPV for heart failure in our validation study was slightly lower than reported previously.[77-79] The PPV for heart failure was also lower than for several other cardiovascular diseases. It could have been interesting to investigate whether true-positive and false-positive cases differed in systematic ways; however, because of the relatively low numbers of false-positive cases, inferences based on such analyses would not be sound. As compared to myocardial infarction, for example, the diagnosis of heart failure is fairly complex because the nonspecific symptoms often progress over days to weeks and it is based on several criteria. During our medical record review, we observed that some patients had prevalent heart failure but were categorized as false positive because we validated first-time events.

In our study, the PPV for unstable angina pectoris was higher than in a previous study with inclusion of patients from 1993−2003 (PPV=42%),[109] which could trace to the implementation of strict criteria for myocardial infarction and unstable angina pectoris during our study period.[110] We found a considerably higher PPV for cardiac arrest than in a previous study (PPV=50%).[109] The reason for this discrepancy might be the fact that the previous study could not retrieve the medical records for one third of the cardiac arrest patients and that the authors also sampled outpatients, in whom cardiac arrest occurs very rarely.[109] Our PPV estimates of stable angina pectoris, cardiomyopathies, bradycardia, valvular heart disease, endocarditis, myocarditis, aortic diseases, cardiac tumors, and cardiac interventions recorded in the DNPR are novel findings. It is important to emphasize that our validation studies included only cardiovascular diagnoses and cardiac interventions during 2010−2012 and will therefore not necessarily translate to earlier study periods.

Depression as a prognostic factor in heart failure

Numerous studies have examined the association between depression and mortality among patients with heart failure.[27-29] Studies conducted to date were highly heterogeneous in terms of characteristics of the study population, heart failure severity, measures to assess depression (*i.e.* self-reported questionnaires, prescription of antidepressants, clinical interviews, or registry-based diagnoses), and duration of follow-up. Despite these differences, most studies have consistently linked depression with all-cause mortality in patients with ischemic[111,112] and non-ischemic heart failure,[113] both inpatients[114,115] and outpatients.[116-118] The finding seems consistent regardless of geographical region as it has been identified in cohorts from Europe,[111,114,116] Japan,[112] and the United States.[115,119]Although preserved LVEF and depression have not been widely studied, the connection to increased mortality also seems uniform in these patients.[112] The vast majority of previous studies have investigated the impact of depression among patients with reduced LVEF; one study from the US indicated that heart failure with high levels of pro-brain natriuretic peptide – a proxy for those with more severe heart failure – had a higher mortality associated with depression than those with normal pro-brain natriuretic peptide levels.[112] In accordance with that study, our data also suggested that depression was predictive only of increased mortality in those with severely impaired LVEF. Patients with a low LVEF may be more susceptible to the potential underlying mechanisms discussed in section 2.5 than patients with higher ejection fraction, *e.g.*, non-adherence to heart failure medication and lifestyle recommendations is likely more common among depressed than non-depressed patients and likely to have higher prognostic importance in patients with severely impaired ejection fraction. The strength of the associations increased in current users of antidepressants, suggesting that active depression may play a prognostic role for all-cause mortality in patients with heart failure. It should be noted that the prevalence of comorbid conditions was lower in our heart failure cohort than reported in other studies.[23] Our results, however, reflect a different health care system and inclusion of all hospital contacts with heart failure. The etiology for heart failure may also vary by geographic region.

Heart failure and risk of dementia

Several studies have linked heart failure with impaired cognitive performance (*e.g.* low Mini-Mental State Examination scores);[120] however, a poorly understood aspect is the association between heart failure and dementia. The Finnish population-based CAIDE cohort study of 2000 individuals from the general population with more than 25 years of follow-up showed that mid-life heart failure was not associated with all-cause dementia (aHR=0.84; 95% CI, 0.33−2.13) or Alzheimer's disease (aHR=1.11; 95% CI, 0.43−2.81),[51] although the relatively wide CIs prevented firm conclusions. In contrast, the same study revealed that among those with late-life heart failure, the risk of dementia (aHR=2.06; 95% CI, 1.00−4.27) and Alzheimer's disease (aHR=1.82; 95% CI, 0.84−3.37) was higher relative to those without heart failure. This finding was also apparent in a Swedish population-based cohort of 205 heart failure patients and 1096 individuals without heart failure (aHR for all-cause dementia=1.84; 95% CI, 1.35−2.51; and aHR for Alzheimer's disease=1.80; 95% CI, 1.25−2.61).[52] Of particular interest, the associations slightly attenuated when restricted to heart failure patients receiving antihypertensive drugs, defined as antiadrenergics, diuretics, or beta blockers (aHR for all-cause dementia=1.38; 95% CI, 0.99−1.94; and aHR for Alzheimer's disease=1.39; 95% CI, 0.93−2.07), indicating that guideline-based treatment of heart failure may at least partially reverse the association between heart failure and dementia. Two population-based cohorts (AGES-Reykjavik study[121] and the Framingham Offspring cohort study[122]) of individuals without heart failure also support an association between heart failure and dementia. In the AGES-Reykjavik study of 931 individuals, for each 10 mL reduction in left ventricular stroke volume, the adjusted odds ratio for mild cognitive impairment or dementia was 1.40 (95% CI,

0.99−2.00), and for each 1 L/min reduction in cardiac output, the adjusted odds ratio was 1.24 (95% CI, 0.99−1.57). Among 1039 Framingham Offspring cohort study participants, each standard deviation unit decrease in cardiac index increased the risk of dementia (aHR=1.66; 95% CI, 1.11−2.47) and Alzheimer's disease (aHR=1.65; 95% CI, 1.07−2.54).

Heart failure and risk of stroke

Few studies have compared the risk of stroke among patients with heart failure with that in the general population.[57-59] Our findings are confirmatory, pointing towards a higher stroke rate among patients with heart failure, in particular in the short term. In the Danish Diet, Cancer, and Health cohort study, comprising 1239 patients with incident heart failure and 50,314 individuals free of heart failure, the aHR for ischemic stroke was 2.3 (95% CI, 1.8−3.0); for hemorrhagic stroke, it was 1.8 (95% CI, 1.0−3.3).[58] In analyses stratified by various time intervals since heart failure diagnoses, the risk of a composite of death and any stroke was markedly elevated in the first 30 days (aHR=35.7; 95% CI, 27.5−46.4), while it attenuated but persisted between 30 days and 6 months and beyond 6 months. In the Rotterdam cohort study based on 7546 participants of whom 1247 had heart failure, the overall aHR for ischemic stroke was 1.02 (95% CI, 0.77−1.37).[57] However, the 0–30-day ischemic stroke rate was elevated almost five fold (aHR=4.60; 95% CI, 1.70−12.49) but decreased from 30 days to 6 months (aHR=2.75; 95% CI, 1.53−4.94), even reversing the risk association from 6 months to 5 years (aHR=0.58; 95% CI, 0.37−0.92). In a US cohort study that included 630 heart failure patients, the risk of ischemic stroke was also substantially increased during the first 30 days (standardized morbidity ratio=17.4; 95% CI, 8.4−32.1),[59] but in contrast to the Dutch study, the risk persisted over 5 years of follow-up (standardized morbidity ratio=2.9; 95% CI, 2.2−3.8). Among patients with heart failure, declining LVEF has in several studies been shown to predict increased rates of stroke[123-125] – a trend also observed in our analyses using length of hospital and stay in intensive care as proxies for heart failure severity.

METHODOLOGICAL CONSIDERATIONS

Epidemiological studies are prone to bias, which broadly can be classified as selection bias, information bias, and confounding. Below, we discuss potential sources and directions of bias in relation to each of the individual studies I–V.

Selection bias

Selection bias arises when an association between exposure and outcome is different in study participants than in non-participants.[46] Our studies I-II are susceptible to selection bias because we restricted the study population to those in the Central Denmark Region due to study feasibility. Although there may be some regional differences in coding practices for cardiovascular diseases and interventions, the Danish health care system is relatively homogeneous with respect to patient characteristics, health care usage, and use of medication.[126] Inherent to the nationwide population-based design with virtually no loss to follow-up, selection bias was minimized in studies III–V and is unlikely to explain the findings.

Information bias

The quality of our data is dependent on the validity of the coding used in each study.

Because the PPV of the heart failure diagnosis is around 80% in the DNPR, we have likely included some patients without heart failure. A high PPV of the study population is of particular importance to ensure that any effect of an exposure really applies to the study population of interest. Thus, we repeated our analyses in study III, restricted to heart failure patients from the Danish Heart Failure Registry, which did not change the results.

Misclassification of depression

The most widely applied criteria for diagnosing depression are based on the ICD-10. However, potential misclassification of depression is very likely. Because diagnoses from general practitioners are not recorded in the Danish registries, the sensitivity of depression is assumed to be low in analyses solely based on hospital-based depression diagnoses. As such, the cohort of non-depressed patients would comprise patients with depression, which would potentially bias the results toward the null and therefore probably cannot explain the findings of an association between depression and all-cause mortality reported for patients with LVEF ≤35%.[46] Although antidepressants can be used for indications other than depression (*e.g.* panic disorder, obsessive compulsive disorder, neurogenic pain), we redefined depression based on redeemed prescription for antidepressants or hospital-based diagnoses of depression, which resulted in slightly larger associations. Whereas the PPV of depression is appropriate in the DPCR, the validity of depression in the DNPR is unknown, but separate analyses of patients with depression recorded from the DNPR or the DPCR produced similar adjusted MRRs. For almost 60% of the patients with a depression diagnosis, we had no information on severity of depression, which may contribute to the lack of a linear increase between the severity of depression and risk of mortality.

Misclassification of outcomes

In study III, the results of our cause-specific mortality analysis should be interpreted with caution because causes of death are assessed by physician-subjective judgment, which very rarely is confirmed by findings from autopsy. In study IV, the possibility of surveillance bias should be considered, as should overestimation of the risk of dementia as a consequence because patients with heart failure may be in contact with the medical establishment more often than the general population. Moreover, data on cognitive tests and diagnostic brain images are not available in the Danish registries to confirm the diagnoses of dementia and stroke. Although we lacked data on the results of computer tomography or magnetic resonance scans of the brain to confirm diagnoses, our results in study V remained unchanged when stroke outcomes were defined according to the combination of ICD codes and a procedure code for computer tomography or magnetic resonance scans of the brain. In addition, a higher prevalence of cardiovascular risk factors in the heart failure cohort than in the general population comparison cohort may have promoted diagnostic bias, explaining some of the association with vascular dementia and the null association with Alzheimer's disease. In study V, we classified a large number of unspecified strokes as ischemic stroke; however, recording is presumably independent of presence or absence of heart failure, resulting in non-differential misclassification and thus conservative SRRs, but likely an overestimation of the absolute ischemic stroke risks in the heart failure and comparison cohorts.

Confounding

Confounding is an important issue to consider in all epidemiologic studies. Confounding relates to a mixture of effects between the exposure and other variables, resulting in biased estimates, and it can be classified as unknown and known confounding, as well as measured (including insufficiently measured confounders, which is often referred to as residual confounding) and unmeasured confounding.[46] To fulfill the confounder criteria, a variable must be associated with the exposure and the outcome, should not be on the causal pathway, and should be unequally distributed among the exposed and unexposed groups.[46] As we did, confounding can be addressed by matching, restriction, multivariable analysis, and stratification. In our studies, potential confounders such as apolipoprotein E status (study IV),[127] lifestyle factors including smoking (studies IV-V) and physical exercise (studies III–V), socioeconomic status (studies IV-V), and depression (studies IV-V) were unavailable or were available only for some of the studies. In study III, data were available on smoking habits and alcohol use for the Danish Heart Failure cohort, but additional adjustment for these variables left the results broadly unchanged, suggesting that we, at least partly, indirectly adjusted for these covariables by adjusting for comorbidity reflecting chronic exposure to alcohol and smoking and socioeconomic variables. In general, there was no missing data problem in our studies, except for study III, where data on smoking and alcohol were missing for 15%–25% of the patients in the Danish Heart Failure cohort, which we tried to account for by using multiple imputation techniques.[96] Data on education were missing exclusively from the oldest age group in the heart failure cohort and were thus not data missing at random, preventing the use of multiple imputation to account for missing data on education.

Limitations of long-term studies

Assessing long-time risk associated with an exposure is complex. First, the difficulty is that the composition of the population is continuously changing.[128] We observed a markedly high mortality rate in our cohort of heart failure patients, and those at highest risk tend to die first. It should be emphasized that our long-term risk estimates relate only to those who survived until the subsequent follow-up period. Thus, for 1- to 30-year estimates, for example, these results relate only to one-year survivors. Second, in long-term studies, diagnostic criteria for study cohorts, exposures, and outcomes as well as treatment guidelines and the organization of the health care system may change over time, which should be taken into account. Third, we studied the clinical course after a first hospitalization for heart failure, and because changes in depression status or cardiovascular risk factors over time are on the causal pathway to a subsequent event, this factor was not accounted for in the analyses. The causal question is complex, and many mediators cannot be subtracted from the Danish registries while others have complex patterns over time. Thus, determining post-exposure and time-varying effects was not the aim of our studies.

PERSPECTIVES

Our findings have some implications. Unlike sensitivity and specificity, PPV is affected by the prevalence of a disease.[46,129] We conducted these validation studies to provide context to epidemiologic studies of cardiovascular diseases and cardiac interventions in the DNPR. Researchers should always prioritize among measures of data quality (*i.e.* sensitivity, specificity, and PPV) based on intended use.[129] Prioritizing a high PPV is particularly important when sampling study cohorts.[129] Depending on their respective aims, our studies indicate that the DNPR is useful for assessing prognosis related to most cardiovascular diseases and interventions. Future validation studies should address and quantify potential misclassification of cardiovascular diagnoses and cardiac interventions across exposure groups, focus on improving algorithms for identifying diseases and intervention with low or moderate PPV (*e.g.* recurrent events and heart failure), and include other measures of data quality, including sensitivity, specificity, and negative predictive value.

As the prevalence of heart failure rises, it will become increasingly important to evaluate related prognostic factors and complications. Although randomized trials have been neutral on use of selective serotonin reuptake inhibitors for treating heart failure patients with depression, clinicians should be aware of depression in patients with heart failure to improve quality of life and ensure high adherence, particularly among patients with severely impaired LVEF. More studies identifying who is susceptible to depression and to develop treatment strategies are highly warranted.

Finally, the results of our studies add to emerging evidence implying that clinicians should consider heart failure as a risk factor for all-cause dementia and stroke. Future studies should focus on developing strategies to prevent or delay onset of dementia and stroke in patients with heart failure to improve prognosis in these patients (tertiary prophylaxis).

SUMMARY

Heart failure is a complex clinical syndrome and one of the leading causes of morbidity and mortality with a prevalence of 1%–2% of the adult population. The prognosis is poor with a 5-year mortality rate of 50%, which partly can be attributed to the presence of concomitant comorbidity, including neurological and psychiatric comorbidities. However, the prognostic impact of depression and the role of heart failure as a risk factor for dementia and stroke are not fully understood.

Denmark is well-known for its unique health registries. The DNPR has been widely used in cardiovascular research in the past decades, although the accuracy of several diseases and interventions is largely unknown.

This thesis explored the PPV of a range of cardiovascular diagnoses including heart failure (study I) and cardiac interventions (study II) recorded in the DNPR. In addition, we aimed to provide new insights into the impact of depression on mortality in heart failure patients with reduced and preserved left ventricular ejection fraction (study III). Finally, we studied the association between heart failure and subsequent short-term and long-term risks of dementia (study IV) and ischemic and hemorrhagic stroke (study V).

In studies I-II, we identified 3386 patients with various cardiovascular diagnoses or cardiac interventions during 2010−2012 using the DNPR. Patient medical charts served as the gold standard for diagnosis confirmation and were adjudicated by physicians. We found a high PPV (≥90%) for the majority of the patients while the PPV was somewhat lower for myocarditis, heart failure, and recurrent events.

In study III, we analyzed 205,719 patients with incident heart failure during 1995−2014. A history of depression was associated with 15%–20% increased mortality rate in patients with LVEF ≤35% and when defining depression based on a combination of

redeemed antidepressant prescription and hospital-based diagnoses, but not when depression was ascertained based solely on diagnoses.

In study IV, we included 324,418 heart failure patients and a general population comparison cohort comprising 1,622,079 individuals matched for age and sex during 1980–2012. The heart failure cohort had a 21% increased rate of all-cause dementia, mainly driven by increased hazards of vascular dementia and other dementia, whereas heart failure was not associated with Alzheimer's disease.

In study V, we identified and followed 289,353 patients with heart failure and 1,446,765 individuals from the general population matched for age, sex, and calendar year. Heart failure patients had a five-fold elevated rate of ischemic stroke, two-fold increased rate of ICH, and a four-fold increased rate of SAH within 30 days. These associations receded towards the null but persisted over 30 years.

In conclusion, the DNPR contains data on several cardiovascular diagnoses and cardiac interventions recorded with high PPVs. Our data also suggest that a history of depression is an adverse prognostic factor for death in patients with heart failure and low LVEF. Finally, heart failure emerged as a risk factor for all-cause dementia as well as for both ischemic and hemorrhagic stroke.

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