AARHUS
UNIVERSITY

Neurological and psychiatric comorbidity in patients with heart failure

– Risk and prognosis –

PhD dissertation

Kasper Adelborg

Health
Aarhus University
Department of Clinical Epidemiology, Aarhus University Hospital
Department of Cardiology, Aarhus University Hospital

2017

Supervisors

Henrik Toft Sørensen, MD, PhD, DMSc, Professor (main supervisor)

Department of Clinical Epidemiology

Aarhus University Hospital, Denmark

Hans Erik Bøtker, MD, PhD, DMSc, Professor

Department of Cardiology

Aarhus University Hospital, Denmark

Poul Videbech, MD, PhD, DMSc, Professor

Centre for Neuropsychiatric Depression Research

Mental Health Centre Glostrup, Denmark

Morten Schmidt, MD, PhD

Department of Clinical Epidemiology

Aarhus University Hospital, Denmark

Assessment committee

Hans Eiskjær, MD, PhD, DMSc (chairman)
Department of Cardiology
Aarhus University Hospital, Denmark

Torben Bjerregaard Larsen, MD, PhD, Associate professor
Aalborg Thrombosis Research Unit
Aalborg University, Denmark

Irwin Nazareth, MD, PhD, Professor
Department of Primary care and Population Health
University College London, United Kingdom

Collaborators

Victor W. Henderson, MD, MS, Professor
Departments of Health Research and Policy (Epidemiology) and of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA

Lars Pedersen, MSc, PhD, Professor
Department of Clinical Epidemiology
Aarhus University Hospital, Denmark

Jens Sundbøll, MD
Department of Clinical Epidemiology
Aarhus University Hospital, Denmark

Troels Munch, MD
Department of Clinical Epidemiology
Aarhus University Hospital, Denmark

Trine Frøslev, MSc
Department of Clinical Epidemiology
Aarhus University Hospital, Denmark

Erzsébet Horváth-Puhó, MSc, PhD,
Department of Clinical Epidemiology
Aarhus University Hospital, Denmark

Szimonetta Szépligeti, MSc
Department of Clinical Epidemiology
Aarhus University Hospital, Denmark

Anne Ording, PhD
Department of Clinical Epidemiology
Aarhus University Hospital, Denmark

Kenneth Egstrup, MD, PhD, DMSc, Professor
Department of Medical Research
Odense University Hospital, Svendborg, Denmark

Acknowledgement

The work presented in this thesis was conducted from August 2014 to April 2017, during my employment at the Department of Clinical Epidemiology, Aarhus University Hospital. I feel privileged that I was given the opportunity to work with leading experts within clinical epidemiology, biostatistics, psychiatry, and cardiology, and I am very grateful to all the persons who made this work possible.

First of all, my deep gratitude goes to Henrik Toft Sørensen for outstanding mentorship, patience, and engagement in my projects and for teaching me how to write a scientific paper. With Henrik as my mentor, I never doubted that all challenges could be solved, and I hope our collaboration will continue for many years to come. I would also like to thank Morten Schmidt for persistent support and dedication and for always paying careful attention to every single detail in a project.

My sincere appreciation goes to Hans Erik Bøtker for excellent supervision and for sharing his clinical knowledge. I warmly thank Poul Videbech for inspiring and fruitful discussions.

I would like to extend my thanks to my great colleagues at the Department of Clinical Epidemiology — thank you for interesting discussions, support, and joyful lunch hours during the years. Lars Pedersen, Erzsébet Horváth-Puhó, and Szimonetta Szépligeti — it has truly been a pleasure working with you and learning from your insights into advanced statistical methods. A special thank you goes to Jens Sundbøll for being a great friend and colleague.

Finally, I give my warmest thanks to my family, Sofie, Clara, and Tine, for their unconditional support, love, and understanding of my need to conduct research.

Kasper Adelborg, 2017

Grants

- Aarhus University
- The Program for Clinical Research Infrastructure (PROCRIN), established by the Lundbeck Foundation and the Novo Nordisk Foundation
- The Aarhus University Research Foundation
- Augustinusfonden

Abbreviations

aHR	Adjusted hazard ratio
aSRR	Adjusted stroke rate ratio
CI	Confidence interval
DNPR	Danish National Patient Registry
DPCR	Danish Psychiatric Central Research Register
HR	Hazard ratio
ICD	International Classification of Diseases
ICH	Intracerebral hemorrhage
LVEF	Left ventricular ejection fraction
MRR	Mortality rate ratio
NYHA	New York Heart Association
PPV	Positive predictive value
SAH	Subarachnoid hemorrhage

Contents

1. 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]

2. 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]

2.1 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]

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

2.2 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] 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]

2.3 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]

2.4 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.

2.5 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]

2.6 Neurological complications of heart failure

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

2.6.1 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]

2.6.2 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.

2.7 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.

2.8 Literature review

To review the literature, we searched Medline and Scopus using a free-text search to ensure inclusion of the most recently published articles. The search was performed during February–March 2017. Because the free-text search in study V resulted in too many hits, we also did a Medical Subject Headings search. For studies III–V, we excluded studies published in languages other than English, Danish, Swedish, and Norwegian, those published before 1995, and nonclinical reports. The search was restricted to clinical studies, clinical trials, meta-analyses, observational studies, and literature reviews. Titles and abstracts were reviewed and relevant papers selected. A summary of the selected literature is provided in Table 2.

2.9 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).

Table 2. Summary of the literature.

Study I – Cardiovascular diagnoses in the DNPR			
Author, journal, year	**Design, setting, registries, period**	**Population, exposure, outcome**	**Results**
Lasota et al. [80] - Eur J of Vasc Endovasc Surg - 2017	- Validation study - Denmark - DNPR - 1993–2009	- Patients with peripheral artery disease (n=1435) - Reference: Medical record (clinical information, symptoms, signs, examinations, procedures)	PPV=69% (95% CI, 67%–72%) PPV_{IN}=81% (95% CI, 76%–85%); PPV_{OUT}=67% (95% CI, 64%–69%) PPV_{A}=76% (95% CI, 73%–79%); PPV_{B}=59% (95% CI, 50%–67%)
Schmidt et al.[81] - BMJ Open - 2013	- Cohort and validation study - Denmark - DNPR - 1977–2010	- Male patients with hypertension (n=524) - Reference: Prescription of antihypertensives - PPV	PPV=88% (95% CI, 85%–91%)
Nielsen et al.[82] - Ugeskr laeger - 1996	- Validation study - Denmark - DNPR - 1983–1990	- Patients with hypertension (n=310) - Reference: Medical record review - PPV	PPV=40% (95% CI, 26%–55%) to 60% (95% CI, 49%–70%)
Joensen et al.[83] - J Clin Epidemiol - 2009	- Validation study - Denmark - DNPR - 1993–2003	- Patients with acute coronary syndrome (n=1558), unstable angina (n=444), MI (n=1072), and cardiac arrest (n=42) - Reference: Medical record, blood test, electrocardiogram - PPV	Acute coronary syndrome: $PPV_{IN/OUT/ED}$=66% (95% CI, 63%–68%); PPV_{IN}=80% (95% CI, 78%–82%) Unstable angina*:* $PPV_{IN/OUT/ED}$=28% (95% CI, 23%–32%); PPV_{IN}=42% (95% CI, 36%–48%) Myocardial infarction: $PPV_{IN/OUT/ED}$=82% (95% CI, 80%–84%); PPV_{IN}=92% (90%–94%); $PPV_{IN;\ A}$=94% (95% CI, 93%–96%) Cardiac arrest: $PPV_{IN/OUT/ED}$=50% (95% CI, 34%–66%); PPV_{IN}=53% (95% CI, 37%–69%)
Coloma et al.[84] - BMJ Open - 2013	- Validation study - Denmark - DNPR - 1996–2009	- Patients with acute MI (n=148) - Reference: Medical record - PPV	PPV=100% (95% CI, 98%–100%)
Thygesen et al.[79] - BMC Med Res Methodol - 2011	- Validation study - Denmark - DNPR - 1998–2007	- Patients with MI (n=50) and heart failure (n=50) - Reference: Medical record - PPV	Myocardial infarction: PPV=98% (95% CI, 89%–100%) Heart failure: PPV=100% (95% CI, 93%–100%)
Madsen et al.[85] - J Clin Epidemiol - 2003	- Validation study - Denmark - DNPR - 1982–1991	- Patients with acute MI (n=5022) - Reference: DANMONICA definite or possible cases including cardiac arrest - PPV	PPV_{A}=94% (95% CI, 94%–95%); $PPV_{A+B=}$93% (95% CI, 93%–94%)
Madsen et al.[86] - Ugeskr laeger - 1990	- Validation study - Denmark - DNPR - 1979–1980	- Patients with acute MI (n=527) - Reference: Medical record - PPV	PPV=92% (95% CI, 90%–94%)

Drljevic et al.[87] - Clin Epidemiol - 2014	- Validation study - Denmark - DNPR - 1995–2012	- Prostate cancer patients with venous thromboembolism (n=120) - Reference: Medical record - PPV	PPV=86% (95% CI, 79%–92%)
Severinsen et al.[88] - J Clin Epidemiol - 2010	- Validation study - Denmark - DNPR - 1994–2006	- Patients with VTE (n=1135) - Reference: Medical record, blood tests; ultrasound; venography; echo; V-P lung scan; CT - PPV	Pulmonary embolism: PPV_{All}=67% (95% CI, 61%–71%); PPV_{IN}=82% (95% CI, 77%–86%); PPV_{ED}=30% (95% CI, 21%–39%); PPV_{A}=87% (95% CI, 82%–91%) Deep vein thrombosis: PPV_{All}=55% (95% CI, 51%–58%); PPV_{IN}=71% (95% CI, 67%–75%); PPV_{ED}=32% (95% CI, 27%–37%); PPV_{A}=73% (95% CI, 68%–76%)
Larsen et al.[89] - J Clin Epidemiol - 2005	- Validation study - Denmark - DNPR - 1980–2001	- Patients with VTE during pregnancy and postpartum (n=311) - Reference: Medical record - PPV	Pulmonary embolism: $PPV_{preg+postpartum}$=82% (95% CI, 60%–95%); PPV_{preg}=64% (95% CI, 41%–83%) Deep vein thrombosis: $PPV_{preg+postpartum}$=86% (95% CI, 80%–91%); $PPV_{preg=}$=75% (95% CI, 67%–81%)
Ingeman et al.[90] - J Clin Epidemiol - 2003	- Validation study - Denmark - DNPR - 2003–2006	- Patients with VTE after stroke (n=19) - Reference: Medical record - PPV	Pulmonary embolism: PPV=91% (95% CI, 59%–100%) Deep vein thrombosis: PPV=88% (95% CI, 47%–100%)
Schmidt et al.[91] - J Thromb Haemost - 2014	- Validation study - Denmark - DNPR - 2004–2012	- Patients with VTE (n=20) - Reference: Medical record - PPV	PPV=90% (95% CI, 70%–97%)
Rix et al.[92] - Scan Cardiovasc J - 2012	- Validation study - Denmark - DNPR - 1977–1999	- Patients with atrial flutter and atrial fibrillation (n=408) - Reference: Medical record and heart rhythm documentation - PPV	Atrial fibrillation or atrial flutter: PPV=93% (95% CI, 89%–95%) Atrial flutter: PPV=50% (95% CI, 41%–59%)
Frost et al.[93] - Am J Med - 2007	- Validation study - Denmark - DNPR - 1980–2002	- Patients with atrial fibrillation and flutter (n=174) - Reference: Medical record and heart rhythm documentation - PPV	PPV=99% (95% CI, 96%–100%)
Frost et al.[94] - Arch Intern Med - 2004	- Validation study - Denmark - DNPR - 1980–2002	- Patients with atrial fibrillation and flutter (n=116) - Reference: Medical record and heart rhythm documentation - PPV	PPV=97% (95% CI, 92%–99%)
Mard et al.[77] - Clin Epidemiol - 2010	- Validation study - Denmark - DNPR - 2005–2007	- Patients with HF (n=758) - Reference: Medical record - PPV	PPV=84% (95% CI, 81%–87%); $PPV_{First\text{-}time\ events}$=78% (95% CI, 74%–82%)
Kümler et al.[78] - Eur J Heart Fail - 2008	- Validation study - Denmark - DNPR - 1980–1999	- Patients with HF (n=156) - Reference: Clinical examination - PPV	PPV=81% (95% CI, 74%–86%)

Egholm et al.[95] - Clin Epidemiol - 2016	- Validation study - Denmark - DNPR - 2006–2012	- Patients undergoing percutaneous coronary intervention with MI (n=285) - Reference: Medical record - PPV	Different algorithms: PPV=42% (95% CI, 38%–46%) to 87% (95% CI, 81%–91%)
Study II – Cardiovascular interventions in the DNPR			
Author, journal, year	**Design, setting, registries, period**	**Population, exposure, outcome**	**Results**
Nielsen et al.[96] - Clin Epidemiol - 2014	- Validation study - Denmark - DNPR - 2008–2012	- Patients with cardiac CT angiogram (n=289) - Reference: Medical record - PPV	PPV=100% (95% CI, 99%–100%)
Study III – Mortality risk among heart failure patients with depression			
Author, journal, year	**Design, setting, registries, period**	**Population, exposure, outcome**	**Results**
Rutledge et al. [27] - JACC - 2006	- Meta-analysis of 8 studies	- Refer to the individual studies - Pooled estimates	Mortality and associated cardiac events: aHR=2.10 (95% CI, 1.71–2.58)
Fan et al.[28] - Prev Med - 2014	- Meta-analysis of 9 studies	- Refer to the individual studies - Pooled estimates	All-cause mortality: aHR=1.51 (95% CI, 1.19–1.91) All-cause mortality (mild depression): aHR=1.04 (95% CI, 0.75–1.45) All-cause mortality (severe depression): aHR=1.98 (95% CI, 1.23–3.19) Cardiovascular mortality (2 studies): aHR=2.19 (95% CI, 1.46–3.29)
Sokoreli et al.[29] - Heart Fail Rev - 2016	- Meta-analysis of 26 studies	- Refer to individual studies - Pooled estimates	All-cause mortality: aHR=1.40 (95% CI, 1.22–1.60) Larger studies associated with smaller effect size
Albert et al.[97] - Am J Med - 2009	- Cohort study - US - 2003–2004	- HF inpatients in the OPTIMIZE-HF registry (n=48,612) - History of depression (medical record review) - Mortality	All-cause mortality: adjusted odds ratio=1.46 (95% CI, 1.05–2.03)
Alhurani et al.[98] - Psychosomatics - 2015	- Cohort study - US and international sites - Study period not reported	- HF patients (n=1260) - Depression assessed by PHQ-9 - Mortality	All-cause mortality: aHR=1.06 (95% CI, 1.01–1.11)
Coyne et al.[99] - Psychosom Med - 2011	- Cohort study - Dutch - 2002–2005	HF inpatients (n=706) from the COACH trial - Depression assessed by CES-D scale - Mortality	All-cause mortality: aHR=1.02 (95% CI, 1.00–1.04)
Volz et al.[100] - J Behav Med - 2011	- Cohort study - Switzerland - 2004–2008	- HF outpatients (n=111) - Depression assessed by HADS scale - Mortality	Depression (≤7 vs. >7), all-cause mortality: aHR=0.89 (95% CI, 0.23–3.40)
Friedmann et al.[101] - Am Heart J - 2006	- RCT substudy - Multinational - 2004–2008	- HF outpatients (n=153) from the SCD-HeFT study - Depression assessed by BDI-II scale	All-cause mortality: aHR=2.58 (95% CI, 0.23–5.43)
Smith et al.[102] - Psychosom Med - 2012	- Cohort study - Dutch - 2003–2006	- HF outpatients (n=380) - Depression assessed by BDI scale	All-cause mortality: aHR=1.41 (95% CI, 1.05–1.88)

Macchia et al.[103] - Eur J Heart Failure - 2008	- Cohort study - Italy (6 local health authorities) - 2000–2004	- HF in- and outpatients (n=48,117) - Prescription for antidepressants within 12 months - Mortality and cardiovascular outcomes	All-cause mortality: aHR=1.20 (95% CI, 1.08–1.33) Stroke/TIA/MI: aHR=1.23 (95% CI, 1.13–1.34) HF hospitalization: aHR=1.06 (95% CI, 0.93–1.20) Any hospitalization: 1.00 (95% CI, 0.94–1.06)
Zuluaga et al.[104] - Am Heart J - 2010	- Cohort study - Spain (4 hospitals) - 2000–2001	- HF inpatients (n=433) - Depression assessed by GDS - Mortality	All-cause mortality (mild depression): aHR=0.99 (95% CI, 0.74–1.34); all-cause mortality (severe): aHR=1.27 (95% CI, 0.95–1.70) All-cause mortality (severe): aHR=1.10 (95% CI, 0.82–1.49) in the fully adjusted model
Dies-Quevedo et al.[105] - Int J Cardiol - 2013	- Cohort study - Spain - 2001–2010	- HF outpatients (n=1017) - Depression assessed by GDS score and use of antidepressants - Mortality	All-cause mortality: aHR=1.31 (95% CI, 1.07–1.60) Use of any antidepressant: aHR=0.99 (95% CI, 0.98–0.99)
Cully et al.[106] - Psychosomatics - 2009	- Cohort study - US - 2000–2002	- HF outpatients (n=12,028) - Depression assessed by depression diagnosis codes - Mortality	All-cause mortality: adjusted odds ratio=0.93 (95% CI, 0.71–1.15)
Jiang et al.[107] - Arch Intern Med - 2001	- Cohort study - US (1 hospital) - 1997–1998	- HF inpatients (n=374) - Depression assessed by BDI score - Mortality	3 months– All-cause mortality (mild): adjusted odds ratio=1.43 (95% CI, 0.44–4.67) All-cause mortality (major): adjusted odds ratio=2.68 (95% CI, 0.93–7.72) 1-year– All-cause mortality (mild): adjusted odds ratio=0.87 (95% CI, 0.33–2.26) All-cause mortality (major): adjusted odds ratio=2.12 (95% CI, 0.94–4.81)
Jiang et al.[108] - Amer Heart J - 2007	- Cohort study - US - 1997–2003	- HF inpatients (n=1006) - Depression assessed with BDI scale - Mortality	All-cause mortality: aHR=1.36 (95% CI, 1.09-1.70)
Broek et al.[109] - American J Card - 2010	- Cohort study - US (4 geographic communities) - 1989–1995	- HF in- and outpatients (n=208) - Depression assessed by CES-D - Low depression and low NT-proBNP as reference - Mortality	All-cause mortality– Depression+high NT-proBNP: aHR=3.15 (95% CI, 1.75–5.69) Depressed+low NT-proBNP: aHR=1.32 (95% CI, 0.60–2.88) Cardiovascular related mortality– Depression+high NT-proBNP: aHR=5.42 (95% CI, 2.38-12.36) Depressed+low NT-proBNP: aHR=1.91 (95% CI, 0.65-5.64)
Brouwers et al.[110] - Int J Cardiol - 2016	- Cohort study - Danish - 1997–2010	- HF inpatients (n=121,252) - Depression assessed by use of antidepressant and diagnoses - Mortality	All-cause mortality– No antidepressant, depression diagnosis: aHR=1.25 (95% CI, 1.15–1.36) Antidepressant, no depression diagnosis: aHR=1.24 (95% CI, 1.22–1.27) Antidepressant, depression diagnosis: aHR=1.21 (95% CI, 1.16–1.27)
Rollman et al.[111] - J Cardiac Failure - 2012	- Cohort study - US (4 hospitals) - 2007–2009	- HF inpatients (n=471) - Depression assessed by PHQ-2 - Mortality	All-cause mortality: aHR=3.1 (95% CI, 1.4–6.7) Cardiovascular mortality: aHR=2.7 (95% CI, 1.1–6.6)
Faller et al.[112] - Eur J Heart Failure - 2007	- Cohort study - German (2 university hospitals) - 2002–2003	- HF outpatients (n=231) - Depression assessed by PHQ-9	All-cause mortality: major depression, aHR=2.4 (95% CI, 1.3–4.6); minor depression, HR=1.6 (95% CI, 0.8–3.1) – this was unadjusted

Faller et al.[113] - J Psychosom Res - 2015	- Cohort study - German (2 university hospitals) - 2002–2003	- HF outpatients (n=863) - Depression assessed by PHQ-9 - Mortality	All-cause mortality: aHR=1.04 (95% CI 1.01–1.07)
Kato et al.[114] - J Cardiac Failure - 2009	- Cohort study - Japanese (1 university hospital) - 2006	- HF outpatients (n=115) - Depression assessed by CES-D - Mortality	Cardiac death or HF hospitalization: aHR=3.29 (95% CI, 1.24–8.70) All-cause mortality: aHR=5.52 (95% CI, 1.65–18.46)
Sullivan et al.[115] - American J Card - 2004	- Cohort study - US (single center) - 1999–2001	- HF outpatients (n=142) - Interview performed by nurse: Hamilton Depression Rating Scale - Self-reported: Hopkins symptom checklist scale (SCL-20) - Mortality	All-cause mortality or transplantation (any depression): adjusted odds ratio=2.41 (95% CI, 1.24–4.68)
Moraska et al.[116] - Circ Heart Fail - 2013	- Cohort study - US (4-5 centers) - 2007–2010	- HF in- and outpatients (n=402) - Depression assessed by PHQ-9 - Mortality	All-cause mortality (mild): aHR=1.59 (95% CI, 0.89–2.83) All-cause mortality (moderate to severe): aHR=4.06 (95% CI, 2.35–7.01)
Adams et al.[117] - Psychosomatics - 2012	- Cohort study - US (single center) - 1997-2003	- HF inpatients (n=985) - Depression assessed by BDI - Mortality	All-cause mortality (BDI <5 as reference), BDI 5–9: aHR=1.03 (95% CI, 0.84–1.26); BDI 10–18: aHR=1.24 (95% CI, 0.98–1.58); BDI >18: aHR=2.02 (95% CI, 1.48–2.76)
O' Connor et al.[118] - Arch Intern Med - 2008	- Cohort study - US (single center) - 1997-2003	- HF in- or outpatients (n=1006) - Depression assessed by BDI - Mortality	All-cause mortality: aHR=1.39 (95% CI, 1.12–1.74)
Faris et al.[119] - Eur J Heart Fail - 2002	- Cohort study - UK (single center) - 1994–1998	- Patients with dilated cardiomyopathy, inpatients (n=396) - Diagnosis of previous depression in the medical records - Mortality	All-cause mortality: aHR=3.0 (95% CI, 1.4–6.6)
Lesman-Leegte et al.[120] - Eur J Heart Fail - 2009	- Cohort study - Dutch (multicenter) - COACH substudy - 2002–2005	- HF inpatients (n=958) - Depression assessed by CES-D - Mortality and readmission	HF readmission or mortality (per 10-point increase in CES-D): aHR=1.13 (95% CI, 1.02–1.26); mortality (per 10-point increase in CES-D): aHR=1.17 (95% CI, 1.03–1.34)
Vaccarino et al.[121] - J Am Coll Cardiol - 2001	- Cohort study - US (single center) - 1996–1998	- HF patients (n=391) - Depression assessed by GDS - Mortality	All-cause mortality– Mild depression: adjusted relative risk=1.07 (95% CI, 0.49–2.33), Moderate depression: adjusted relative risk=1.25 (95% CI, 0.58–2.70) Severe depression: adjusted relative risk =1.68 (95% CI, 0.63–4.45)
Jünger et al.[122] - Eur J Heart Fail - 2005	- Cohort study - Germany (single center) - 1996–1999	- HF outpatients (n=209) - Depression assessed by HADS - Mortality	All-cause mortality: aHR=1.08 (95% CI, 1.01–1.15)
Murberg et al.[123] - Int J Psych in Med - 1999	- Cohort study - Norway (single center) - Study period not reported	- HF outpatients (n=119) - Depression assessed by SDS - Mortality	All-cause mortality (per 1-point increase in SDS)**:** aHR=1.08 (no valid CI reported)
Murberg et al.[124] - Med Sci Monit - 2004	- Cohort study - Norway (single center) - Study period not reported	- HF outpatients (n=119) - Depression assessed by SDS - Mortality	All-cause mortality (per 1-point increase in SDS): aHR=1.05 (1.00–1.08)

De Denus et al.[125] - Pharmacotherapy - 2004	- Cohort study - US (single center) - ADHERE substudy - 2002	- HF inpatients (n=171) - Medical record depression diagnoses - Mortality	In-hospital death or resuscitation: adjusted odds ratio=3.3 (95% CI, 1.01–10.6)
Sherwood et al.[126] - Arch Intern Med - 2007	- Cohort study - US - 2000–2002	- HF outpatients (n=204) - Depression assessed by BDI - Mortality	Death or cardiovascular hospitalization: aHR=1.56 (95% CI, 1.07–2.29)
Sherwood et al.[127] - J Am Coll Cardiol - 2011	- Cohort study - US - 2000–2002	- HF outpatients (n=147) - Depression assessed by BDI over one year - Mortality	Death or all-cause hospitalization: aHR=1.06 (95% CI, 1.01–1.11)
Murad et al.[128] - JACC Heart Fail - 2015	- Cohort study (data from the Cardiovascular Health Study) - US - 1990–2002	- HF outpatients (n=558) - Depression assessed by CES-D - Mortality	All-cause mortality: aHR=1.44 (95% CI, 1.09–1.90)
Suzuki et al.[129] - J Cardiol - 2014	- Cohort study - Japan - 2006–2008	- HF inpatients (n=221) - Depression assessed by SDS - Mortality	All-cause mortality and rehospitalization for heart failure: aHR=1.69 (95% CI, 0.97–2.95)
Testa et al.[130] - Eur J Clin Invest - 2011	- Cohort study - Italy - 1992	- HF patients (n=1268) - Depression assessed by GDS - Mortality	All-cause mortality: aHR=1.08 (95% CI, 1.01–1.15)
Banta et al.[131] - Mil Med - 2010	- Cohort study - US - 2001	- HF inpatients (n=15,498) - Depression assessed by diagnostic codes - Mortality	All-cause mortality: adjusted odds ratio=1.30 (95% CI, 1.07–1.59)
Veien et al.[132] - Int J Cardiol - 2011	- Cohort study (Hjerterplus system) - Danish - 2002–2006	- HF outpatients (n=3346) - Depression assessed by use of antidepressants - Mortality	All-cause mortality: aHR=1.49 (95% CI, 1.03–2.16)
Fosbøl et al.[133] - Circ Heart Fail - 2009	- Cohort study - Danish - 1997–2005	- HF inpatients (n=99,335) - Depression assessed by use of antidepressants - Mortality	All-cause mortality (tricyclic antidepressants): aHR=1.47 (95% CI, 1.39–1.54) All-cause mortality (selective serotonin reuptake inhibitors): aHR=1.51 (95% CI, 1.48–1.55)
Schiffer et al.[134] - J Clin Psychiatry - 2009	- Cohort study - Dutch - 2003–2007	- HF outpatients (n=3346) - Depression assessed by BDI - Mortality	All-cause mortality (somatic/affective symptoms): aHR=1.80 (95% CI, 1.03–3.07)
Frasure-Smith et al.[135] - Circulation - 2009	- Cohort study - Multinational - Substudy from AF-CHF trial - 2001–2005	- HF patients (n=974) - Depression assessed by BDI-II - Mortality	All-cause mortality: aHR=1.38 (95% CI, 1.07–1.77)
Johansson et al.[136] - Scand Cardiovasc J - 2007	- Cohort study - Swedish - 1995–1996	- HF primary care (n=3346) - Depression assessed by mental health index - Mortality	All-cause mortality: aHR=2.2 (95% CI, 1.3–3.7) Cardiovascular mortality: aHR=3.0 (95% CI, 1.6–5.5)
Rumsfeld et al.[137] - Am Heart J - 2005	- Cohort study - US, UK, Canada - Substudy from the EPHESUS trial - 1999–2001	- MI patients with HF (n=634) - Depression assessed by Medical Outcomes Study-Depression score - Mortality	All-cause mortality: aHR=1.75 (95% CI, 1.15–2.68)

Freedland et al.[138] - Psychosom Med - 2016	- Cohort study - US - 1994–1999	- HF inpatients (n=662) - Depression assessed by mental health index - Mortality	All-cause mortality (major depression): aHR=1.64 (95% CI, 1.27–2.11)
Ramos et al.[139] - J Affect Disord - 2016	- Cohort study - Portuguese	- HF outpatients (n=130) - Depression assessed by a psychiatrist according to diagnostic criteria and BDI-II - Mortality	All-cause mortality: adjusted odds ratio=2.91 (95% CI, 1.23–6.87)
Study IV – Heart failure and risk of dementia			
Author, journal, year	**Design, setting, registries, period**	**Population, exposure, outcome**	**Results**
Rusanen et al.[51] - J Alzheimers Dis - 2014	- Cohort study (CAIDE study) - Finland - 1972, 1977, 1982, 1987	- HF patients (n=141) - All-cause dementia and Alzheimer's disease	Midlife heart failure– All-cause dementia: aHR=0.84 (95% CI, 0.33–2.13) Alzheimer's disease: aHR=1.11 (95% CI, 0.43–2.81) Late-life heart failure– All-cause dementia: aHR=2.06 (95% CI, 1.00–4.27) Alzheimer's disease: aHR=1.82 (95% CI, 0.84–3.97)
Qiu et al.[52] - Arch Intern Med - 2006	- Cohort study - Sweden - 1987–1989	- HF patients (n=205) >75 years - All-cause dementia and Alzheimer's disease	All-cause dementia: aHR=1.84 (95% CI, 1.35–2.51) Alzheimer's disease: aHR=1.80 (95% CI, 1.25–2.61)
Habeych et al.[140] - J Nerv Ment Dis - 2015	- Case–control study - US - 2010	- Patients with vascular dementia (n=898)	Heart failure as risk factor: Age- and sex-controlled odds ratio=1.8 (95% CI, 1.6–4.7)
Jefferson et al.[141] - Circulation - 2015	- Cohort study - US - 1998–2001	- Framingham Offspring Cohort (n=1039) - Cardiac index (normal vs. impaired) - All-cause dementia and Alzheimer's disease	All-cause dementia: aHR=2.07 (95% CI, 1.02–4.19) Alzheimer's disease: aHR=2.10 (95% CI, 0.96–4.61)
Sabayan et al.[142] - J Am Heart Assoc -2015	- Cohort study - Iceland - 2002–2006	- AGES Reykjavik study population (n=931) - Cardiac function - Risk of mild cognitive impairment or dementia	For each 10% decrease in left ventricle ejection fraction (aOR=1.02, 95% CI, 0.75–1.38), 10 mL decrease in left ventricular stroke volume (aOR=1.24, 95% CI, 0.99–1.57), and 1 L/min decrease in cardiac output (aOR=1.40, 95% CI, 0.99–2.00)
Bruijn et al.[143] - Neurology - 2015	- Cohort study - Dutch - 2002-2005	- Rotterdam study population (n=3291) - Subclinical cardiac dysfunction (*e.g.* high vs. low E/A ratio and fractional shortening per standard deviation) - Dementia	All-cause dementia– E/A ratio: aHR=0.82 (95% CI, 0.70–0.96) Fractional shortening: aHR=0.98 (95% CI, 0.85–1.13) Alzheimer's disease– E/A ratio: aHR=0.78 (95% CI, 0.66–0.92) Fractional shortening: aHR=0.97 (95% CI, 0.83–1.13)

Study V – Heart failure and risk of stroke			
Author, journal, year	**Design, setting, registries, period**	**Population, exposure, outcome**	**Results**
Lip et al.[58] - BMJ open - 2012	- Cohort study - Danish - 1995–2009	- Patients with heart failure in the Diet, Cancer and Health cohort (n=1239) compared with patients without heart failure (n=50,314) - Stroke and death	All stroke: aHR=2.1 (95% CI, 1.7–2.7) Ischemic stroke: aHR=2.3 (95% CI, 1.8–3.0) Hemorrhagic stroke: aHR=1.8 (95% CI, 1.0–3.3) Stronger associations in the short term than in the long term (for a composite of death and stroke)
Alberts et al.[57] - Eur J Epidemiol - 2010	- Cohort study - Dutch - 1990–1993	- HF patients (n=1247) - General population without HF (n=6299) - Stroke	All stroke: aHR=1.07 (95% CI, 0.86–1.32) Ischemic stroke: aHR=1.02 (95% CI, 0.77–1.37) Hemorrhagic stroke: aHR=0.80 (95% CI, 0.37–1.76) All stroke– 0–30 days: aHR=3.59 (95% CI, 1.59–8.10) 30 days: aHR=6 months 1.60 (95% CI, 0.93–2.73 6 months–5 years aHR=0.78 (95% CI, 0.58–1.05) Ischemic stroke– 0–30 days: aHR=4.60 (95% CI, 1.70–12.49) 30 days: aHR=6 months 2.75 (95% CI, 1.53–4.94) 6 months–5 years aHR=0.58 (95% CI, 0.37–0.92)
Witt et al.[59] - American Heart J - 2006	- Cohort study - US - 1979–1999	- Incident HF (n=630) - General population cohort (standardized morbidity ratios) - Ischemic stroke	Ischemic stroke– 0–30 days: standardized morbidity ratio=17.4 (95% CI, 8.4–32.1) 5 years: standardized morbidity ratio=2.9 (95% CI, 2.2–3.8)
Pullicino et al.[144] - Stroke - 2009	- Cross sectional - US - 2003–2007	- HF patients (n=251) - General population without HF (n=21,202)	Prevalent stroke/TIA was present in 26.3% and 8.5% of participants with and without HF, respectively. Stroke/TIA: adjusted odds ratio=2.2 (95% CI 1.5–3.4)

Abbreviations: aHR, adjusted hazard ratio; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies–Depression; CI, confidence interval; DNPR, Danish National Patient Registry; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; HF, heart failure; PE, pulmonary embolism; PHQ, Patient Health Questionnaire; PPV, positive predictive value; SDS, Zung Self-rating Depression Scale; MI, myocardial infarction; TIA, transitory ischemic attack; VTE, venous thromboembolism

MEDLINE search query:
Studies I-II: "positive predictive value" AND "Danish National Patient Registry" OR "Danish Hospital Discharge Registry" OR "Danish National Hospital Registry" OR "Danish Hospital Registers" OR "Danish National Registry of Patients"=227 in Medline and 58 in Scopus
Study III: "Depression"[All Fields] AND "heart failure"[All Fields] AND "mortality"[All Fields] AND ("loattrfull text"[sb] AND ("1995/01/01"[PDAT]: "3000/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])=462 in Medline and 1155 in Scopus
Study IV: "dementia"[All Fields] AND "heart failure"[All Fields] AND ("loattrfull text"[sb] AND ("1995/01/01"[PDAT]: "3000/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])=480 in Medline and 1420 in Scopus
Study V: "Heart Failure/epidemiology"[Mesh] AND "Stroke/epidemiology"[Mesh] AND ("loattrfull text"[sb] AND ("1995/01/01"[PDAT]: "3000/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])=541 in Medline and 793 in Scopus (free text search: "heart failure" AND "stroke" AND "epidemiology")

3. Methods

3.1 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.

3.2 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.[145]

The Danish Heart Failure Registry

This registry, launched in February 2003, is a part of the Danish Clinical Registries,[146,147] 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.[148] 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.[149]

Danish Psychiatric Central Research Register

All patients admitted to psychiatric hospitals and psychiatric wards in general hospitals in Denmark are included in this registry.[150] 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.[151]

3.3 Study designs

We conducted two validation studies and three cohort studies. A summary of the objectives and methods used in the study is provided in Table 3.

Table 3. Overview of the objectives and methods.

	Studies I-II	Study III	Study IV	Study V
Objectives	We examined the PPV of codes for cardiovascular diseases and cardiac interventions in the DNPR	We examined the influence of depression on mortality risk in patients with HF	We examined the risk of dementia among patients with HF and members of a general population comparison cohort	We examined short-term and long-term risk of ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage in HF patients and in a general population comparison cohort
Design	Validation studies (cross-sectional studies analogous to diagnostic tests)	Population-based cohort study	Population-based matched cohort study	Population-based matched cohort study
Data sources	CRS, DNPR, EPJ	CRS, DNPR, DPCR, DPR, DRPLMA, DHFR, RCD	CRS, DNPR, DPCR	CRS, DNPR, NHSPD
Study region and study period	Central Denmark Region (Aarhus University Hospital, Randers and Herning regional hospitals), 2010–2012	Nationwide: 1 July 1995 to 1 February 2014	Nationwide: 1 January 1980 to 1 September 2012	Nationwide: 1 January 1980 to 30 November 2013
Study population	Patients with cardiovascular diagnoses and patients who underwent cardiac interventions	Patients with first-time inpatient HF hospitalization	Patients with first-time HF hospitalization; general population comparison cohort	Patients with first-time HF hospitalization; general population comparison cohort
Exposures	N/A	A history of depression defined as hospital-based diagnoses or redeemed prescription for antidepressants	N/A	N/A
Outcomes	PPVs with information in the medical record as reference standard	All-cause mortality, cause-specific mortality (immediate death causes)	All-cause dementia, Alzheimer's disease, vascular dementia, and other dementias	Ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage
Covariables	N/A	MI, hypertension, AFF, stroke, cancer, obesity, DM, chronic pulmonary disease, chronic kidney disease, peptic ulcer, alcohol/smoking/illicit drug abuse, dementia, anemia, peripheral arterial disease, gross income, and employment	MI, angina pectoris, AFF, valvular heart disease, hypercholesterolemia, hypertension, stroke, obesity, DM, chronic pulmonary disease, myxedema, alcoholism-related diseases, head trauma, osteoarthritis, anemia, chronic kidney disease, and a modified CCI	MI, angina pectoris, AFF, valvular heart disease, hypertension, intermittent claudication, venous thromboembolism, hypercholesterolemia, hypertriglyceridemia, obesity, DM, chronic kidney disease, cancer, chronic pulmonary disease, alcoholism-related disease, and dementia
Statistics	Wilson score method for confidence interval calculation	Cox proportional hazard regression, Kaplan–Meier method; multiple imputation to account for missing data	Stratified Cox proportional hazard regression, cumulative incidence risk function Standardized incidence ratios	Stratified Cox proportional hazard regression, cumulative incidence risk function Standardized incidence ratios
Confounder control	N/A	Adjustment for covariables Stratification	Age, sex, and calendar period matching Adjustment for covariables Stratification	Age, sex, and calendar period matching Adjustment for covariables Stratification
Subgroup analyses	Age, sex, index year, primary/secondary diagnoses, inpatient/outpatients, hospital type	Age, sex, index year, HF cause, LVEF, NYHA class, comorbidity, comedication, socioeconomic factors	Age, sex, index year, HF cause, comorbidity	Age, sex, index year, AFF, HF causes
Sensitivity analyses	N/A	Analysis of patients with depression recorded in the DNPR and DPCR, restriction to recent depression diagnoses, adjustment for education, anxiolytics/hypnotics and antipsychotics, omitting MI, stroke, hypertension, and DM from the models, restriction to patients in the DHFR	Redefining the HF cohort to include both in- and outpatients, sequentially excluding the initial 2, 3, 5, and 10 years of follow-up, reclassification of Alzheimer's disease to include codes for unspecified dementia in the Alzheimer's disease definition	Restriction to stroke patients with a brain scan, separate analysis of unspecified/specified ischemic stroke, adjustment for antithrombotic and anticongestive drugs, allowing patient to be at risk for other strokes after first stroke, restriction to first-time outpatient HF patients and HF primary diagnoses, stratification by length of stay and intensive care unit

Abbreviations: AFF, atrial fibrillation or atrial flutter; CCI, Charlson Comorbidity Index; CRS, Civil Registration System; DHFR, Danish Heart Failure Registry; DNPR, Danish National Patient Registry; DPCR, Danish Psychiatric Central Research Register; DPR, Danish National Prescription Registry; DRPLMA, Danish registers on personal labor market affiliation; DM, diabetes mellitus; EPJ, electronic patient journal; HF, heart failure; ICD, International Classification of Diseases; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NHSPD, National Health Service Prescription Database; NYHA, New York Heart Association functional class; PPV, positive predictive value; RCD, Register of Causes of Deaths

3.4 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.

3.5 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.[152] The PPV of depression in the DNPR is unknown.

3.6 Outcomes

3.6.1 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.[153] 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.

3.6.2 Mortality

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

3.6.3 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.[154]

3.6.4 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.[155] 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.

3.7 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.[156,157] 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.[156,157] 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]

3.8 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,[158] indicating the necessity of also using other data sources for assessment of these covariables.

3.9 Statistical analyses

The statistical analyses used for the studies are summarized in Table 3 and in detail for the individual studies in appendices I–V. For studies I-II, we applied the Wilson score method for CI calculation.[159] 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[160] (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.[161] 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.[161]

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.

3.10 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).

4. Results

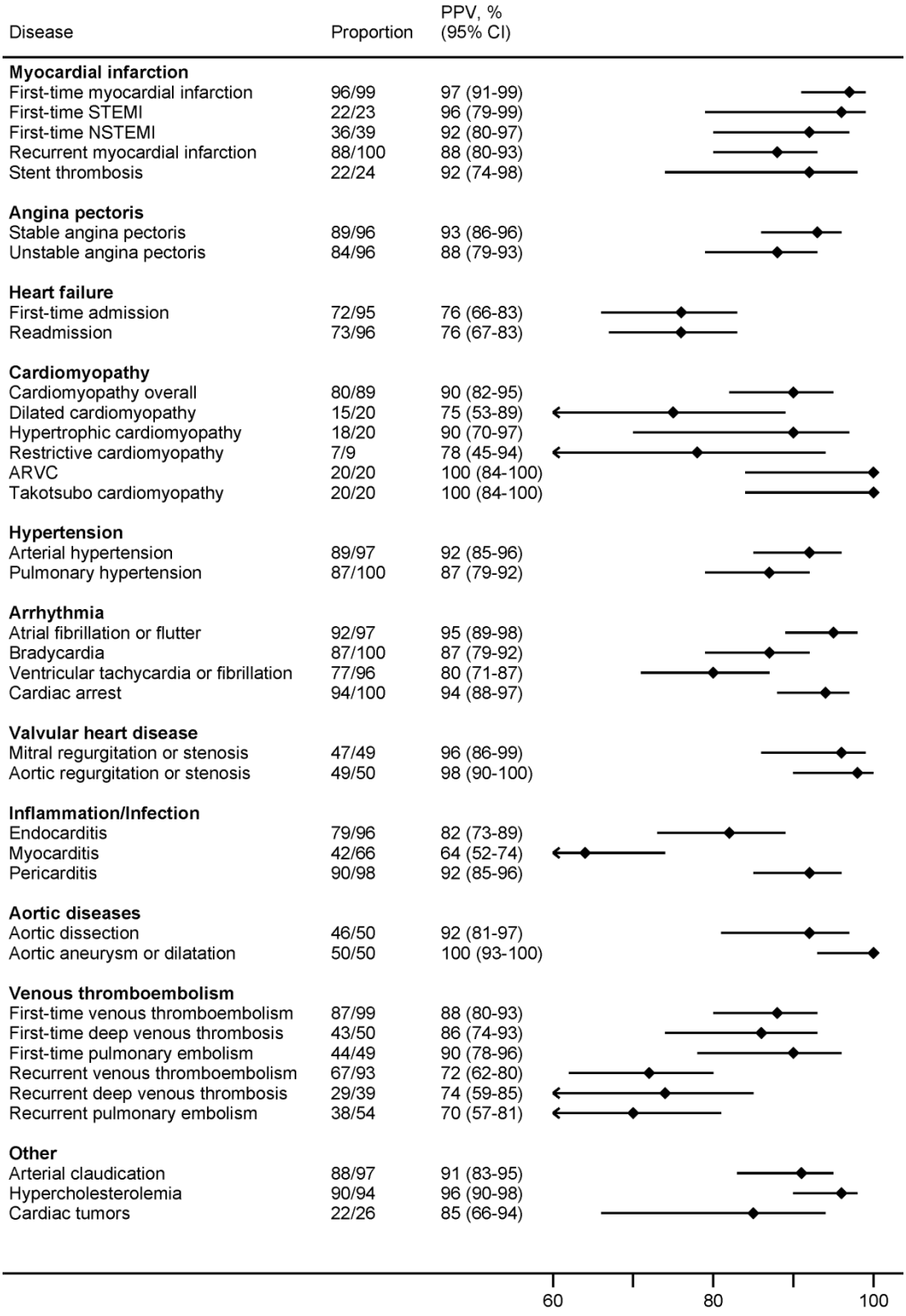
The main findings from studies I–V are presented in the following section and in detail in appendices I–V.

4.1 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.

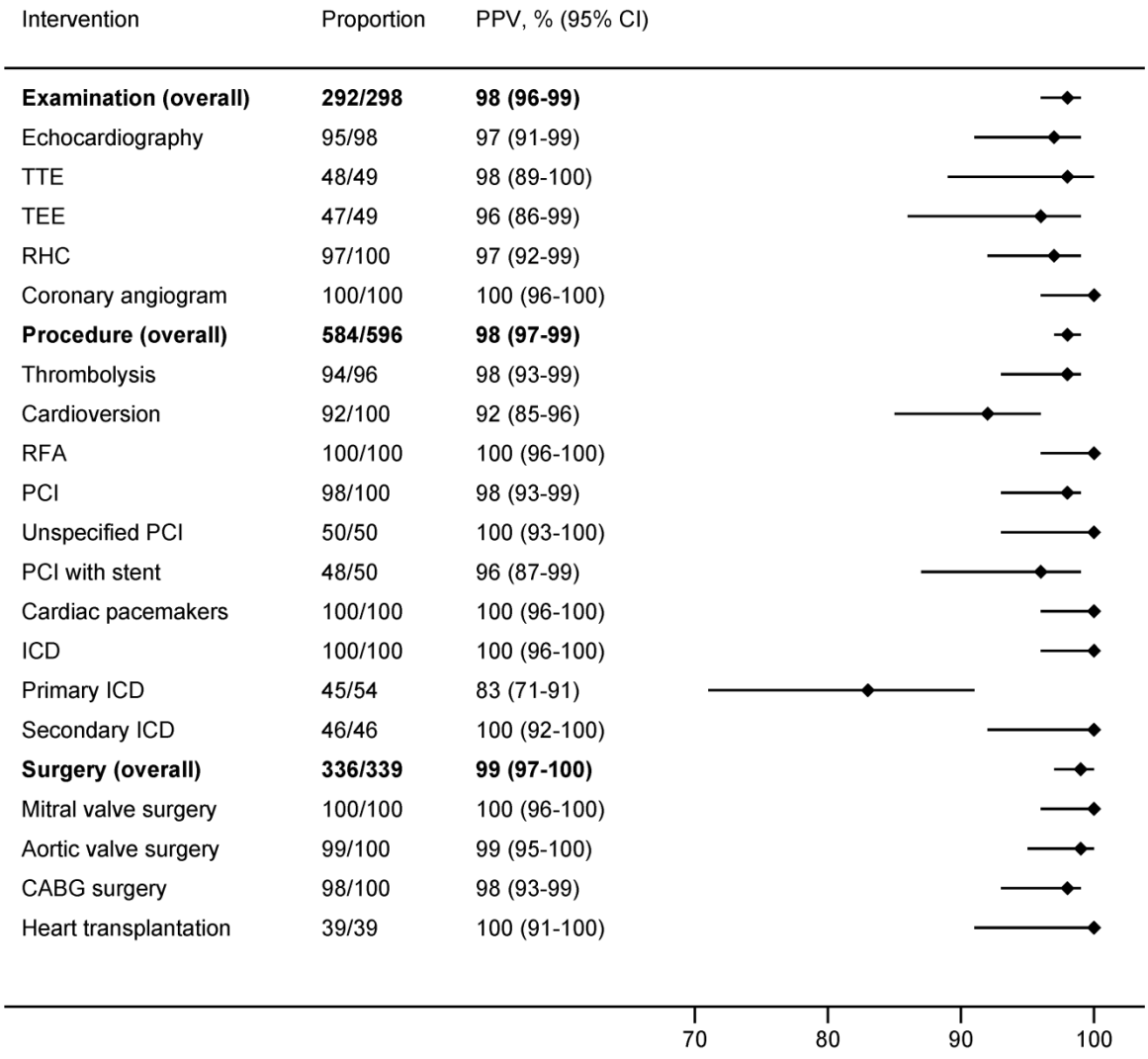
The PPVs ranged from 64% to 100% (Figures 1-2). For the cardiovascular diagnoses, a majority of the PPVs were above 85%, except for first-time and readmission for heart failure (76% for both), dilated cardiomyopathy (75%), restrictive cardiomyopathy (78%), ventricular tachycardia or fibrillation (80%), 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.[162]



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.[163]



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

4.2 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).

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.[164]

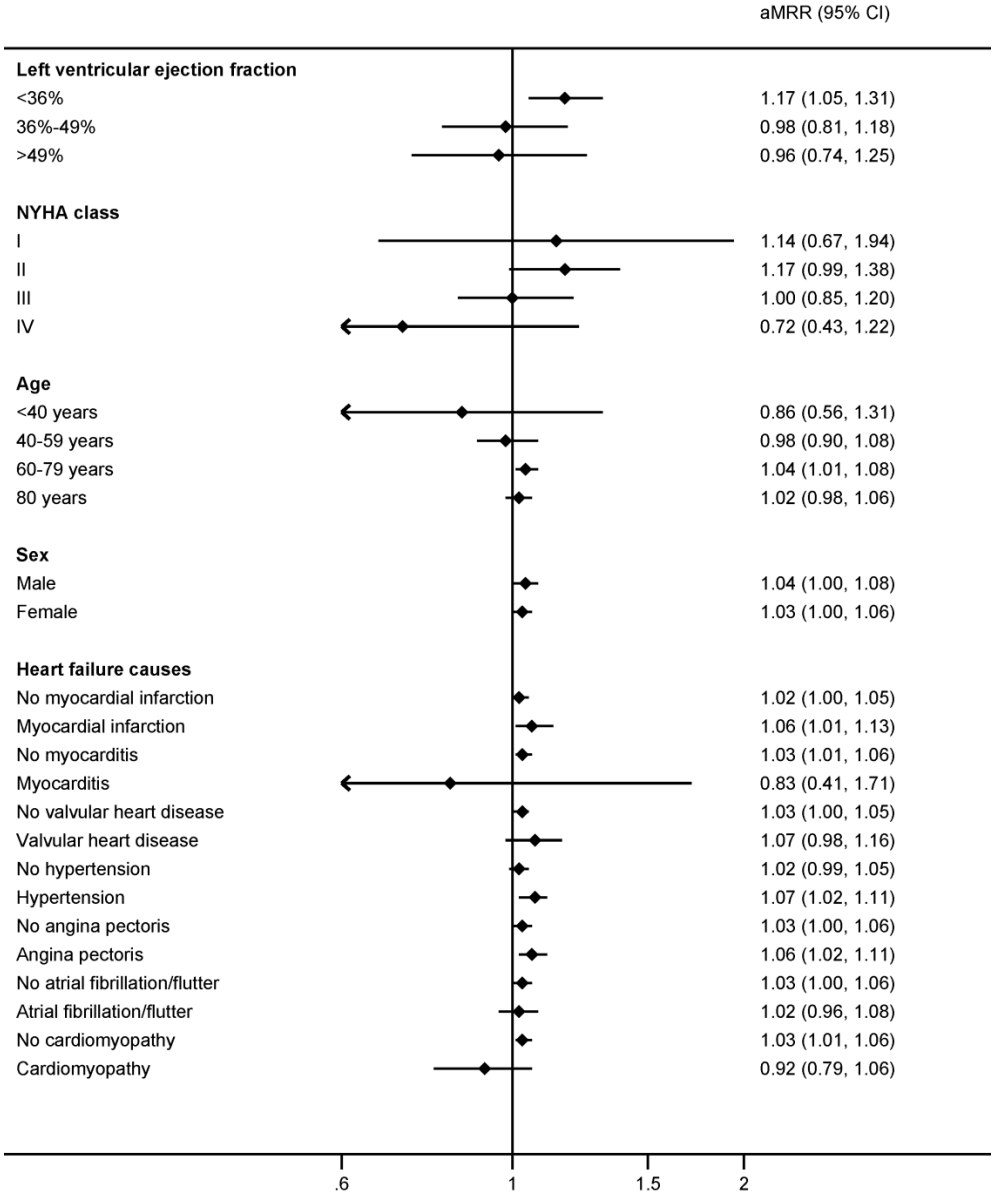
Depression diagnosis	**Use of antidepressants**	**Unadjusted MRR (95% CI)**	**Adjusted MRR (95% CI)**
No depression	N/A	Reference	Reference
Depression (n=9636)	N/A	1.14 (1.12–1.17)	1.03 (1.01–1.06)
Mild (n=1379)	N/A	1.27 (1.20–1.35)	1.06 (1.00–1.13)
Moderate (n=2914)	N/A	1.16 (1.11–1.21)	1.03 (0.99–1.08)
Severe (n=1305)	N/A	1.05 (0.99–1.12)	1.02 (0.96–1.09)
No depression	Non-use (n=156,168)	Reference	Reference
	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)
Depression	Non-use (n=1912)	1.07 (1.02–1.13)	1.00 (0.95–1.06)
	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

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).

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.[164]

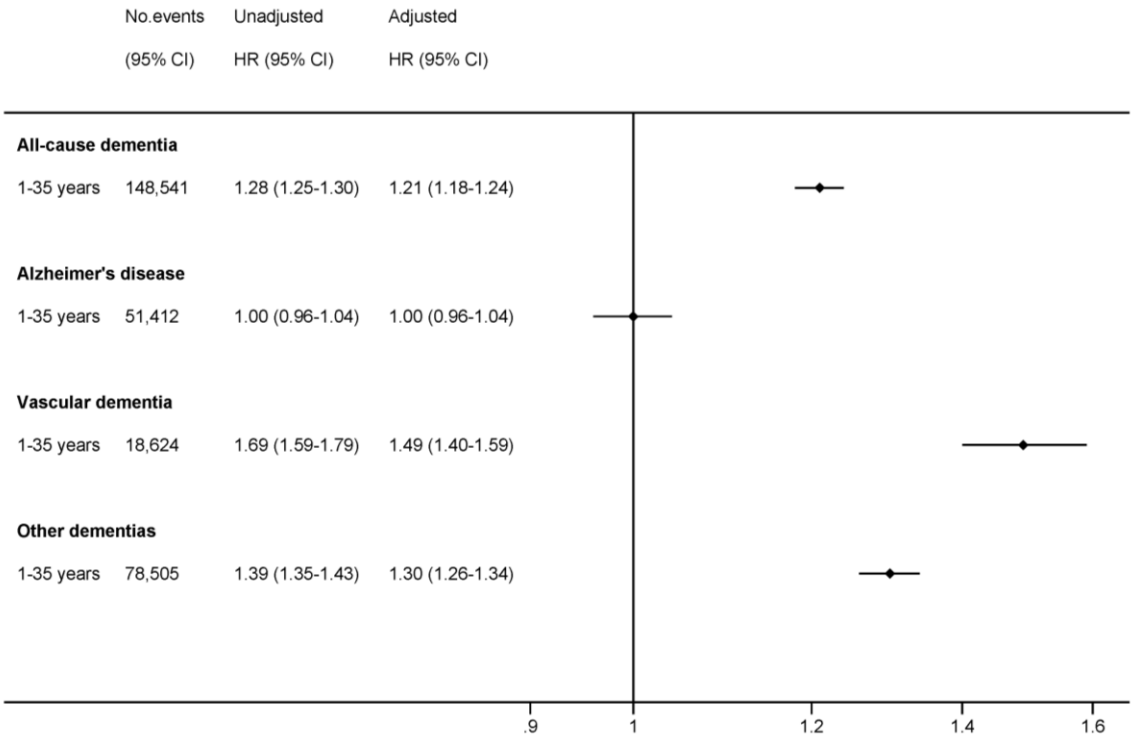


Abbreviations: aMRR, adjusted mortality rate ratio; CI, confidence interval; NYHA class, New York Heart Association functional class

4.3 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.

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.[165]

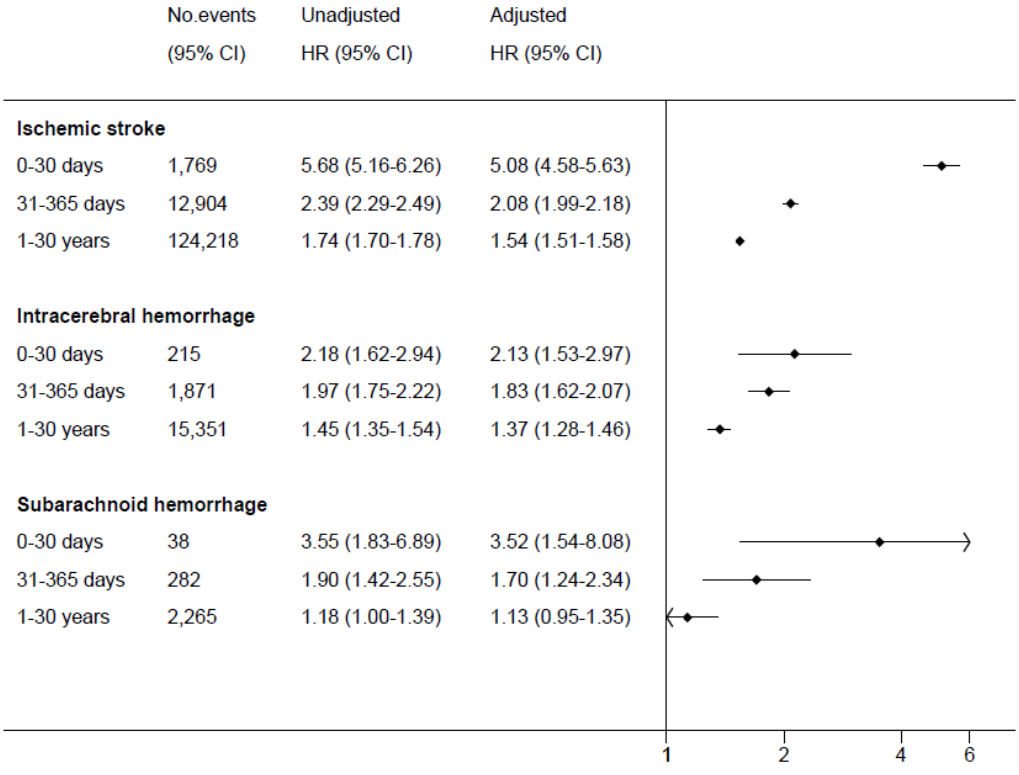


Abbreviations: CI: confidence interval; HR: hazard ratio

4.4 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.[166]



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.

5. Discussion

5.1 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.

5.2 Comparison with existing literature

Below, we discuss our findings in the context of the literature (Table 2).

5.2.1 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%),[84,86] arterial hypertension (PPV~88%),[81] atrial fibrillation or atrial flutter (PPV~93%–99%),[93,94] and first-time venous thromboembolism

(PPV~75%–90%).[88,91] In line with a previous study, our PPV for recurrent venous thromboembolism was lower than for first-time venous thromboembolism,[91] 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%),[83] which could trace to the implementation of strict criteria for myocardial infarction and unstable angina pectoris during our study period.[167] We found a considerably higher PPV for cardiac arrest than in a previous study (PPV=50%).[83] 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.[83] 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.

5.2.2 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[103,168] and non-ischemic heart failure,[119] both inpatients[104,107] and outpatients.[112,114,122] The finding seems consistent regardless of geographical region as it has been identified in cohorts from Europe,[103,104,112] Japan,[168] and the United States.[107,115]Although preserved LVEF and depression have not been widely studied, the connection to increased mortality also seems uniform in these patients.[168] 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.[168] 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.

5.2.3 Heart failure and risk of dementia

Several studies have linked heart failure with impaired cognitive performance (*e.g.* low Mini-Mental State Examination scores);[169] 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[142] and the Framingham Offspring cohort study[141]) 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).

5.2.4 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[170-172] – a trend also observed in our analyses using length of hospital and stay in intensive care as proxies for heart failure severity.

5.3 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.

5.3.1 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.[173] 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.

5.3.2 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.

5.3.2.1 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.

5.3.2.2 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.

5.3.3 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),[174] 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.[161] 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.

5.3.4 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.[175] 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.

5.4 Perspectives

Our findings have some implications. Unlike sensitivity and specificity, PPV is affected by the prevalence of a disease.[46,176] 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.[176] Prioritizing a high PPV is particularly important when sampling study cohorts.[176] 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).

6. 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.

7. Dansk resume

Hjertesvigt en klinisk tilstand med symptomer og tegn på nedsat hjertepumpefunktion. Prævalensen anslås til 1%-2%. Hjertesvigt indebærer overordnet en dårlig prognose med en 5-års mortalitet på omkring 50%, hvilket til dels synes at kunne være forklaret ved tilstedeværelse af komorbiditet, herunder neurologisk og psykiatrisk komorbiditet. Den prognostiske betydning af depression hos patienter med hjertesvigt og om hjertesvigt er en risikofaktor for udvikling af demens og apoplexi er dog ikke fuldt klarlagt.

Danmark har helt unikke sundhedsregistre. Landspatientregistret er hyppigt anvendt indenfor forskning i hjertekarsygdomme, men det er væsentligt at vide, at der er en begrænset evidens for validiteten af visse diagnoser og koder, som bør tages i betragtning forud for gennemførelse af alle registerstudier.

Formålet med denne afhandling var at undersøge den positive prædiktive værdi (PPV) af en række kardiovaskulære udskrivningsdiagnoser herunder hjertesvigtsdiagnosen (studie I) samt kardiovaskulære undersøgelser, procedurer, og kirurgiske indgreb (studie II). Derudover undersøgte vi den prognostiske betydning af depression for dødeligheden hos patienter med hjertesvigt (studie III), og vi undersøgte om hjertesvigt er en risikofaktor vi udviklingen af demens (studie IV) og apoplexi (studie V).

I studie I og II brugte vi Landspatientregistret til at identificere 3386 patienter med en kardiovaskulær udskrivningsdiagnose eller en kardiologisk undersøgelse, procedure eller kirurgiske indgreb i perioden 2010–2012. Med oplysninger i patientjournalen som reference, fandt vi en høj PPV (≥90%) for de fleste diagnoser, undersøgelser, procedurer, og kirurgiske indgreb, mens PPV var lavere for få sygdomme (myocarditis, hjertesvigt og gentagne events).

Studie III inkluderede 205,719 patienter med hjertesvigt identificeret i perioden 1995–2014. Vi fandt, at depression var associeret med en øget dødelighed i en subgruppe af patienter med en venstre ventrikel ejection fraction ≤35% og hvis man definerede depression ved kombinationen af diagnoser og indløste recepter på antidepressiva, men ikke hos andre hjertesvigtspatienter.

Studie IV inkluderede 324,418 hjertesvigtspatienter og 1,622,079 kontroller af samme alder og køn fra baggrundsbefolkningen i perioden 1980–2012. Overordnet fandt vi en 21% øget risiko for demens i hjertesvigtskohorten sammenlignet med baggrundsbefolkningskohorten. Hjertesvigt var ikke associeret med en øget risiko for Alzheimer's demens, men det overordnede estimatet var drevet af en øget risiko for vaskulær demens og andre demenstyper.

Studie V inkluderede 289,353 patienter med hjertesvigt og 1,446,765 kontroller af samme alder og køn fra baggrundsbefolkningen i perioden 1980–2013. Sammenlignet med baggrundbefolkningskohorten var 30-dages risikoen hos hjertesvigtskohorten 5-fold øget for iskæmisk apoplexi, 2-fold for intracerebral blødning, samt 4-fold for subarachnoidal blødning. Hjertesvigtskohorten forblev i højere risiko for alle apoplexityper sammenlignet med baggrundsbefolkningkohorten fra 31 dage efter og indtil 30 år efter deres diagnose.

Sammenfattende viste vores studier en høj PPV for en lang række kardiovaskulære diagnoser, undersøgelser, procedurer samt kirurgiske indgreb kodet i Landspatientregistret. Derudover fandt vi, at depression var en prognostisk factor for død, men kun hos hjertesvigtspatienter med venstre ventrikel ejection fraction ≤35%. Endelig tyder vores resultater på at hjertesvigt er en risikofaktor for udviklingen af demens og alle apoplexi typer.

8. References

1. Roger VL. Epidemiology of heart failure. *Circ Res.* 2013;113(6):646-659.

2. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol.* 2016;13(6):368-378.

3. Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016;37(27):2129-2200.

4. Lloyd-Jones DM, Larson MG, Leip EP et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation.* 2002;106(24):3068-3072.

5. van Riet EE, Hoes AW, Limburg A, Landman MA, van der Hoeven H, Rutten FH. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. *Eur J Heart Fail.* 2014;16(7):772-777.

6. Levy D, Kenchaiah S, Larson MG et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med.* 2002;347(18):1397-1402.

7. Roger VL, Weston SA, Redfield MM et al. Trends in heart failure incidence and survival in a community-based population. *JAMA.* 2004;292(3):344-350.

8. Schmidt M, Ulrichsen SP, Pedersen L, Bøtker HE, Sørensen HT. Thirty-year trends in heart failure hospitalization and mortality rates and the prognostic impact of co-morbidity: a Danish nationwide cohort study. *Eur J Heart Fail.* 2016 May;18(5):490-9

9. Christiansen MN, Køber L, Weeke P et al. Age-specific Trends in Incidence, Mortality and Comorbidities of Heart Failure in Denmark 1995-2012. *Circulation.* 2017 Mar 28;135(13):1214-1223

10. Nakano A, Johnsen SP, Frederiksen BL et al. Trends in quality of care among patients with incident heart failure in Denmark 2003-2010: a nationwide cohort study. *BMC Health Serv Res.* 2013;13:391-6963-13-391.

11. Blecker S, Agarwal SK, Chang PP et al. Quality of care for heart failure patients hospitalized for any cause. *J Am Coll Cardiol.* 2014;63(2):123-130.

12. Curtis LH, Whellan DJ, Hammill BG et al. Incidence and prevalence of heart failure in elderly persons, 1994-2003. *Arch Intern Med.* 2008;168(4):418-424.

13. Hoes AW, Mosterd A, Grobbee DE. An epidemic of heart failure? Recent evidence from Europe. *Eur Heart J.* 1998;19 Suppl L:L2-9.

14. Braunwald E. Shattuck lecture--cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med.* 1997;337(19):1360-1369.

15. Heidenreich PA, Albert NM, Allen LA et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail.* 2013;6(3):606-619.

16. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med.* 1971;285(26):1441-1446.

17. Carlson KJ, Lee DC, Goroll AH, Leahy M, Johnson RA. An analysis of physicians' reasons for prescribing long-term digitalis therapy in outpatients. *J Chronic Dis.* 1985;38(9):733-739.

18. Eriksson H, Caidahl K, Larsson B et al. Cardiac and pulmonary causes of dyspnoea--validation of a scoring test for clinical-epidemiological use: the Study of Men Born in 1913. *Eur Heart J.* 1987;8(9):1007-1014.

19. Redfield MM. Heart Failure with Preserved Ejection Fraction. *N Engl J Med.* 2016;375(19):1868-1877.

20. Yancy CW, Jessup M, Bozkurt B et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;62(16):e147-239.

21. Fletcher R, Fletcher S, Fletcher G. Clinical Epidemiology. The Essentials. Fifth edition. Lippincott Williams & Wilkins. 2014.

22. Sridharan L, Klein L. Prognostic factors in patients hospitalized for heart failure. *Curr Heart Fail Rep.* 2013;10(4):380-386.

23. Blecker S, Paul M, Taksler G, Ogedegbe G, Katz S. Heart failure-associated hospitalizations in the United States. *J Am Coll Cardiol.* 2013;61(12):1259-1267.

24. Kemp CD, Conte JV. The pathophysiology of heart failure. *Cardiovasc Pathol.* 2012;21(5):365-371.

25. Ording AG, Sørensen HT. Concepts of comorbidities, multiple morbidities, complications, and their clinical epidemiologic analogs. *Clin Epidemiol.* 2013;5:199-203.

26. McMurray JJ, Adamopoulos S, Anker SD et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2012;33(14):1787-1847.

27. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol.* 2006;48(8):1527-1537.

28. Fan H, Yu W, Zhang Q et al. Depression after heart failure and risk of cardiovascular and all-cause mortality: a meta-analysis. *Prev Med.* 2014;63:36-42.

29. Sokoreli I, de Vries JJ, Pauws SC, Steyerberg EW. Depression and anxiety as predictors of mortality among heart failure patients: systematic review and meta-analysis. *Heart Fail Rev.* 2016;21(1):49-63.

30. Newhouse A, Jiang W. Heart Failure and Depression. *Heart Fail Clin.* 2014;10(2):295-304.

31. Joynt KE, Whellan DJ, O'connor CM. Why is depression bad for the failing heart? A review of the mechanistic relationship between depression and heart failure. *J Card Fail.* 2004;10(3):258-271.

32. Plotsky PM, Owens MJ, Nemeroff CB. Psychoneuroendocrinology of depression. Hypothalamic-pituitary-adrenal axis. *Psychiatr Clin North Am.* 1998;21(2):293-307.

33. Owen BM, Eccleston D, Ferrier IN, Young AH. Raised levels of plasma interleukin-1beta in major and postviral depression. *Acta Psychiatr Scand.* 2001;103(3):226-228.

34. Papanicolaou DA, Wilder RL, Manolagas SC, Chrousos GP. The pathophysiologic roles of interleukin-6 in human disease. *Ann Intern Med.* 1998;128(2):127-137.

35. Mikova O, Yakimova R, Bosmans E, Kenis G, Maes M. Increased serum tumor necrosis factor alpha concentrations in major depression and multiple sclerosis. *Eur Neuropsychopharmacol.* 2001;11(3):203-208.

36. Seidel A, Arolt V, Hunstiger M, Rink L, Behnisch A, Kirchner H. Cytokine production and serum proteins in depression. *Scand J Immunol.* 1995;41(6):534-538.

37. Kop WJ, Gottdiener JS, Tangen CM et al. Inflammation and coagulation factors in persons > 65 years of age with symptoms of depression but without evidence of myocardial ischemia. *Am J Cardiol.* 2002;89(4):419-424.

38. Gorman JM, Sloan RP. Heart rate variability in depressive and anxiety disorders. *Am Heart J.* 2000;140(4 Suppl):77-83.

39. Pacher P, Kecskemeti V. Cardiovascular side effects of new antidepressants and antipsychotics: new drugs, old concerns? *Curr Pharm Des.* 2004;10(20):2463-2475.

40. Nemeroff CB, Musselman DL. Are platelets the link between depression and ischemic heart disease? *Am Heart J.* 2000;140(4 Suppl):57-62.

41. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med.* 2000;160(14):2101-2107.

42. O'Connor CM, Jiang W, Kuchibhatla M et al. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. *J Am Coll Cardiol.* 2010;56(9):692-699.

43. Angermann CE, Gelbrich G, Stork S et al. Effect of Escitalopram on All-Cause Mortality and Hospitalization in Patients With Heart Failure and Depression: The MOOD-HF Randomized Clinical Trial. *JAMA.* 2016;315(24):2683-2693.

44. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med.* 2008;5(2):e45.

45. Hammond MF. Rating depression severity in the elderly physically ill patient: reliability and factor structure of the Hamilton and the Montgomery-Asberg Depression Rating Scales. *Int J Geriatr Psychiatry.* 1998;13(4):257-261.

46. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology 3rd edn.Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2008.

47. Burns A, Iliffe S. Dementia. *BMJ.* 2009;338:b75.

48. The epidemiology and impact of dementia. Current state and future trends. World Health Organization 2015. Available at: http://www.who.int/mental_health/neurology/dementia/en/ (accessed 1 January 2017).

49. Chen JH, Lin KP, Chen YC. Risk factors for dementia. *J Formos Med Assoc.* 2009;108(10):754-764.

50. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry.* 2006;63(5):530-538.

51. Rusanen M, Kivipelto M, Levalahti E et al. Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE study. *J Alzheimers Dis.* 2014;42(1):183-191.

52. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. *Arch Intern Med.* 2006;166(9):1003-1008.

53. Cermakova P, Eriksdotter M, Lund LH, Winblad B, Religa P, Religa D. Heart failure and Alzheimer's disease. *J Intern Med.* 2015;277(4):406-425.

54. Shimizu A, Sakurai T, Mitsui T et al. Left ventricular diastolic dysfunction is associated with cerebral white matter lesions (leukoaraiosis) in elderly patients without ischemic heart disease and stroke. *Geriatr Gerontol Int.* 2014;14 Suppl 2:71-76.

55. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol.* 2012;11(11):1006-1012.

56. Writing Group Members, Mozaffarian D, Benjamin EJ et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation.* 2016;133(4):e38-360.

57. Alberts VP, Bos MJ, Koudstaal P et al. Heart failure and the risk of stroke: the Rotterdam Study. *Eur J Epidemiol.* 2010;25(11):807-812.

58. Lip GY, Rasmussen LH, Skjoth F, Overvad K, Larsen TB. Stroke and mortality in patients with incident heart failure: the Diet, Cancer and Health (DCH) cohort study. *BMJ Open.* 2012;2(4):10.1136/bmjopen-2012-000975. Print 2012.

59. Witt BJ, Brown RD,Jr, Jacobsen SJ et al. Ischemic stroke after heart failure: a community-based study. *Am Heart J.* 2006;152(1):102-109.

60. Haeusler KG, Laufs U, Endres M. Chronic heart failure and ischemic stroke. *Stroke.* 2011;42(10):2977-2982.

61. Lip GY, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. *J Am Coll Cardiol.* 1999;33(5):1424-1426.

62. Cokkinos DV, Haralabopoulos GC, Kostis JB, Toutouzas PK, HELAS investigators. Efficacy of antithrombotic therapy in chronic heart failure: the HELAS study. *Eur J Heart Fail.* 2006;8(4):428-432.

63. Homma S, Thompson JL, Pullicino PM et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med.* 2012;366(20):1859-1869.

64. Cleland JG, Findlay I, Jafri S et al. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J.* 2004;148(1):157-164.

65. Homma S, Thompson JL, Qian M et al. Quality of anticoagulation control in preventing adverse events in patients with heart failure in sinus rhythm: Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction trial substudy. *Circ Heart Fail.* 2015;8(3):504-509.

66. Zannad F, Greenberg B, Cleland JG et al. Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial. *Eur J Heart Fail.* 2015;17(7):735-742.

67. Sørensen HT. Regional administrative health registries as a resource in clinical epidemiology. A study of options, strengths, limitations and data quality provided with examples of use. *Int J Risk Saf Med.* 1997;10(1):1-22.

68. Benchimol EI, Smeeth L, Guttmann A et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med.* 2015;12(10):e1001885.

69. Nicholls SG, Langan SM, Sørensen HT, Petersen I, Benchimol EI. The RECORD reporting guidelines: meeting the methodological and ethical demands of transparency in research using routinely-collected health data. *Clin Epidemiol.* 2016;8:389-392.

70. Ehrenstein V, Petersen I, Smeeth L et al. Helping everyone do better: a call for validation studies of routinely recorded health data. *Clin Epidemiol.* 2016;8:49-51.

71. Public Policy Committee, International Society of Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practice (GPP). *Pharmacoepidemiol Drug Saf.* 2016;25(1):2-10.

72. Schmidt M, Pottegaard A, Schmidt SAJ, Christiansen CF. Validering er forskning - et holdningspapir fra Dansk Selskab for Farmakoepidemiologi. 2016. Available at: https://www.dsfe.dk (accessed 4 April 2017).

73. Lash TL, Olshan AF. EPIDEMIOLOGY Announces the "Validation Study" Submission Category. *Epidemiology.* 2016;27(5):613-614.

74. Frank L. Epidemiology. When an entire country is a cohort. *Science.* 2000;287(5462):2398-2399.

75. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol.* 2014;29(8):541-549.

76. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol.* 2015;7:449-490.

77. Mard S, Nielsen FE. Positive predictive value and impact of misdiagnosis of a heart failure diagnosis in administrative registers among patients admitted to a University Hospital cardiac care unit. *Clin Epidemiol.* 2010;2:235-239.

78. Kumler T, Gislason GH, Kirk V et al. Accuracy of a heart failure diagnosis in administrative registers. *Eur J Heart Fail.* 2008;10(7):658-660.

79. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol.* 2011;11:83-2288-11-83.

80. Lasota AN, Overvad K, Eriksen HH, Tjonneland A, Schmidt EB, Gronholdt MM. Validity of Peripheral Arterial Disease Diagnoses in the Danish National Patient Registry. *Eur J Vasc Endovasc Surg.* 2017;.

81. Schmidt M, Bøtker HE, Pedersen L, Sørensen HT. Obesity in young men and long-term risk of atrial fibrillation: 33-year follow-up of 12,850 young healthy men. *Circulation.* 2013;128(22).

82. Nielsen HW, Tuchsen F, Jensen MV. Validity of the diagnosis "essential hypertension" in the National Patient Registry. *Ugeskr Laeger.* 1996;158(2):163-167.

83. Joensen AM, Jensen MK, Overvad K et al. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish National Patient Registry. *J Clin Epidemiol.* 2009;62(2):188-194.

84. Coloma PM, Valkhoff VE, Mazzaglia G et al. Identification of acute myocardial infarction from electronic healthcare records using different disease coding systems: a validation study in three European countries. *BMJ Open.* 2013;3(6):10.1136/bmjopen-2013-002862.

85. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol.* 2003;56(2):124-130.

86. Madsen M, Balling H, Eriksen LS. The validity of the diagnosis of acute myocardial infarction in 2 registries: the Heart Registry compared to the National Patient Registry. *Ugeskr Laeger.* 1990;152(5):308-314.

87. Drljevic A, Borre M, Hoyer M, Ehrenstein V, Nguyen-Nielsen M. Quality of venous thromboembolism diagnoses among prostate cancer patients in the Danish National Registry of Patients. *Clin Epidemiol.* 2014;6:351-357.

88. Severinsen MT, Kristensen SR, Overvad K, Dethlefsen C, Tjonneland A, Johnsen SP. Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution. *J Clin Epidemiol.* 2010;63(2):223-228.

89. Larsen TB, Johnsen SP, Møller CI, Larsen H, Sørensen HT. A review of medical records and discharge summary data found moderate to high predictive values of discharge diagnoses of venous thromboembolism during pregnancy and postpartum. *J Clin Epidemiol.* 2005;58(3):316-319.

90. Ingeman A, Andersen G, Hundborg HH, Johnsen SP. Medical complications in patients with stroke: data validity in a stroke registry and a hospital discharge registry. *Clin Epidemiol.* 2010;2:5-13.

91. Schmidt M, Cannegieter SC, Johannesdottir SA, Dekkers OM, Horvath-Puho E, Sørensen HT. Statin use and venous thromboembolism recurrence: a combined nationwide cohort and nested case-control study. *J Thromb Haemost.* 2014;12(8):1207-1215.

92. Rix TA, Riahi S, Overvad K, Lundbye-Christensen S, Schmidt EB, Joensen AM. Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry. *Scand Cardiovasc J.* 2012;46(3):149-153.

93. Frost L, Andersen LV, Vestergaard P, Husted S, Mortensen LS. Trend in mortality after stroke with atrial fibrillation. *Am J Med.* 2007;120(1):47-53.

94. Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. *Arch Intern Med.* 2004;164(18):1993-1998.

95. Egholm G, Madsen M, Thim T et al. Evaluation of algorithms for registry-based detection of acute myocardial infarction following percutaneous coronary intervention. *Clin Epidemiol.* 2016;8:415-423.

96. Nielsen LH, Nørgaard BL, Tilsted HH et al. The Western Denmark Cardiac Computed Tomography Registry: a review and validation study. *Clin Epidemiol.* 2014;7:53-64.

97. Albert NM, Fonarow GC, Abraham WT et al. Depression and clinical outcomes in heart failure: an OPTIMIZE-HF analysis. *Am J Med.* 2009;122(4):366-373.

98. Alhurani AS, Dekker RL, Abed MA et al. The association of co-morbid symptoms of depression and anxiety with all-cause mortality and cardiac rehospitalization in patients with heart failure. *Psychosomatics.* 2015;56(4):371-380.

99. Coyne JC, Jaarsma T, Luttik ML, van Sonderen E, van Veldhuisen DJ, Sanderman R. Lack of prognostic value of type D personality for mortality in a large sample of heart failure patients. *Psychosom Med.* 2011;73(7):557-562.

100. Volz A, Schmid JP, Zwahlen M, Kohls S, Saner H, Barth J. Predictors of readmission and health related quality of life in patients with chronic heart failure: a comparison of different psychosocial aspects. *J Behav Med.* 2011;34(1):13-22.

101. Friedmann E, Thomas SA, Liu F et al. Relationship of depression, anxiety, and social isolation to chronic heart failure outpatient mortality. *Am Heart J.* 2006;152(5):940.e1-940.e8.

102. Smith OR, Kupper N, Schiffer AA, Denollet J. Somatic depression predicts mortality in chronic heart failure: can this be explained by covarying symptoms of fatigue? *Psychosom Med.* 2012;74(5):459-463.

103. Macchia A, Monte S, Pellegrini F et al. Depression worsens outcomes in elderly patients with heart failure: an analysis of 48,117 patients in a community setting. *Eur J Heart Fail.* 2008;10(7):714-721.

104. Zuluaga MC, Guallar-Castillon P, Rodriguez-Pascual C, Conde-Herrera M, Conthe P, Rodriguez-Artalejo F. Mechanisms of the association between depressive symptoms and long-term mortality in heart failure. *Am Heart J.* 2010;159(2):231-237.

105. Diez-Quevedo C, Lupon J, Gonzalez B et al. Depression, antidepressants, and long-term mortality in heart failure. *Int J Cardiol.* 2013;167(4):1217-1225.

106. Cully JA, Johnson M, Moffett ML, Khan M, Deswal A. Depression and anxiety in ambulatory patients with heart failure. *Psychosomatics.* 2009;50(6):592-598.

107. Jiang W, Alexander J, Christopher E et al. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Arch Intern Med.* 2001;161(15):1849-1856.

108. Jiang W, Kuchibhatla M, Clary GL et al. Relationship between depressive symptoms and long-term mortality in patients with heart failure. *Am Heart J.* 2007;154(1):102-108.

109. van den Broek KC, Defilippi CR, Christenson RH, Seliger SL, Gottdiener JS, Kop WJ. Predictive value of depressive symptoms and B-type natriuretic peptide for new-onset heart failure and mortality. *Am J Cardiol.* 2011;107(5):723-729.

110. Brouwers C, Christensen SB, Damen NL et al. Antidepressant use and risk for mortality in 121,252 heart failure patients with or without a diagnosis of clinical depression. *Int J Cardiol.* 2016;203:867-873.

111. Rollman BL, Herbeck Belnap B, Mazumdar S et al. A positive 2-item Patient Health Questionnaire depression screen among hospitalized heart failure patients is associated with elevated 12-month mortality. *J Card Fail.* 2012;18(3):238-245.

112. Faller H, Stork S, Schowalter M et al. Depression and survival in chronic heart failure: does gender play a role? *Eur J Heart Fail.* 2007;9(10):1018-1023.

113. Faller H, Stork S, Gelbrich G, Schowalter M, Ertl G, Angermann CE. Depressive symptoms in heart failure: Independent prognostic factor or marker of functional status? *J Psychosom Res.* 2015;78(6):569-572.

114. Kato N, Kinugawa K, Yao A, Hatano M, Shiga T, Kazuma K. Relationship of depressive symptoms with hospitalization and death in Japanese patients with heart failure. *J Card Fail.* 2009;15(10):912-919.

115. Sullivan MD, Levy WC, Crane BA, Russo JE, Spertus JA. Usefulness of depression to predict time to combined end point of transplant or death for outpatients with advanced heart failure. *Am J Cardiol.* 2004;94(12):1577-1580.

116. Moraska AR, Chamberlain AM, Shah ND et al. Depression, healthcare utilization, and death in heart failure: a community study. *Circ Heart Fail.* 2013;6(3):387-394.

117. Adams J, Kuchibhatla M, Christopher EJ et al. Association of depression and survival in patients with chronic heart failure over 12 Years. *Psychosomatics.* 2012;53(4):339-346.

118. O'Connor CM, Jiang W, Kuchibhatla M et al. Antidepressant use, depression, and survival in patients with heart failure. *Arch Intern Med.* 2008;168(20):2232-2237.

119. Faris R, Purcell H, Henein MY, Coats AJ. Clinical depression is common and significantly associated with reduced survival in patients with non-ischaemic heart failure. *Eur J Heart Fail.* 2002;4(4):541-551.

120. Lesman-Leegte I, van Veldhuisen DJ, Hillege HL, Moser D, Sanderman R, Jaarsma T. Depressive symptoms and outcomes in patients with heart failure: data from the COACH study. *Eur J Heart Fail.* 2009;11(12):1202-1207.

121. Vaccarino V, Kasl SV, Abramson J, Krumholz HM. Depressive symptoms and risk of functional decline and death in patients with heart failure. *J Am Coll Cardiol.* 2001;38(1):199-205.

122. Junger J, Schellberg D, Muller-Tasch T et al. Depression increasingly predicts mortality in the course of congestive heart failure. *Eur J Heart Fail.* 2005;7(2):261-267.

123. Murberg TA, Bru E, Svebak S, Tveteras R, Aarsland T. Depressed mood and subjective health symptoms as predictors of mortality in patients with congestive heart failure: a two-years follow-up study. *Int J Psychiatry Med.* 1999;29(3):311-326.

124. Murberg TA, Furze G. Depressive symptoms and mortality in patients with congestive heart failure: a six-year follow-up study. *Med Sci Monit.* 2004;10(12):CR643-8.

125. de Denus S, Spinler SA, Jessup M, Kao A. History of depression as a predictor of adverse outcomes in patients hospitalized for decompensated heart failure. *Pharmacotherapy.* 2004;24(10):1306-1310.

126. Sherwood A, Blumenthal JA, Trivedi R et al. Relationship of depression to death or hospitalization in patients with heart failure. *Arch Intern Med.* 2007;167(4):367-373.

127. Sherwood A, Blumenthal JA, Hinderliter AL et al. Worsening depressive symptoms are associated with adverse clinical outcomes in patients with heart failure. *J Am Coll Cardiol.* 2011;57(4):418-423.

128. Murad K, Goff DC,Jr, Morgan TM et al. Burden of Comorbidities and Functional and Cognitive Impairments in Elderly Patients at the Initial Diagnosis of Heart Failure and Their Impact on Total Mortality: The Cardiovascular Health Study. *JACC Heart Fail.* 2015;3(7):542-550.

129. Suzuki T, Shiga T, Kuwahara K et al. Impact of clustered depression and anxiety on mortality and rehospitalization in patients with heart failure. *J Cardiol.* 2014;64(6):456-462.

130. Testa G, Cacciatore F, Galizia G et al. Depressive symptoms predict mortality in elderly subjects with chronic heart failure. *Eur J Clin Invest.* 2011;41(12):1310-1317.

131. Banta JE, Andersen RM, Young AS, Kominski G, Cunningham WE. Psychiatric comorbidity and mortality among veterans hospitalized for congestive heart failure. *Mil Med.* 2010;175(10):732-741.

132. Veien KT, Videbaek L, Schou M et al. High mortality among heart failure patients treated with antidepressants. *Int J Cardiol.* 2011;146(1):64-67.

133. Fosbøl EL, Gislason GH, Poulsen HE et al. Prognosis in heart failure and the value of {beta}-blockers are altered by the use of antidepressants and depend on the type of antidepressants used. *Circ Heart Fail.* 2009;2(6):582-590.

134. Schiffer AA, Pelle AJ, Smith OR, Widdershoven JW, Hendriks EH, Pedersen SS. Somatic versus cognitive symptoms of depression as predictors of all-cause mortality and health status in chronic heart failure. *J Clin Psychiatry.* 2009;70(12):1667-1673.

135. Frasure-Smith N, Lesperance F, Habra M et al. Elevated depression symptoms predict long-term cardiovascular mortality in patients with atrial fibrillation and heart failure. *Circulation.* 2009;120(2):134-40, 3p following 140.

136. Johansson P, Dahlstrom U, Alehagen U. Depressive symptoms and six-year cardiovascular mortality in elderly patients with and without heart failure. *Scand Cardiovasc J.* 2007;41(5):299-307.

137. Rumsfeld JS, Jones PG, Whooley MA et al. Depression predicts mortality and hospitalization in patients with myocardial infarction complicated by heart failure. *Am Heart J.* 2005;150(5):961-967.

138. Freedland KE, Hesseler MJ, Carney RM et al. Major Depression and Long-Term Survival of Patients With Heart Failure. *Psychosom Med.* 2016;78(8):896-903.

139. Ramos S, Prata J, Bettencourt P, Goncalves FR, Coelho R. Depression predicts mortality and hospitalization in heart failure: A six-years follow-up study. *J Affect Disord.* 2016;201:162-170.

140. Habeych ME, Castilla-Puentes R. Comorbid Medical Conditions in Vascular Dementia: A Matched Case-Control Study. *J Nerv Ment Dis.* 2015;203(8):604-608.

141. Jefferson AL, Beiser AS, Himali JJ et al. Low cardiac index is associated with incident dementia and Alzheimer disease: the Framingham Heart Study. *Circulation.* 2015;131(15):1333-1339.

142. Sabayan B, van Buchem MA, Sigurdsson S et al. Cardiac hemodynamics are linked with structural and functional features of brain aging: the age, gene/environment susceptibility (AGES)-Reykjavik Study. *J Am Heart Assoc.* 2015;4(1):e001294.

143. de Bruijn RF, Portegies ML, Leening MJ et al. Subclinical cardiac dysfunction increases the risk of stroke and dementia: the Rotterdam Study. *Neurology.* 2015;84(8):833-840.

144. Pullicino PM, McClure LA, Wadley VG et al. Blood pressure and stroke in heart failure in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Stroke.* 2009;40(12):3706-3710.

145. Helweg-Larsen K. The Danish Register of Causes of Death. *Scand J Public Health.* 2011;39(7 Suppl):26-29.

146. Nørgaard M, Johnsen SP. How can the research potential of the clinical quality databases be maximized? The Danish experience. *J Intern Med.* 2016;279(2):132-140.

147. Mainz J, Krog BR, Bjornshave B, Bartels P. Nationwide continuous quality improvement using clinical indicators: the Danish National Indicator Project. *Int J Qual Health Care.* 2004;16 Suppl 1:i45-50.

148. Schjodt I, Nakano A, Egstrup K, Cerqueira C. The Danish Heart Failure Registry. *Clin Epidemiol.* 2016;8:497-502.

149. Pottegaard A, Schmidt SA, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. *Int J Epidemiol.* 2016 Oct 27 (Epub ahead of print)

150. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health.* 2011;39(7 Suppl):54-57.

151. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health.* 2011;39(7 Suppl):95-98.

152. Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV. Validity of the diagnosis of a single depressive episode in a case register. *Clin Pract Epidemiol Ment Health.* 2009;5:4-0179-5-4.

153. Teaching Epidemiology: A guide for teachers in epidemiology, public health and clinical medicine. Olsen J, Saracci R, Trichopoulos D. Third Edition. In: Baron JA, Sørensen HT. Registries and medical databases. Oxford Scholarship Online: May 2010.

154. Phung TK, Andersen BB, Hogh P, Kessing LV, Mortensen PB, Waldemar G. Validity of dementia diagnoses in the Danish hospital registers. *Dement Geriatr Cogn Disord.* 2007;24(3):220-228.

155. Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology.* 2007;28(3):150-154.

156. Heide-Jørgensen U, Kahlert J, Adelborg K, Pedersen L. Validity of sampling strategies for the selection of comparison cohorts from general population registries in matched cohort studies (in preparation).

157. Stuart EA. Matching methods for causal inference: A review and a look forward. *Stat Sci.* 2010;25(1):1-21.

158. Søgaard M, Heide-Jørgensen U, Nørgaard M, Johnsen SP, Thomsen RW. Evidence for the low recording of weight status and lifestyle risk factors in the Danish National Registry of Patients, 1999-2012. *BMC Public Health.* 2015;15:1320-015-2670-9.

159. Wilson E. Probable inference, the law of succession, and statistical inference. *J Amer Statist Assoc* 1927;22:209-12.

160. Therneau T. Modeling Survival Data: Extending the Cox Model. Springer Science & Business Media.; 2000:44-48.

161. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med.* 2011;30(4):377-399.

162. Sundbøll J, Adelborg K, Munch T et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open.* 2016;6(11):e012832-2016-012832.

163. Adelborg K, Sundbøll J, Munch T et al. Positive predictive value of cardiac examination, procedure and surgery codes in the Danish National Patient Registry: a population-based validation study. *BMJ open.* 2016;6:e012817.

164. Adelborg K, Schmidt M, Sundbøll J et al. Mortality Risk Among Heart Failure Patients With Depression: A Nationwide Population-Based Cohort Study. *J Am Heart Assoc.* 2016;5(9):10.1161/JAHA.116.004137.

165. Adelborg K, Horvath-Puho E, Ording A, Pedersen L, Toft Sørensen H, 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

166. 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)

167. Thygesen K, Alpert JS, White HD et al. Universal definition of myocardial infarction. *Circulation.* 2007;116(22):2634-2653.

168. Kato N, Kinugawa K, Shiga T et al. Depressive symptoms are common and associated with adverse clinical outcomes in heart failure with reduced and preserved ejection fraction. *J Cardiol.* 2012;60(1):23-30.

169. Cohen MB, Mather PJ. A review of the association between congestive heart failure and cognitive impairment. *Am J Geriatr Cardiol.* 2007;16(3):171-174.

170. Dries DL, Rosenberg YD, Waclawiw MA, Domanski MJ. Ejection fraction and risk of thromboembolic events in patients with systolic dysfunction and sinus rhythm: evidence

for gender differences in the studies of left ventricular dysfunction trials. *J Am Coll Cardiol.* 1997;29(5):1074-1080.

171. Freudenberger RS, Hellkamp AS, Halperin JL et al. Risk of thromboembolism in heart failure: an analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation.* 2007;115(20):2637-2641.

172. Loh E, Sutton MS, Wun CC et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. *N Engl J Med.* 1997;336(4):251-257.

173. Henriksen DP, Rasmussen L, Hansen MR, Hallas J, Pottegaard A. Comparison of the Five Danish Regions Regarding Demographic Characteristics, Healthcare Utilization, and Medication Use--A Descriptive Cross-Sectional Study. *PLoS One.* 2015;10(10):e0140197.

174. Haan MN, Mayeda ER. Apolipoprotein E Genotype and Cardiovascular Diseases in the Elderly. *Curr Cardiovasc Risk Rep.* 2010;4(5):361-368.

175. Hernan MA, Alonso A, Logroscino G. Cigarette smoking and dementia: potential selection bias in the elderly. *Epidemiology.* 2008;19(3):448-450.

176. Chubak J, Pocobelli G, Weiss NS. Tradeoffs between accuracy measures for electronic health care data algorithms. *J Clin Epidemiol.* 2012;65(3):343-349.e2.

9. Appendices

Full version of studies I–V including supplementary material

Study I

Study II

Study III

Study IV

Study V

Study I

BMJ Open

Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study

Jens Sundbøll,[1,2] Kasper Adelborg,[1,2] Troels Munch,[1] Trine Frøslev,[1] Henrik Toft Sørensen,[1] Hans Erik Bøtker,[2] Morten Schmidt[1,3]

To cite: Sundbøll J, Adelborg K, Munch T, *et al*. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016;**6**:e012832. doi:10.1136/bmjopen-2016-012832

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-012832).

Received 26 May 2016
Revised 21 September 2016
Accepted 30 September 2016

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark
[2]Department of Cardiology, Aarhus University Hospital, Skejby, Aarhus N, Denmark
[3]Department of Internal Medicine, Regional Hospital of Randers, Randers, Denmark

Correspondence to
Dr Jens Sundbøll; jens.sundboll@clin.au.dk

ABSTRACT

Objective: The majority of cardiovascular diagnoses in the Danish National Patient Registry (DNPR) remain to be validated despite extensive use in epidemiological research. We therefore examined the positive predictive value (PPV) of cardiovascular diagnoses in the DNPR.

Design: Population-based validation study.

Setting: 1 university hospital and 2 regional hospitals in the Central Denmark Region, 2010–2012.

Participants: For each cardiovascular diagnosis, up to 100 patients from participating hospitals were randomly sampled during the study period using the DNPR.

Main outcome measure: Using medical record review as the reference standard, we examined the PPV for cardiovascular diagnoses in the DNPR, coded according to the International Classification of Diseases, 10th Revision.

Results: A total of 2153 medical records (97% of the total sample) were available for review. The PPVs ranged from 64% to 100%, with a mean PPV of 88%. The PPVs were ≥90% for first-time myocardial infarction, stent thrombosis, stable angina pectoris, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, takotsubo cardiomyopathy, arterial hypertension, atrial fibrillation or flutter, cardiac arrest, mitral valve regurgitation or stenosis, aortic valve regurgitation or stenosis, pericarditis, hypercholesterolaemia, aortic dissection, aortic aneurysm/dilation and arterial claudication. The PPVs were between 80% and 90% for recurrent myocardial infarction, first-time unstable angina pectoris, pulmonary hypertension, bradycardia, ventricular tachycardia/fibrillation, endocarditis, cardiac tumours, first-time venous thromboembolism and between 70% and 80% for first-time and recurrent admission due to heart failure, first-time dilated cardiomyopathy, restrictive cardiomyopathy and recurrent venous thromboembolism. The PPV for first-time myocarditis was 64%. The PPVs were consistent within age, sex, calendar year and hospital categories.

Conclusions: The validity of cardiovascular diagnoses in the DNPR is overall high and sufficient for use in research since 2010.

Strengths and limitations of this study

- This is the first validation study to include all major cardiovascular diagnoses in the Danish National Patient Registry.
- We sampled patients only from hospitals in the Central Denmark Region. However, our results are most likely generalisable to other parts of the country as the Danish healthcare system is homogeneous in structure and practice.
- We only validated patients diagnosed during 2010–2012 and therefore cannot extrapolate our results to previous periods.

INTRODUCTION

Remarkable improvements have occurred in the prevention and treatment of cardiovascular diseases during recent decades.[1–4] Still, cardiovascular diseases remain a leading cause of death worldwide,[5] underscoring the need for further research. Registries constitute an important source of data for cardiovascular research in Denmark. The key registry is the Danish National Patient Registry (DNPR),[6] which contains long-term longitudinal data, prospectively collected since 1977. The registry has nationwide coverage of a homogeneous healthcare system with free and equal access and holds the possibility of individual-level data linkage with other registries.[7 8] However, the quality of registry-based research largely depends on the validity of the diagnostic codes used. Existing validation studies for cardiovascular diagnoses in the DNPR have been limited to relatively few diagnoses.[6] We therefore conducted a validation study to examine the positive predictive value (PPV) of diagnoses in the DNPR for all major cardiovascular diseases.

METHODS

Setting

Denmark is divided into five regions, each of which is representative of the Danish population with respect to demographic and socioeconomic characteristics as well as healthcare usage and medication use.[9] Each region typically has one major university hospital (including a high volume cardiac centre) and several smaller regional hospitals. The Danish National Health Service provides free universal tax-supported healthcare, guaranteeing unfettered access to general practitioners and hospitals.[6]

Study population

We used the DNPR to randomly sample inpatient and outpatient hospital diagnoses from the Central Denmark Region between 1 January 2010 and 31 December 2012. The Central Denmark Region has a source population of 1.2 million inhabitants. Within the Central Denmark Region, we sampled specifically from the university hospital (Aarhus University Hospital) and two regional hospitals (Regional Hospitals of Randers and Herning).[8] The DNPR has recorded data on dates of admission and discharge from all Danish non-psychiatric hospitals since 1977 and on dates of emergency room and outpatient clinic visits since 1995.[6] Each hospital discharge or outpatient visit is recorded with one primary diagnosis and one or more secondary diagnoses classified according to the International Classification of Diseases, 8th Revision (ICD-8) until the end of 1993 and 10th Revision (ICD-10) thereafter.[6]

Our study population consisted of patients discharged with a primary or secondary first-time diagnosis from departments of cardiology, internal medicine, acute medicine and neurology in the three hospitals. For myocardial infarction, heart failure and venous thromboembolism, we also validated recurrent events. For most diseases, both inpatient and outpatient diagnoses were included (see online supplementary table S1). However, for diseases expected only to be diagnosed at inpatient admission (eg, myocardial infarction, aortic dissection, cardiac arrest), we only sampled inpatient diagnoses to avoid potential misclassification. Up to 100 patients were sampled from the DNPR for each of the diagnoses, which included first-time acute myocardial infarction (subsequently stratified by ST-elevation (STEMI) and non-ST-elevation myocardial infarction (NSTEMI)), recurrent myocardial infarction, stent thrombosis, stable angina pectoris, unstable angina pectoris, first-time heart failure, heart failure readmission, arterial hypertension, pulmonary hypertension, atrial fibrillation or flutter, bradycardia, ventricular tachycardia or fibrillation, cardiac arrest with indication for resuscitation, endocarditis, myocarditis, pericarditis, first-time venous thromboembolism (subsequently stratified by deep venous thrombosis and pulmonary embolism), recurrent venous thromboembolism (subsequently stratified by deep venous thrombosis and pulmonary embolism), arterial claudication, hypercholesterolaemia and cardiac tumours. We sampled up to 100 cases for cardiomyopathy (by sampling 20 diagnoses each for dilated, hypertrophic, restrictive, arrhythmogenic right ventricular and takotsubo cardiomyopathy), valvular heart disease (sampling 50 diagnoses each for mitral valve regurgitation or stenosis, and aortic valve regurgitation or stenosis) and aortic diseases (sampling 50 diagnoses each for aortic dissection and aneurysm/dilation).

Recurrent myocardial infarction and readmission due to heart failure were defined as the first readmission after the initial diagnosis. Sampling of first-time and recurrent events was independent. Hence, recurrent events could potentially include patients also included in the random sample for validation of first-time events. To avoid situations in which a transfer from one department to another was registered as a new diagnosis, we required that patients should be discharged for >24 hours before readmission could be registered as a true recurrent event. Bradycardia was defined as sinus node dysfunction or atrioventricular block. For venous thromboembolism, we defined recurrent events as admissions occurring >3 months after the initial diagnosis as guidelines recommend at least 3 months of anticoagulant therapy following venous thromboembolism.[10] All ICD codes used in the study are provided in online supplementary table S1. The patients were sampled using SAS V.9.2 (SAS Institute, Cary, North Carolina, USA).

Medical record review

Medical record review was used as the reference standard. We did not have access to ECGs or other paraclinical recordings that supported the clinician's decision. However, descriptions of such recordings were available in the medical records and included in the review process. Three physicians (JS, KA and TM) reviewed the medical records and judged whether they confirmed the cardiovascular diagnosis coded in the DNPR. If the diagnosis was not described in the discharge summary or if the discharge summary was not available, the full medical record was reviewed to examine whether the diagnosis code could be confirmed. Review of the discharge summary/medical records began with confirmation of the Civil Personal Register number (unique personal identifier) and discharge date for each hospital contact retrieved from the DNPR. The diagnoses from the discharge summary and/or medical records were then compared with the diagnoses in the DNPR. Events coded in the DNPR as recurrent were considered correct if they were truly new events (for myocardial infarction and venous thromboembolism) and for heart failure if the readmission was due to a heart failure exacerbation. If the reviewing physician was uncertain whether the discharge summary or medical record agreed with the ICD-10 code, a second independent review was performed by one of the two other physicians. In case of disagreement, a consensus agreement was reached.

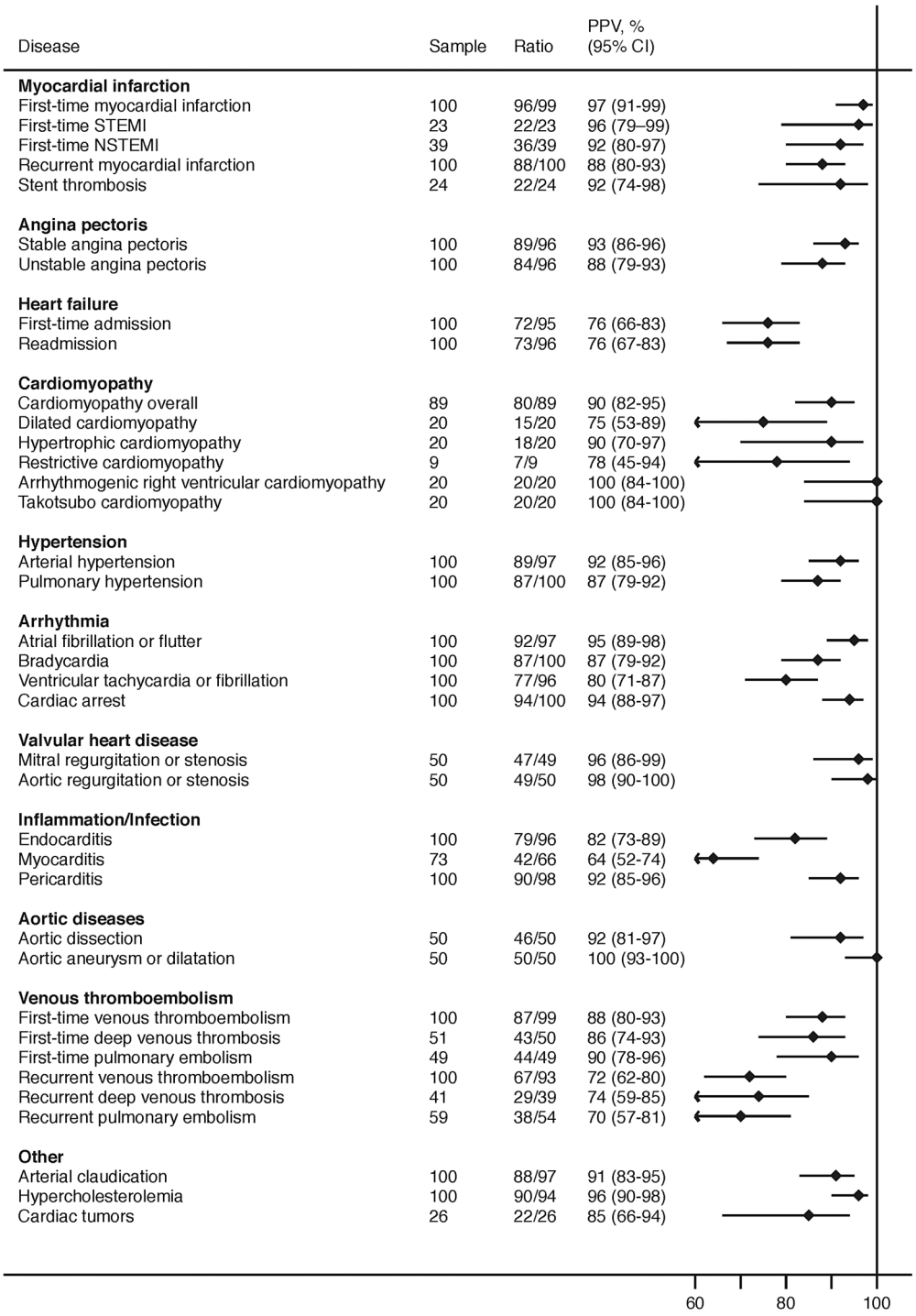


Figure 1 Positive predictive values of cardiovascular diagnoses in the Danish National Patient Registry. Ratio, denotes confirmed diagnoses/available records; PPV, positive predictive value; STEMI, ST segment elevation myocardial infarction; NSTEMI, non-STEMI.

Data were entered into Epidata V.3.1 (EpiData Association, Odense, Denmark, http://www.epidata.dk) using a medical chart extraction form (see online supplementary table S2).

Statistical analysis

For each diagnosis, we computed the PPV with 95% CIs according to the Wilson score method.[11] The PPV was computed as the proportion of diagnoses retrieved from the DNPR that could be confirmed in the discharge summary or medical record. For venous thromboembolism (including deep venous thrombosis and pulmonary embolism), we recalculated the PPVs for patients having an ultrasound and/or CT scan recorded in the registry during the index admission and for those who had neither of these registered. To calculate the mean PPV

Table 1 Positive predictive values of venous thromboembolism diagnoses in the Danish National Patient Registry, by diagnostic modalities during admission

	Number of patients sampled	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)
First-time venous thromboembolism	100	87/99	88 (80 to 93)
No ultrasound or CT scan during admission	22	17/22	77 (57 to 90)
Ultrasound or CT scan during admission	77	70/77	91 (82 to 96)
Ultrasound and CT scan during admission	13	13/13	100 (77 to 100)
Recurrent venous thromboembolism	100	67/93	72 (62 to 80)
No ultrasound or CT scan during admission	25	11/25	44 (27 to 63)
Ultrasound or CT scan during admission	72	56/68	82 (72 to 90)
Ultrasound and CT scan during admission	7	5/7	71 (36 to 92)

for all cardiovascular diseases, we divided the total number of correct cases by the total number of validated cases. We stratified the analyses by age group (<60 years, 60–80 years and >80 years), sex, calendar year (2010, 2011 and 2012), hospital type (regional or university hospital), type of diagnosis (primary or secondary) and type of hospital contact (inpatient or outpatient). Furthermore, we performed subgroup analyses for myocardial infarction (STEMI and NSTEMI diagnoses) and first-time and recurrent venous thromboembolism (deep venous thrombosis and pulmonary embolism diagnoses).

RESULTS

We identified 2212 patients from the DNPR with cardiovascular diagnoses during 2010–2012. Medical records were available for 2153 patients (97% of the total sample). For the most common diseases, 100 patients were sampled; for rare diseases, fewer patients were available for sampling (figure 1). PPVs ranged between 64% and 100% with a mean PPV of 88%. PPVs were ≥90% for first-time myocardial infarction (including STEMI and NSTEMI), stent thrombosis, stable angina pectoris, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, takotsubo cardiomyopathy, arterial hypertension, atrial fibrillation or flutter, cardiac arrest with indication for resuscitation, mitral valve regurgitation or stenosis, aortic valve regurgitation or stenosis, pericarditis, hypercholesterolaemia, aortic dissection, aortic aneurysm/dilation and arterial claudication (figure 1). The distribution of cardiac arrest was 57% out of hospital, 30% inhospital and 13% undetermined. Apart from myocarditis (PPV=64%), the remaining PPVs were between 80% and 90% for recurrent myocardial infarction, unstable angina pectoris, pulmonary hypertension, bradycardia, ventricular tachycardia or fibrillation, endocarditis, cardiac tumours, first-time venous thromboembolism and between 70% and 80% for first-time and recurrent admission for heart failure, dilated cardiomyopathy, restrictive cardiomyopathy and recurrent venous thromboembolism. The PPV for venous thromboembolism improved when the following additional criteria were applied: receipt of CT or ultrasound scan during hospitalisation (PPV=91%), and receipt of both a CT and ultrasound scan during hospitalisation (PPV=100%; table 1).

The PPVs were consistent within age, sex, calendar year and hospital categories (tables 2 and 3). The stratified analyses by type of diagnosis and type of hospital contact revealed that the main results were driven by primary diagnoses from inpatient admissions. Thus, primary and inpatient diagnoses occurred most frequently, and the PPVs associated with these diagnosis types overall tended to be higher than for secondary and outpatient diagnoses (table 4).

DISCUSSION

The DNPR accurately recorded diagnoses of the most common cardiovascular diseases during 2010–2012, with the PPV exceeding 90% for myocardial infarction, arterial hypertension, atrial fibrillation or flutter, valvular heart disease, aortic diseases and first-time venous thromboembolism. As an exception among the most frequent diseases, the PPV for heart failure was lower. For less common conditions, the PPV varied from 64% for myocarditis to 100% for takotsubo cardiomyopathy. The PPV for recurrent myocardial infarction was 88%, but somewhat lower for readmission for heart failure (76%) and recurrent venous thromboembolism (72%). The lower PPVs for recurrent events are most likely influenced by secondary recordings of the initial event as part of follow-up visits or during successive hospital contacts without the occurrence of a truly new event. The results were consistent in age, sex and calendar year categories.

This is the first validation study to include all major cardiovascular diagnoses in the DNPR. Comparing our results with previous Danish validation studies, it is apparent that the PPVs have improved over time for many cardiovascular diagnoses in the DNPR.[6] This may be explained by increased awareness of correct coding, implementation of clear guidelines and definitions of individual diseases, and improved availability of diagnostic modalities.[6] Thus, the PPV of coding has improved for myocardial infarction (PPV=100% during 1996–2009,[12] 98% during 1998–2007,[13] 92% during

Table 2 Positive predictive values of cardiovascular diagnoses in the Danish National Patient Registry, by age groups and sex

	<60 years		60–80 years		>80 years		Men		Women	
	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)
Myocardial infarction										
First-time myocardial infarction	29/30	97 (83 to 99)	47/48	98 (89 to 100)	20/21	95 (77 to 99)	61/63	97 (89 to 99)	35/36	97 (86 to 100)
Recurrent myocardial infarction	17/19	89 (69 to 97)	51/57	89 (79 to 95)	20/24	83 (64 to 93)	61/69	88 (79 to 94)	27/31	87 (71 to 95)
Stent thrombosis	9/9	100 (70 to 100)	11/13	85 (58 to 96)	2/2	100 (34 to 100)	15/16	94 (72 to 99)	7/8	88 (53 to 98)
Angina pectoris										
Stable angina pectoris	25/29	86 (69 to 95)	51/54	94 (85 to 98)	13/13	100 (77 to 100)	63/69	91 (82 to 96)	26/27	96 (82 to 99)
Unstable angina pectoris	24/28	86 (69 to 94)	51/57	89 (79 to 95)	9/11	82 (52 to 95)	48/55	87 (76 to 94)	36/41	88 (74 to 95)
Heart failure										
First-time heart failure	13/13	100 (77 to 100)	37/50	74 (60 to 84)	22/32	69 (51 to 82)	50/60	83 (72 to 91)	22/35	63 (46 to 77)
Readmission for heart failure	7/14	50 (27 to 73)	42/50	84 (71 to 92)	24/32	75 (58 to 87)	45/56	80 (68 to 89)	28/40	70 (55 to 82)
Cardiomyopathy										
Cardiomyopathy overall	32/33	97 (85 to 99)	40/44	91 (79 to 96)	8/12	67 (39 to 86)	38/44	86 (73 to 94)	42/45	93 (82 to 98)
Dilated cardiomyopathy	3/3	100 (44 to 100)	11/13	85 (58 to 96)	1/4	25 (5 to 70)	6/10	60 (31 to 83)	9/10	90 (60 to 98)
Hypertrophic cardiomyopathy	5/5	100 (57 to 100)	9/10	90 (60 to 98)	4/5	80 (38 to 96)	12/13	92 (67 to 99)	6/7	86 (49 to 97)
Restrictive cardiomyopathy	2/3	67 (21 to 94)	5/6	83 (44 to 97)	0/0	N/A	4/5	80 (38 to 96)	3/4	75 (30 to 95)
Arrhythmogenic right ventricular cardiomyopathy	14/14	100 (78 to 100)	6/6	100 (61 to 100)	0/0	N/A	14/14	100 (78 to 100)	6/6	100 (61 to 100)
Takotsubo cardiomyopathy	8/8	100 (68 to 100)	9/9	100 (70 to 100)	3/3	100 (44 to 100)	2/2	100 (34 to 100)	18/18	100 (82 to 100)
Hypertension										
Arterial hypertension	20/24	83 (64 to 93)	52/55	95 (85 to 98)	17/18	94 (74 to 99)	48/55	87 (76 to 94)	41/42	98 (88 to 100)
Pulmonary hypertension	24/28	86 (69 to 94)	41/50	82 (69 to 90)	22/22	100 (85 to 100)	36/41	88 (74 to 95)	51/59	86 (75 to 93)
Cardiac arrhythmias										
Atrial fibrillation or flutter	14/15	93 (70 to 99)	49/53	92 (82 to 97)	29/29	100 (88 to 100)	50/53	94 (85 to 98)	42/44	95 (85 to 99)
Bradycardia	14/14	100 (78 to 100)	35/40	88 (74 to 95)	38/46	83 (69 to 91)	49/55	89 (78 to 95)	38/45	84 (71 to 92)
Ventricular tachycardia or fibrillation	27/31	87 (71 to 95)	37/51	73 (59 to 83)	13/14	93 (69 to 99)	50/60	83 (72 to 91)	27/36	75 (59 to 86)
Cardiac arrest	31/31	100 (89 to 100)	43/45	96 (85 to 99)	20/24	83 (64 to 93)	69/73	95 (87 to 98)	25/27	93 (77 to 98)
Valvular heart disease										
Mitral regurgitation or stenosis	8/9	89 (57 to 98)	22/23	96 (79 to 99)	17/17	100 (82 to 100)	20/22	91 (72 to 97)	27/27	100 (88 to 100)
Aortic regurgitation or stenosis	6/6	100 (61 to 100)	22/23	96 (79 to 99)	21/21	100 (85 to 100)	21/22	95 (78 to 99)	28/28	100 (88 to 100)
Inflammation/infection										
Endocarditis	21/24	88 (69 to 96)	40/47	85 (72 to 93)	18/25	72 (52 to 86)	62/75	83 (73 to 90)	17/21	81 (60 to 92)
Myocarditis	33/39	85 (70 to 93)	8/18	44 (25 to 66)	1/9	11 (2 to 44)	30/43	70 (55 to 81)	12/23	52 (33 to 71)

Continued

Table 2 Continued

	<60 years		60–80 years		>80 years		Men		Women	
	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)
Pericarditis	50/55	91 (80 to 96)	36/39	92 (80 to 97)	4/4	100 (51 to 100)	59/65	91 (81 to 96)	31/33	94 (80 to 98)
Aortic diseases										
Aortic dissection	18/19	95 (75 to 99)	24/27	89 (72 to 96)	4/4	100 (51 to 100)	30/31	97 (84 to 99)	16/19	84 (62 to 94)
Aortic aneurysm/dilation	4/4	100 (51 to 100)	34/34	100 (90 to 100)	12/12	100 (76 to 100)	31/31	100 (89 to 100)	19/19	100 (83 to 100)
Venous thromboembolism										
First-time venous thromboembolism	25/29	86 (69 to 95)	47/51	92 (82 to 97)	15/19	79 (57 to 91)	36/42	86 (72 to 93)	51/57	89 (79 to 95)
First-time deep venous thrombosis	16/19	84 (62 to 94)	22/24	92 (74 to 98)	5/7	71 (36 to 92)	21/23	91 (73 to 98)	22/27	81 (63 to 92)
First-time pulmonary embolism	9/10	90 (60 to 98)	25/27	93 (77 to 98)	10/12	83 (55 to 95)	15/19	79 (57 to 91)	29/30	97 (83 to 99)
Recurrent venous thromboembolism	18/26	69 (50 to 84)	31/42	74 (59 to 85)	18/25	72 (52 to 86)	40/53	75 (62 to 85)	27/40	68 (52 to 80)
Recurrent deep venous thrombosis	12/16	75 (51 to 90)	12/17	71 (47 to 87)	5/6	83 (44 to 97)	18/24	75 (55 to 88)	11/15	73 (48 to 89)
Recurrent pulmonary embolism	6/10	60 (31 to 83)	19/25	76 (57 to 89)	13/19	68 (46 to 85)	22/29	76 (58 to 88)	16/25	64 (45 to 80)
Other										
Arterial claudication	10/10	100 (72 to 100)	63/70	90 (81 to 95)	15/17	88 (66 to 97)	49/57	86 (75 to 93)	39/40	98 (87 to 100)
Hypercholesterolaemia	35/37	95 (82 to 99)	44/46	96 (85 to 99)	11/11	100 (74 to 100)	55/58	95 (86 to 98)	35/36	97 (86 to 100)
Cardiac tumours	11/11	100 (74 to 100)	10/13	77 (50 to 92)	1/2	50 (9 to 91)	9/11	82 (52 to 95)	13/15	87 (62 to 96)

Table 3 Positive predictive values of cardiovascular diagnoses in the Danish National Patient Registry, by calendar year and type of hospital

	2010		2011		2012		University hospital		Regional hospital	
	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)
Myocardial infarction										
First-time myocardial infarction	34/35	97 (85 to 99)	28/29	97 (83 to 99)	34/35	97 (85 to 99)	59/61	97 (89 to 99)	37/38	97 (87 to 100)
Recurrent myocardial infarction	28/33	85 (69 to 93)	35/38	92 (79 to 97)	25/29	86 (69 to 95)	47/51	92 (82 to 97)	41/49	84 (71 to 91)
Stent thrombosis	6/6	100 (61 to 100)	7/9	78 (45 to 94)	9/9	100 (70 to 100)	20/21	95 (77 to 99)	2/3	67 (21 to 94)
Angina pectoris										
Stable angina pectoris	32/35	91 (78 to 97)	27/29	93 (78 to 98)	30/32	94 (80 to 98)	63/68	93 (84 to 97)	26/28	93 (77 to 98)
Unstable angina pectoris	26/29	90 (74 to 96)	31/36	86 (71 to 94)	27/31	87 (71 to 95)	40/46	87 (74 to 94)	44/50	88 (76 to 94)
Heart failure										
First-time heart failure	25/31	81 (64 to 91)	27/38	71 (55 to 83)	20/26	77 (58 to 89)	29/40	73 (57 to 84)	43/55	78 (66 to 87)
Readmission for heart failure	21/28	75 (57 to 87)	30/38	79 (64 to 89)	22/30	73 (56 to 86)	27/37	73 (57 to 85)	46/59	78 (66 to 87)
Cardiomyopathy										
Cardiomyopathy overall	22/25	88 (70 to 96)	22/24	92 (74 to 98)	36/40	90 (77 to 96)	61/66	92 (83 to 97)	19/23	83 (63 to 93)
Dilated cardiomyopathy	1/2	50 (9 to 91)	6/7	86 (49 to 97)	8/11	72 (43 to 90)	6/8	75 (41 to 93)	9/12	75 (47 to 91)
Hypertrophic cardiomyopathy	4/5	80 (38 to 96)	5/5	100 (57 to 100)	9/10	90 (60 to 98)	11/12	92 (65 to 99)	7/8	88 (53 to 98)
Restrictive cardiomyopathy	3/4	75 (30 to 95)	1/2	50 (9 to 91)	3/3	100 (44 to 100)	7/9	78 (45 to 94)	0/0	N/A
Arrhythmogenic right ventricular cardiomyopathy	8/8	100 (68 to 100)	7/7	100 (65 to 100)	5/5	100 (57 to 100)	20/20	100 (84 to 100)	0/0	N/A
Takotsubo cardiomyopathy	6/6	100 (61 to 100)	3/3	100 (44 to 100)	11/11	100 (74 to 100)	17/17	100 (82 to 100)	3/3	100 (44 to 100)
Hypertension										
Arterial hypertension	14/15	93 (70 to 99)	39/43	91 (78 to 96)	36/39	92 (80 to 97)	35/41	85 (72 to 93)	54/56	96 (88 to 99)
Pulmonary hypertension	24/28	86 (69 to 94)	26/31	84 (67 to 93)	37/41	90 (77 to 96)	49/60	82 (70 to 89)	38/40	95 (84 to 99)
Cardiac arrhythmias										
Atrial fibrillation or flutter	27/29	93 (78 to 98)	30/32	94 (80 to 98)	35/36	97 (86 to 100)	30/33	91 (76 to 97)	62/64	97 (89 to 99)
Bradycardia	24/26	92 (76 to 98)	28/35	80 (64 to 90)	35/39	90 (76 to 96)	61/71	86 (76 to 92)	26/29	90 (74 to 96)
Ventricular tachycardia or fibrillation	23/30	77 (59 to 88)	21/27	78 (59 to 89)	33/39	85 (70 to 93)	49/63	78 (66 to 86)	28/33	85 (69 to 93)
Cardiac arrest	29/32	91 (76 to 97)	26/26	100 (87 to 100)	39/42	93 (81 to 98)	72/75	96 (89 to 99)	22/25	88 (70 to 96)
Valvular heart disease										
Mitral regurgitation or stenosis	9/10	90 (60 to 98)	15/16	94 (72 to 99)	23/23	100 (86 to 100)	30/32	94 (80 to 98)	17/17	100 (82 to 100)
Aortic regurgitation or stenosis	13/13	100 (77 to 100)	16/16	100 (81 to 100)	20/21	95 (77 to 99)	29/29	100 (88 to 100)	20/21	95 (77 to 99)
Inflammation/infection										
Endocarditis	25/29	86 (69 to 95)	26/29	90 (74 to 96)	28/38	74 (58 to 85)	49/59	83 (72 to 91)	30/37	81 (66 to 91)
Myocarditis	14/21	67 (45 to 83)	14/24	58 (39 to 76)	14/21	67 (45 to 83)	33/49	67 (53 to 79)	9/17	53 (31 to 74)

Continued

Table 3 Continued

	2010		2011		2012		University hospital		Regional hospital	
	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)
Pericarditis	31/36	86 (71 to 94)	30/31	97 (84 to 99)	29/31	93 (79 to 98)	60/67	90 (80 to 95)	30/31	97 (84 to 99)
Aortic diseases										
Aortic dissection	11/14	79 (52 to 92)	16/16	100 (81 to 100)	19/20	95 (76 to 99)	32/36	89 (75 to 96)	14/14	100 (78 to 100)
Aortic aneurysm/dilation	13/13	100 (77 to 100)	23/23	100 (86 to 100)	14/14	100 (78 to 100)	36/36	100 (90 to 100)	14/14	100 (78 to 100)
Venous thromboembolism										
First-time venous thromboembolism	25/28	89 (73 to 96)	30/33	91 (76 to 97)	32/38	84 (70 to 93)	28/34	82 (66 to 92)	59/65	91 (81 to 96)
First-time deep venous thrombosis	13/15	87 (62 to 96)	13/14	93 (69 to 99)	17/21	81 (60 to 92)	13/16	81 (57 to 93)	30/34	88 (73 to 95)
First-time pulmonary embolism	12/13	92 (67 to 99)	17/19	89 (69 to 97)	15/17	88 (66 to 97)	15/18	83 (61 to 94)	29/31	94 (79 to 98)
Recurrent venous thromboembolism	22/27	81 (63 to 92)	20/29	69 (51 to 83)	25/37	68 (51 to 80)	25/39	64 (48 to 77)	42/54	78 (65 to 87)
Recurrent deep venous thrombosis	9/11	82 (52 to 95)	9/13	69 (42 to 87)	11/15	73 (48 to 89)	6/10	60 (31 to 83)	23/29	79 (62 to 90)
Recurrent pulmonary embolism	13/16	81 (57 to 93)	11/16	69 (44 to 86)	14/22	64 (43 to 80)	19/29	66 (47 to 80)	19/25	76 (57 to 89)
Other										
Arterial claudication	18/20	90 (70 to 97)	33/37	89 (75 to 96)	37/40	93 (80 to 97)	86/95	91 (83 to 95)	2/2	100 (34 to 100)
Hypercholesterolaemia	27/30	90 (74 to 97)	30/31	97 (84 to 99)	33/33	100 (90 to 100)	48/51	94 (84 to 98)	42/43	98 (88 to 100)
Cardiac tumours	2/3	67 (21 to 94)	9/11	82 (52 to 95)	11/12	92 (65 to 99)	17/18	94 (74 to 99)	5/8	63 (31 to 86)

Table 4 Positive predictive values of cardiovascular diagnoses in the Danish National Patient Registry, by type of diagnosis

	Primary diagnosis		Secondary diagnosis		Inpatient diagnosis		Outpatient diagnosis	
	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)
Myocardial infarction								
First-time myocardial infarction	88/89	99 (94 to 100)	8/10	80 (49 to 94)	–	–	–	–
Recurrent myocardial infarction	88/100	88 (80 to 93)	0/0	–	–	–	–	–
Stent thrombosis	14/15	93 (70 to 99)	8/9	89 (57 to 98)	–	–	–	–
Angina pectoris								
Stable angina pectoris	68/73	93 (85 to 97)	21/23	91 (73 to 98)	–	–	–	–
Unstable angina pectoris	80/90	89 (81 to 94)	4/6	67 (30 to 90)	–	–	–	–
Heart failure								
First-time heart failure	31/39	79 (64 to 89)	41/56	73 (60 to 83)	–	–	–	–
Readmission for heart failure	73/96	76 (67 to 83)	0/0	–	–	–	–	–
Cardiomyopathy								
Cardiomyopathy overall	56/61	92 (82 to 96)	24/37	65 (49 to 78)	34/41	83 (69 to 91)	26/27	96 (82 to 99)
Dilated cardiomyopathy	8/10	80 (49 to 94)	7/10	70 (40 to 89)	11/15	73 (48 to 89)	4/5	80 (38 to 96)
Hypertrophic cardiomyopathy	11/12	92 (65 to 99)	7/8	88 (53 to 98)	8/10	80 (49 to 94)	10/10	100 (72 to 100)
Restrictive cardiomyopathy	6/8	75 (41 to 93)	1/1	100 (21 to 100)	7/8	88 (53 to 98)	0/1	0 (0 to 79)
Arrhythmogenic right ventricular cardiomyopathy	11/11	100 (74 to 100)	9/9	100 (70 to 100)	8/8	100 (68 to 100)	12/12	100 (76 to 100)
Takotsubo cardiomyopathy	20/20	100 (84 to 100)	0/0	–	–	–	–	–
Hypertension								
Arterial hypertension	30/33	91 (76 to 97)	59/64	92 (83 to 97)	49/53	92 (82 to 97)	40/44	91 (79 to 96)
Pulmonary hypertension	54/61	89 (78 to 94)	33/39	85 (70 to 93)	58/60	97 (89 to 99)	29/40	73 (57 to 84)
Cardiac arrhythmias								
Atrial fibrillation or flutter	55/58	95 (86 to 98)	37/39	95 (83 to 99)	75/75	100 (95 to 100)	17/22	77 (57 to 90)
Bradycardia	75/79	95 (88 to 98)	12/21	57 (37 to 76)	78/85	92 (84 to 96)	9/15	60 (36 to 80)
Ventricular tachycardia or fibrillation	46/58	79 (67 to 88)	31/38	82 (67 to 91)	70/77	91 (82 to 96)	7/19	37 (19 to 59)
Cardiac arrest	66/67	99 (92 to 100)	28/33	85 (69 to 93)	–	–	–	–
Valvular heart disease								
Mitral regurgitation or stenosis	19/20	95 (76 to 99)	28/29	97 (83 to 99)	21/21	100 (85 to 100)	26/28	93 (77 to 98)
Aortic regurgitation or stenosis	29/30	97 (83 to 99)	20/20	100 (84 to 100)	31/31	100 (89 to 100)	18/19	95 (75 to 99)
Inflammation/infection								
Endocarditis	73/86	85 (76 to 91)	6/10	60 (31 to 83)	75/90	83 (74 to 90)	4/6	67 (30 to 90)
Myocarditis	33/41	80 (66 to 90)	9/25	36 (20 to 55)	37/59	63 (50 to 74)	5/7	71 (36 to 92)
Pericarditis	76/82	93 (85 to 97)	14/16	88 (64 to 97)	74/76	97 (91 to 99)	16/22	73 (52 to 87)
Aortic diseases								
Aortic dissection	45/48	94 (83 to 98)	1/2	50 (9 to 91)	–	–	–	–
Aortic aneurysm/dilation	37/37	100 (91 to 100)	13/13	100 (77 to 100)	20/20	100 (84 to 100)	30/30	100 (89 to 100)
Venous thromboembolism								
First-time venous thromboembolism	76/84	90 (82 to 95)	11/15	73 (48 to 89)	81/90	90 (82 to 95)	6/9	67 (35 to 88)

Continued

Table 4 Continued

	Primary diagnosis		Secondary diagnosis		Inpatient diagnosis		Outpatient diagnosis	
	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)	Confirmed diagnoses/ available records	Positive predictive value, % (95% CI)
First-time deep venous thrombosis	38/44	86 (73 to 94)	5/6	83 (44 to 97)	38/43	88 (76 to 95)	5/7	71 (36 to 92)
First-time pulmonary embolism	38/40	95 (84 to 99)	6/9	67 (35 to 88)	43/47	91 (80 to 97)	1/2	50 (9 to 91)
Recurrent venous thromboembolism	65/77	84 (75 to 91)	2/16	13 (4 to 36)	–	–	–	–
Recurrent deep venous thrombosis	29/36	81 (65 to 90)	0/3	0 (0 to 56)	–	–	–	–
Recurrent pulmonary embolism	36/41	88 (74 to 95)	2/13	15 (4 to 42)	–	–	–	–
Other								
Arterial claudication	83/92	90 (82 to 44)	5/5	100 (57 to 100)	15/17	88 (66 to 97)	73/80	91 (83 to 96)
Hypercholesterolaemia	17/17	100 (82 to 100)	73/77	95 (87 to 98)	62/64	97 (89 to 99)	28/30	93 (79 to 98)
Cardiac tumours	16/18	89 (67 to 97)	6/8	75 (41 to 93)	19/23	83 (63 to 93)	3/3	100 (44 to 100)

1993–2003[14] and 93% during 1982–1991,[15]) arterial hypertension (PPV=88% during 1977–2010[16] and ≈50% during 1990–1993[17]) and first-time venous thromboembolism (PPV=90% during 2004–2012[18] and 75% during 1994–2006[19]). The PPVs were overall in line with previous studies for heart failure (PPV=78% during 2005–2007[20] and 100% during 1998–2007[13]), atrial fibrillation or flutter (PPV=94% during 1993–2009,[21] 99% during 1980–2002[22] and 97% during 1980–2002[23]) and recurrent venous thromboembolism (PPV=79% during 2004–2012 with CT or ultrasound scan during admission and anticoagulant treatment 30 days after admission[18]). Previous studies reported markedly lower PPVs than our findings for unstable angina pectoris (PPV=42% during 1993–2003[14]) and cardiac arrest (PPV=50% during 1993–2003[14]). The finding of lower PPV for cardiac arrest in the previous study[14] may be explained by a small sample size (n=42) and their inclusion of emergency department and outpatient diagnoses, whereas we restricted to inpatient diagnoses. Moreover, the previous study is more than 10 years old and changes in coding practice may also account for part of the difference. For unstable angina pectoris,[14] the study period of the previous study ended in 2003, that is, shortly after the redefinition of myocardial infarction in 2000, which included troponin release as an absolute criterion.[24] This made the discrimination between unstable angina pectoris and myocardial infarction easier and most likely explains the higher PPV found in our study. To the best of our knowledge, the validity of the remaining diagnoses included in our study has not been assessed before.

Several limitations should be considered. Cautious interpretation of the PPV is warranted for diagnoses with sample sizes below 100. These include subgroups of an overall diagnosis and rare diagnoses with less than 100 cases diagnosed during the study period. Original recordings from diagnostic modalities such as ECG and echocardiography were not available. Therefore, the confirmation of the diagnoses was based solely on descriptions of such recordings included in the discharge summary or medical record. This limits the rigorousness of case validation and also could potentially lead to different interpretations between reviewers. We examined patients admitted to hospitals only in the Central Denmark Region. However, our results are most likely generalisable to other parts of the country as the Danish healthcare system is homogeneous in structure and practice.[9] Although some diagnoses (eg, myocardial infarction) have shown consistently high validity across countries despite different registry types and coding systems,[6 12 25] it should be noted that our findings may not per se be generalisable to all countries where coding systems, coding practice, disease definitions and diagnostics differ.

In this study, we chose the PPV as the measure of validity. The PPV is correlated with disease prevalence and is dependent on specificity. However, sensitivity, specificity and negative predictive value could not be calculated because the data were sampled from the codes pertinent

to the diagnosis of interest. The importance of the different measures of data quality depends on the study question and thus the design. A high PPV is important, for example, when identifying patient cohorts in prognosis studies, but cannot stand alone, for example, when identifying disease incidence. Future studies identifying cardiovascular diseases from diagnoses in the DNPR should consider the possibility that differential misclassification may occur between exposure groups (eg, if the exposure is diabetes, these patients may be more prone to have a given outcome registered due to detection bias and hence have a falsely increased risk of the outcome). Also, since diagnoses were only validated during 2010–2012, we cannot necessarily extrapolate our results to previous periods due to potential temporal differences in PPVs as exemplified above.

CONCLUSION

The validity of cardiovascular diagnoses in the DNPR is overall high, and for the vast majority of diseases it is sufficient for use in research since 2010.

Acknowledgements The authors thank Hanne Moeslund Madsen and Henriette Kristoffersen for practical assistance.

Contributors MS, HTS, JS and KA conceived the study idea and designed the study. TF sampled the patients. JS, KA and TM reviewed all medical records. JS performed the statistical analysis. All authors analysed and interpreted the data. JS wrote the initial draft. All authors critically revised the manuscript for important intellectual content and approved the final version.

Funding This work was supported by the Department of Clinical Epidemiology and the Programme for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation.

Competing interests None declared.

Ethics approval In accordance with Danish law governing analysis of registry data, no Ethics Committee approval was required. The study was approved by the Danish Data Protection Agency (record number: 1-16-02-1-08) and the chief physicians of participating departments, as part of quality control.

Data sharing statement No additional data are available.

REFERENCES

1. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. *N Engl J Med* 2012;366:54–63.
2. Schmidt M, Jacobsen JB, Lash TL, *et al*. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ* 2012;344:e356.
3. Søgaard KK, Schmidt M, Pedersen L, *et al*. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation* 2014;130:829–36.
4. Schmidt M, Ulrichsen SP, Pedersen L, *et al*. Thirty-year trends in heart failure hospitalization and mortality rates and the prognostic impact of co-morbidity: a Danish nationwide cohort study. *Eur J Heart Fail* 2016;18:490–9.
5. Lozano R, Naghavi M, Foreman K, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2095–128.
6. Schmidt M, Schmidt SAJ, Sandegaard JL, *et al*. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–90.
7. Sørensen HT. Regional administrative health registries as a resource in clinical epidemiology. A study of options, strengths, limitations and data quality provided with examples of use. *Int J Risk Saf Med* 1997;10:1–22.
8. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–9.
9. Henriksen DP, Rasmussen L, Hansen MR, *et al*. Comparison of the five danish regions regarding demographic characteristics, healthcare utilization, and medication use—a descriptive cross-sectional study. *PLoS ONE* 2015;10:e0140197.
10. Konstantinides SV, Torbicki A, Agnelli G, *et al*. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35:3033–69, 3069a–3069k.
11. Wilson EB. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc* 1927;22:209–12.
12. Coloma PM, Valkhoff VE, Mazzaglia G, *et al*. Identification of acute myocardial infarction from electronic healthcare records using different disease coding systems: a validation study in three European countries. *BMJ Open* 2013;3:e002862.
13. Thygesen SK, Christiansen CF, Christensen S, *et al*. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol* 2011;11:83.
14. Joensen AM, Jensen MK, Overvad K, *et al*. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish National Patient Registry. *J Clin Epidemiol* 2009;62:188–94.
15. Madsen M, Davidsen M, Rasmussen S, *et al*. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol* 2003;56:124–30.
16. Schmidt M, Johannesdottir SA, Lemeshow S, *et al*. Obesity in young men, and individual and combined risks of type 2 diabetes, cardiovascular morbidity and death before 55 years of age: a Danish 33-year follow-up study. *BMJ Open* 2013;3:e002698.
17. Nielsen HW, Tüchsen F, Jensen MV. Validiteten af diagnosen essentiel hypertension i Landspatientregistret. *Ugeskr Laeg* 1996;158:163–7.
18. Schmidt M, Cannegieter SC, Johannesdottir SA, *et al*. Statin use and venous thromboembolism recurrence: a combined nationwide cohort and nested case–control study. *J Thromb Haemost* 2014;12:1207–15.
19. Severinsen MT, Kristensen SR, Overvad K, *et al*. Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution. *J Clin Epidemiol* 2010;63:223–8.
20. Mard S, Nielsen FE. Positive predictive value and impact of misdiagnosis of a heart failure diagnosis in administrative registers among patients admitted to a University Hospital cardiac care unit. *Clin Epidemiol* 2010;2:235–9.
21. Rix TA, Riahi S, Overvad K, *et al*. Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry. *Scand Cardiovasc J* 2012;46:149–53.
22. Frost L, Andersen LV, Vestergaard P, *et al*. Trend in mortality after stroke with atrial fibrillation. *Am J Med* 2007;120:47–53.
23. Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. *Arch Intern Med* 2004;164:1993–8.
24. Alpert JS, Thygesen K, Antman E, *et al*. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36:959–69.
25. Herrett E, Shah AD, Boggon R, *et al*. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ* 2013;346:f2350.

BMJ Open

Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study

Jens Sundbøll, Kasper Adelborg, Troels Munch, Trine Frøslev, Henrik Toft Sørensen, Hans Erik Bøtker and Morten Schmidt

BMJ Open 2016 6:
doi: 10.1136/bmjopen-2016-012832

SUPPLEMENTAL MATERIAL

Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study

Jens Sundbøll; Kasper Adelborg; Troels Munch; Trine Frøslev;
Henrik Toft Sørensen; Hans Erik Bøtker; Morten Schmidt

Corresponding author: Jens Sundbøll, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark; Tel: +45 8716 8246; Fax: +45 8716 7215; Email: jens.sundboll@clin.au.dk

Contents

Supplementary Table 1. ICD-8 and ICD-10 codes for cardiovascular diagnoses.

	ICD-8 code[a]	ICD-10 code	Location of admission
Myocardial infarction			
First-time myocardial infarction	410	I21	Inpatient
STEMI	N/A	I211B, I210B, I213	Inpatient
NSTEMI		I211A, I210A, I214	Inpatient
Recurrent myocardial infarction	410	I21	Inpatient
Stent thrombosis	N/A	T823D, T823E	Inpatient
Angina pectoris			
Stable angina pectoris	413	I20 (without I200), I251, I259	Inpatient
Unstable angina pectoris	411	I200	Inpatient
Heart failure			
First-time heart failure	42709, 42710, 42711, 42719, 42899, 78249	I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429	Inpatient
Readmission for heart failure	42709, 42710, 42711, 42719, 42899, 78249	I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429	Inpatient
Cardiomyopathy	425		
Dilated cardiomyopathy	N/A	I420	Inpatient or outpatient
Hypertrophic cardiomyopathy	N/A	I421, I422	Inpatient or outpatient
Restrictive cardiomyopathy	N/A	I425	Inpatient or outpatient
ARVC	N/A	I428A	Inpatient or outpatient
Takotsubo cardiomyopathy	N/A	I428B	Inpatient
Hypertension			
Arterial hypertension	400–404	I10-I15	Inpatient or outpatient
Pulmonary hypertension	426	I27	Inpatient or outpatient
Cardiac arrhythmias			
Atrial fibrillation or flutter	42793, 42794	I48	Inpatient or outpatient
Bradycardia	42720, 42721, 42722, 42723	I440, I441, I442, I443, I455A, I455B, I455C, I455G	Inpatient or outpatient
VT or VF	42797, 42791	I470, I472, I490	Inpatient or outpatient
Cardiac arrest	42727, 42797	I46	Inpatient
Valvular heart disease			
Mitral regurgitation or stenosis	394	I05, I34, I390, I511A	Inpatient or outpatient
Aortic regurgitation or stenosis	395	I06, I35, I391	Inpatient or outpatient
Inflammation/Infection			
Endocarditis	421	I33, I38, I398	Inpatient or outpatient
Myocarditis	422	I40, I41, I090, I514	Inpatient or outpatient
Pericarditis	39109, 393, 420, 423	I30-132	Inpatient or outpatient
Aortic diseases			
Aortic dissection	44109	I710	Inpatient
Aortic aneurysm/dilatation	44110, 44111, 44119, 44120, 44121, 44129, 44199	I711-I716, I718-I719	Inpatient or outpatient
VTE			
First-time VTE	45100, 45108, 45109, 45099	I801-I803, I26	Inpatient or outpatient
First-time DVT	45100, 45108, 45109	I801-3	Inpatient or outpatient
First-time PE	45099	I26	Inpatient or outpatient
Recurrent VTE	45100, 45108, 45109, 45099	I801-I803, I26	Inpatient
Recurrent DVT	45100, 45108, 45109	I801-3	Inpatient
Recurrent PE	45099	I26	Inpatient
Other			
Arterial claudication	44389-44399	I739A	Inpatient or outpatient
Hypercholesterolemia	27200	E780	Inpatient or outpatient
Cardiac tumors	N/A	C38, C380, C388, D151, D487A, C380X, ZM88400	Inpatient or outpatient
Diagnostic modalities			
CT scan	N/A	UXCA	N/A
Ultra sound scan	N/A	UXUG	N/A

[a]ICD-8 codes were used to identify first-time and recurrent ICD-10 diagnoses.

Abbreviations: ICD, international classification of diseases; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; ARVC, arrhythmogenic right ventricular cardiomyopathy; VT or VF, ventricular tachycardia or ventricular fibrillation; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; CT, computed tomography.

Supplementary Table 2. Medical chart extraction form

Variables	Explanation
Date	Date of the medical record review
Initials	Initials of the investigator
CPR number	Unique 10-digit Civil Personal Register number
CPR number (check)	Confirmation of the CPR number
SKS code	ICD-10 code of the diagnosis
Name of disease	An abbreviation of the diagnosis
Date of discharge	The date the patient was examined/discharged
Correct diagnosis	0=No, 1=Yes
Correct diagnosis for subgroups	0=No, 1=Yes
Data source	1=Discharge summary 2=Other medical record 3=Both 1+2
Algorithm	1=One investigator made the decision 2=A second independent reviewer agreed with the first reviewer 3=Consensus agreement
Comments	Any relevant comments

Study II

BMJ Open

Positive predictive value of cardiac examination, procedure and surgery codes in the Danish National Patient Registry: a population-based validation study

Kasper Adelborg,[1,2] Jens Sundbøll,[1,2] Troels Munch,[1] Trine Frøslev,[1] Henrik Toft Sørensen,[1] Hans Erik Bøtker,[2] Morten Schmidt[1,3]

To cite: Adelborg K, Sundbøll J, Munch T, *et al*. Positive predictive value of cardiac examination, procedure and surgery codes in the Danish National Patient Registry: a population-based validation study. *BMJ Open* 2016;**6**:e012817. doi:10.1136/bmjopen-2016-012817

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-012817).

Received 26 May 2016
Revised 9 November 2016
Accepted 10 November 2016

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[2]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
[3]Department of Internal Medicine, Randers Regional Hospital, Randers, Denmark

Correspondence to
Dr Kasper Adelborg;
kade@clin.au.dk

ABSTRACT

Objective: Danish medical registries are widely used for cardiovascular research, but little is known about the data quality of cardiac interventions. We computed positive predictive values (PPVs) of codes for cardiac examinations, procedures and surgeries registered in the Danish National Patient Registry during 2010–2012.

Design: Population-based validation study.

Setting: We randomly sampled patients from 1 university hospital and 2 regional hospitals in the Central Denmark Region.

Participants: 1239 patients undergoing different cardiac interventions.

Main outcome measure: PPVs with medical record review as reference standard.

Results: A total of 1233 medical records (99% of the total sample) were available for review. PPVs ranged from 83% to 100%. For examinations, the PPV was overall 98%, reflecting PPVs of 97% for echocardiography, 97% for right heart catheterisation and 100% for coronary angiogram. For procedures, the PPV was 98% overall, with PPVs of 98% for thrombolysis, 92% for cardioversion, 100% for radiofrequency ablation, 98% for percutaneous coronary intervention, and 100% for both cardiac pacemakers and implantable cardiac defibrillators. For cardiac surgery, the overall PPVs was 99%, encompassing PPVs of 100% for mitral valve surgery, 99% for aortic valve surgery, 98% for coronary artery bypass graft surgery, and 100% for heart transplantation. The accuracy of coding was consistent within age, sex, and calendar year categories, and the agreement between independent reviewers was high (99%).

Conclusions: Cardiac examinations, procedures and surgeries have high PPVs in the Danish National Patient Registry.

Strengths and limitations of this study

- This is the first study to examine the positive predictive value of the most commonly performed cardiac examinations, procedures and surgeries recorded in the Danish National Patient Registry.
- Medical charts information served as the reference for the validation. The agreement between independent reviewers was high (99%).
- Our study was restricted to one out of five Danish regions; however, owing to a highly homogeneous Danish healthcare system, our results are likely generalisable to other Danish regions.

INTRODUCTION

The mortality rate among patients with cardiovascular disease has declined over the past two decades.[1] However, it remains the leading cause of death worldwide. Danish medical registries are widely recognised as being among the best population-based data sources in the world,[2] owing to the capability for individual-level data linkage across registries and the possibility for long-term follow-up.[2] As the key register, the Danish National Patient Registry (DNPR) has provided registration of all hospital admissions in Denmark since 1977.[3] It has been extensively used to identify cardiovascular diagnoses, but to a lesser extent used to ascertain information on cardiac examinations, procedures and surgeries, partly due to lack of knowledge about the validity of these variables.[4] The data validity is important for several reasons. First, misclassification threatens study findings. Second, validation studies permit researchers to quantify the extent of misclassification and evaluate its impact on the study results. Finally, reporting findings from validation studies may motivate physicians to improve coding accuracy.[5] We

therefore examined the positive predictive value (PPV) of codes for cardiac examinations, procedures and surgeries in the DNPR.

METHODS

Setting and design

This study was conducted in the Central Denmark Region with a source population of 1.2 million residents. The study period was from 1 January 2010 to 31 December 2012.[6] All Danish residents have unfettered access to healthcare services, including all types of cardiac examinations, procedures and surgeries.[3] The DNPR has maintained information on all non-psychiatric hospital admissions since 1977.[3] Cardiac surgeries have been recorded in the DNPR according to the Nordic Medico-statistical Committee's Classification of Surgical Procedures (NOMESCO) since 1996.[3] Denmark is divided into five regions, which each are representative of the Danish population with respect to demographic, and socioeconomic characteristics as well as healthcare usage and medication use.[7] Each region typically has one major university hospital (including a high volume cardiac intervention centre) and several smaller regional hospitals (performing some, but not all cardiac interventions). Registration of cardiac procedures in the DNPRs is performed by the treating physician. Each hospital is required by law to submit their data to the DNPR at least monthly.[3] Data from the DNPR are used by Danish researchers, but collaboration with foreign researchers is common.

Study population

We used the DNPR to randomly sample patients from different types of hospitals in the Central Denmark Region. Specifically, we sampled from the region's university hospital (Aarhus University Hospital) and from two larger regional hospitals (Regional Hospital of Randers and Regional Hospital of Herning). Given the homogeneity of the Danish healthcare system, we considered these hospitals representative for hospitals of similar size in other Danish regions.[7] Patients were sampled from the departments of cardiology, internal medicine, acute medicine, neurology and cardiothoracic surgery. We identified patients who underwent cardiac examinations, which included echocardiography, right heart catheterisation and coronary angiogram. We also identified patients who underwent the following procedures: thrombolysis, cardioversion, radiofrequency ablation (used for cardiac diseases), percutaneous coronary intervention (PCI), and implantation of a cardiac pacemaker or implantable cardiac defibrillator (ICD). We identified patients undergoing cardiac surgery, including mitral valve and aortic valve surgery, coronary artery bypass graft surgery and heart transplantation. We sampled 100 patients for each code (or if fewer were available, the highest number obtainable). For echocardiography and PCI, the sample of 100 patients was attained by sampling 50 patients each for transthoracic echocardiography and transoesophageal echocardiography and 50 patients each for unspecified PCI and PCI with stent implantation. All patients with a given code in the study period were identified and assigned a random number between 0 and 1, and we then selected the 100 lowest numbers. All codes used in the study are given in online supplementary table S1.

Medical record review

We considered the information in the medical record review as the gold standard. One physician (KA) reviewed all medical records. This investigator identified the relevant part of the medical record (ie, the description of the examination, procedure or surgery), and judged if the corresponding record in the DNPR was correct. In cases of doubt, secondary independent reviews (by JS and TM) were planned to reach consensus. As no doubts were raised in any cases, second or third reviews were not performed. However, to investigate whether the assessment of the data extraction could be considered independent, we performed a sensitivity analysis of 100 randomly selected patients, whose medical records were also adjudicated by the two other reviewers (JS and TM). We subsequently calculated the proportion of cases that could be confirmed by these second reviewers.

When validating the indications for ICD implantation, we defined primary prevention and secondary indication according to the definitions given in online supplementary table S2.

All data were entered into Epidata V.3.1 (EpiData Association, Odense, Denmark, http://www.epidata.dk) using a medical chart extraction form (online supplementary table S3).

Statistical analysis

We calculated the PPVs with 95% CIs according to the Wilson Score method.[8] We computed PPVs separately for subgroups of echocardiography (transthoracic vs transoesophageal echocardiography) and PCI (unspecified PCI vs PCI with stent implantation). For ICDs, we disaggregated the sample into patients receiving ICDs for primary versus secondary prophylaxis.

Analyses were stratified by age group (<60, 60–80, and >80 years), sex and calendar year (2010, 2011 and 2012). The patients were sampled using SAS, V.9.2 (SAS Institute, Cary, North Carolina, USA), while the analyses were performed using Microsoft Excel 2010 and Stata statistical software, V.13 (StataCorp LP). In accordance with Danish law, no approval from the Ethics Committee was required.

RESULTS

We identified 1239 patients from the DNPR during 2010–2012. Of these, medical records were available for 1233 (99%) patients. Except for heart transplantation,

100 patients were sampled for each of the codes, while 50 patients were sampled for each prespecified subgroup (figure 1). Majority of patients were sampled from Aarhus University Hospital (89% for examinations, 90% for procedures and 100% for surgery). For cardiac examinations, the overall PPV was 98% (95% CI 96% to 99%), reflecting a PPV of 97% for echocardiography, 97% for right heart catheterisation and 100% for coronary angiogram (figure 1). The overall PPV for cardiac procedures was 98% (95% CI 97% to 99%). Individual PPVs were 98% for thrombolysis, 92% for cardioversion, 100% for radiofrequency ablation, 98% for PCIs, and 100% both for cardiac pacemakers and ICDs. The PPV was 100% for secondary ICDs, but was somewhat lower for primary ICDs (83%). The overall PPV was 99% (95% CI 97% to 100%) for cardiac surgery; individual PPVs were 100% for mitral valve surgery, 99% for aortic valve surgery, 98% for coronary artery bypass graft surgery and 100% for heart transplantation. Analyses stratified by age, sex and calendar year closely agreed with our main findings (tables 1 and 2 and online supplementary table S4). Finally, in the sample of 100 randomly selected patients, the decisions made by the primary reviewer could be confirmed by the second and third reviewer in 99% of the cases.

DISCUSSION

This study showed that cardiac examinations, procedures and surgeries were coded with high accuracy in the DNPR for all sex and age groups during 2010–2012.

Our study provides the first validation of codes for the most frequently performed cardiac examinations, procedures and surgeries in the DNPR. The only previous study to examine the validity of cardiac examinations in the DNPR focused on 282 patients, on whom cardiac CT angiography was performed between 2008 and 2012.[9] Using medical records as reference, this study

Intervention	Sample	Ratio*	PPV, % (95% CI)
Examination (overall)	**300**	**292/298**	**98 (96-99)**
Echocardiography	100	95/98	97 (91-99)
- TTE	50	48/49	98 (89-100)
- TEE	50	47/49	96 (86-99)
RHC	100	97/100	97 (92-99)
Coronary angiogram	100	100/100	100 (96-100)
Procedure (overall)	**600**	**584/596**	**98 (97-99)**
Thrombolysis	100	94/96	98 (93-99)
Cardioversion	100	92/100	92 (85-96)
RFA	100	100/100	100 (96-100)
PCI	100	98/100	98 (93-99)
- Unspecified PCI	50	50/50	100 (93-100)
- PCI with stent	50	48/50	96 (87-99)
Cardiac pacemakers	100	100/100	100 (96-100)
ICD	100	100/100	100 (96-100)
- Primary ICD	54	45/54	83 (71-91)
- Secondary ICD	46	46/46	100 (92-100)
Surgery (overall)	**339**	**336/339**	**99 (97-100)**
Mitral valve surgery	100	100/100	100 (96-100)
Aortic valve surgery	100	99/100	99 (95-100)
CABG surgery	100	98/100	98 (93-99)
Heart transplantation	39	39/39	100 (91-100)

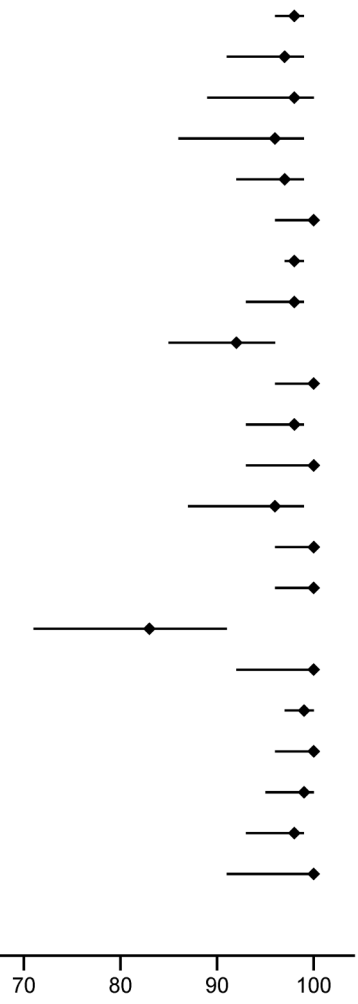


Figure 1 PPV of codes for cardiac examinations, procedures and surgeries in the Danish National Patient Registry, 2010–2012. *Number of correct codes/total number of medical record reviews. CABG, coronary artery bypass graft surgery; ICD, implantable cardiac defibrillator; PCI, percutaneous coronary intervention; PPV, positive predictive value; RFA, radiofrequency ablation; RHC, right heart catheterisation; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Table 1 Positive predictive value of cardiac examinations, procedures and surgeries in the Danish National Patient Registry, by age group

	<60 years		60–80 years		>80 years	
	Number of patients	Positive predictive value (95% CI)	Number of patients	Positive predictive value (95% CI)	Number of patients	Positive predictive value (95% CI)
Examination						
TTE	23	100 (86 to 100)	21	95 (77 to 99)	5	100 (57 to 100)
TEE	19	100 (83 to 100)	22	91 (72 to 97)	8	100 (68 to 100)
RHC	58	95 (86 to 98)	37	100 (91 to 100)	5	100 (57 to 100)
Coronary angiogram	27	100 (88 to 100)	55	100 (93 to 100)	18	100 (82 to 100)
Procedure						
Thrombolysis	23	100 (86 to 100)	52	96 (87 to 99)	21	100 (85 to 100)
Cardioversion	28	96 (82 to 99)	66	91 (82 to 96)	83	83 (44 to 97)
RFA	58	100 (94 to 100)	38	100 (91 to 100)	4	100 (51 to 100)
Unspecified PCI	16	100 (81 to 100)	24	100 (86 to 100)	10	100 (72 to 100)
PCI with stent implantation	17	88 (66 to 97)	29	100 (88 to 100)	4	100 (51 to 100)
Cardiac pacemaker	10	100 (72 to 100)	46	100 (92 to 100)	44	100 (92 to 100)
ICD	33	100 (90 to 100)	63	100 (95 to 100)	4	100 (51 to 100)
Surgery						
Mitral valve surgery	45	100 (92 to 100)	48	100 (93 to 100)	7	100 (65 to 100)
Aortic valve surgery	16	94 (72 to 99)	53	100 (93 to 100)	31	100 (89 to 100)
CABG surgery	19	95 (75 to 99)	70	99 (92 to 100)	11	100 (74 to 100)
Heart transplantation	33	100 (90 to 100)	6	100 (61 to 100)	N/A	N/A

CABG, coronary artery bypass graft surgery; ICD, implantable cardiac defibrillator; PCI, percutaneous coronary intervention; RFA, radiofrequency ablation; RHC, right heart catheterisation; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Table 2 Positive predictive value of cardiac examinations, procedures and surgeries in the Danish National Patient Registry, by gender

	Men		Women	
	Number of patients	Positive predictive value (95% CI)	Number of patients	Positive predictive value (95% CI)
Examination				
TTE	22	95 (78 to 99)	27	100 (88 to 100)
TEE	34	97 (85 to 99)	15	93 (70 to 99)
RHC	54	94 (85 to 98)	46	100 (92 to 100)
Coronary angiogram	62	100 (94 to 100)	38	100 (91 to 100)
Procedure				
Thrombolysis	57	96 (88 to 99)	39	100 (91 to 100)
Cardioversion	60	93 (84 to 97)	40	90 (77 to 96)
RFA	61	100 (94 to 100)	39	100 (91 to 100)
Unspecified PCI	31	100 (89 to 100)	19	100 (83 to 100)
PCI with stent implantation	44	95 (85 to 99)	6	100 (61 to 100)
Cardiac pacemaker	60	100 (94 to 100)	40	100 (91 to 100)
ICD	79	100 (95 to 100)	21	100 (85 to 100)
Surgery				
Mitral valve surgery	63	100 (94 to 100)	37	100 (91 to 100)
Aortic valve surgery	59	100 (94 to 100)	41	98 (87 to 100)
CABG surgery	71	97 (90 to 99)	29	100 (88 to 100)
Heart transplantation	23	100 (86 to 100)	16	100 (81 to 100)

CABG, coronary artery bypass graft surgery; ICD, implantable cardiac defibrillator; PCI, percutaneous coronary intervention; RFA, radiofrequency ablation; RHC, right heart catheterisation; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

found a PPV of 100% (95% CI 99% to 100%) for this examination.[9] The accuracy of the codes for non-cardiac surgery in the DNPR have previously been found to vary substantially.[3] It seems high for gastrointestinal surgery (PPV=99% for appendectomy and 100% for cholestectomia),[3] but lower for orthopaedic surgery procedures (PPV=69%).[3] For different types of gynaecological surgery, the PPVs varied considerably (55% to 99%).[3]

In healthcare systems outside Denmark, the accuracy of codes for cardiac examinations, procedures and surgeries remains largely unknown. However, a survey from the Canadian Institute for Health Information demonstrated that codes for cardiac procedures had high PPVs compared with a prospective clinical registry.[10] In line with our findings, the study reported PPVs of 96% for PCI, 98% for coronary artery bypass graft surgery, 97% for valve surgery and 95% for cardiac catheterisation.[10]

The Diagnosis-Related Group (DRG) system, established in 2002, ensures that public hospitals receive payment for procedures and surgeries.[11] These economic incentives increase the likelihood of accurate coding. Although not examined in this study, they, along with the nationwide coverage, also increase the completeness of registration. Private hospitals and clinics remain a potential source of under-reporting, although registration of procedures at these institutions is mandatory and urged by the Danish Health and Medicines Authority.[3] It remains for future studies to estimate other measures of data quality such as sensitivity and specificity.

The DNPR offers a variety of potential uses in research,[3] given its routine, longitudinal registration of health history and the possibility of individual-level linkage across different registries. Assessing data quality for epidemiological research (sensitivity vs specificity), it is always necessary to consider it in the context of individual study design. A high PPV is particular important when identifying cohorts for prognosis studies or in subanalyses restricted to patients undergoing specific cardiac interventions. In addition to supporting studies of trends and prognosis of cardiac diseases,[1] the DNPR offers the opportunity to study trends in cardiac examinations such as echocardiography,[12] cardiac procedures such as ICD implantation[13] and surgeries. Finally, the DNPR may be used to study prognostic factors, as well as procedure outcomes (eg, revascularisation) that are useful in defining composite outcomes. Still, the DNPR lacks detailed information on other variables, including examination results (eg, left ventricular ejection fraction) and procedure and surgery details (eg, types of cardiac stent).

Our study has potential limitations. It was restricted to one out of five Danish regions. However, the homogeneity of the Danish healthcare system makes it likely that our results also apply to other Danish regions.[7] Our results may not necessarily be applicable to other countries, other healthcare systems or earlier study periods.[3] Still, we find it less likely that the validity of the codes have varied substantially since the introduction of the DRG system in 2002 in Denmark. Most patients in our study were sampled from the university hospital because a majority of cardiac procedures are performed in that setting. We were therefore unable to stratify our results by regional versus university hospital. In the Central Denmark Region, right heart catheterisation, radiofrequency ablation, PCI, ICD implantation and all types of cardiac surgery are performed at the university hospital only, while other cardiac procedures and examinations are performed both at the university and regional hospitals. For the procedures examined in subgroup analyses (echocardiography and PCI), it should be noted that the patient subpopulations were not randomly sampled. Still, PPVs were consistently high within all subgroups.

CONCLUSION

We found consistently high PPVs for cardiac examinations, procedures and surgeries in the DNPR during 2010–2012, confirming the potential of these variables for cardiovascular research.

Contributors KA, JS, MS and HTS were involved in the study design. TF sampled the patients and KA performed the statistical analyses. All authors were involved in the interpretation of the results. KA wrote the manuscript, and all authors commented on and approved the final manuscript. The authors thank Hanne Moeslund Madsen and Henriette Kristoffersen for practical help with the study.

Funding This work was supported by Department of Clinical Epidemiology and the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation.

Competing interests None declared.

Ethics approval The study was approved by the Danish Data Protection Agency (record number: 1-16-02-1-08) and the Chairs of participating departments as part of quality insurance.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. Schmidt M, Jacobsen JB, Lash TL, *et al*. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ* 2012;344:e356.
2. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–9.
3. Schmidt M, Schmidt SA, Sandegaard JL, *et al*. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–90.
4. Mérie C, Køber L, Skov Olsen P, *et al*. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. *JAMA* 2012;308:2118–25.
5. Benchimol EI, Smeeth L, Guttmann A, *et al*. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;12:e1001885.
6. Danish Regions. Statistics. http://www.regioner.dk/om+regionerne/statistik+opdateret+dec+2014 (accessed 14 Oct 2015).

7. Henriksen DP, Rasmussen L, Hansen MR, *et al*. Comparison of the five Danish regions regarding demographic characteristics, healthcare utilization, and medication use—a descriptive cross-sectional study. *PLoS ONE* 2015;10:e0140197.
8. Wilson E. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc* 1927;22:209–12.
9. Nielsen LH, Nørgaard BL, Tilsted HH, *et al*. The Western Denmark Cardiac Computed Tomography Registry: a review and validation study. *Clin Epidemiol* 2014;7:53–64.
10. Lee DS, Stitt A, Wang X, *et al*. Administrative hospitalization database validation of cardiac procedure codes. *Med Care* 2013;51:e22–6.
11. The Diagnosis Related Group (DRG) system and the Danish ambulant grouping system (DAGS). http://www.drg.dk (accessed 12 Dec 2015).
12. Schmidt M, Ulrichsen SP, Pedersen L, *et al*. Thirty-year trends in heart failure hospitalization and mortality rates and the prognostic impact of co-morbidity: a Danish nationwide cohort study. *Eur J Heart Fail* 2016;18:490–9.
13. Schmidt M, Pedersen SB, Farkas DK, *et al*. Thirteen-year nationwide trends in use of implantable cardioverter-defibrillators and subsequent long-term survival. *Heart Rhythm* 2015;12:2018–27.

BMJ Open

Positive predictive value of cardiac examination, procedure and surgery codes in the Danish National Patient Registry: a population-based validation study

Kasper Adelborg, Jens Sundbøll, Troels Munch, Trine Frøslev, Henrik Toft Sørensen, Hans Erik Bøtker and Morten Schmidt

BMJ Open 2016 6:
doi: 10.1136/bmjopen-2016-012817

Online supplementary

The positive predictive value of cardiac examination, procedure, and surgery codes in the Danish National Patient Registry: A population-based validation study

Supplementary Table 1. Codes for cardiac examinations, procedures and surgeries used in the study.

	Code	**Type of admission**
Echocardiography		
- Transthoracic echocardiography	UXUC80	In- or outpatient
- Transoesophageal echocardiography	UXUC81	In- or outpatient
Right Heart Catheterization	KTFC00	Inpatient
Coronary angiogram	UXAC85	Inpatient
Thrombolysis	BOHA1	Inpatient
Cardioversion	BFFA0	In- or outpatient
Radiofrequency Ablation	BFFB	Inpatient
Percutaneous coronary intervention (overall)	KFNG, KFNF	Inpatient
- Unspecified with/without stent	KFNG, KFNF	
- With stent implantation	KFNG05	
Cardiac pacemakers	BFCA0, BFCA6, KFPE00, KFPE10, KFPE20, KFPE96, KFPF00, KFPF10, KFPF20, KFPF96	Inpatient
Implantable cardiac defibrillator	BFCB0, BFCB6, KFPG	Inpatient
Mitral valve surgery	KFK	Inpatient
Aortic valve surgery	KFM	Inpatient
Coronary artery bypass grafting	KFNA-KFNE, KFNH20	Inpatient
Heart transplantation	KFQA	Inpatient

Supplementary Table 2. Definition of primary and secondary indication for implantable cardiac defibrillator and ICD-10 codes to identify patients.

	Definition	ICD-10 codes used to identify patients
Primary indication	(1) coronary artery disease, left ventricle ejection fraction ≤ 35%, and New York Heart Association Functional Class II or III despite optimal medical treatment, or (2) conditions such as long QT-syndrome, arrhythmogenic right ventricular dysplasia/cardiomyopathy, or other congenital heart disease associated with life-threatening arrhythmias	BFCB0, BFCB6, KFPG
Secondary indication	(1) post-cardiac arrest with ventricular fibrillation or ventricular tachycardia, or (2) ventricular tachycardia causing hemodynamic instability in the absence of reversible or transient causes of the arrhythmia and no response to radiofrequency ablation, or (3) unexplained syncope or other serious arrhythmia symptoms, induced in a electrophysiological examination	BFCB0, BFCB6, KFPG and any diagnoses of ventricular fibrillation (DI 49.0), ventricular tachycardia (DI 47.2), or cardiac arrest (DI 46) during or before the admission for implantable cardiac defibrillator implantation

Supplementary Table 3. Variables in the medical record extraction form.

Variables	Explanation
Date	Date of the medical record review
Initials	Initials of the investigator
CPR number	10-digit personal identification number
CPR number (check)	Confirmation of the 10-digit personal identification number
SKS code	The code of the examination, procedure, or surgery
Name of procedure	Abbreviated name for the examination, procedure, or surgery types
Date of discharge	The date the patient was examined/discharged
Correct procedure	0=No, 1=Yes
Correct procedure for subgroups	0=No, 1=Yes
Data source	1=Discharge summary 2=Medical record 3=Both 1+2
Algorithm	1=One investigator made the decision 2=A second independent reviewer agreed with the first reviewer 3=Consensus agreement
Comments	Any relevant comments

Supplementary Table 4. Positive predictive value of cardiac examinations, procedures, and surgeries in the Danish National Patient Registry, by calendar year.

	2010		2011		2012	
	Number of patients	**Positive predictive value (95%CI)**	**Number of patients**	**Positive predictive value (95%CI)**	**Number of patients**	**Positive predictive value (95%CI)**
TTE	16	94 (72-99)	17	100 (82-100)	16	100 (81-100)
TEE	12	100 (76-100)	19	89 (69-97)	18	100 (82-100)
Right heart catheterization	36	94 (82-98)	25	100 (87-100)	39	97 (87-100)
Coronary angiogram	29	100 (88-100)	40	100 (91-100)	31	100 (89-100)
Thrombolysis	26	100 (87-100)	30	100 (89-100)	40	95 (84-99)
Cardioversion	21	90 (71-97)	44	93 (82-98)	35	91 (78-97)
Radiofrequency ablation	29	100 (88-100)	34	100 (90-100)	37	100 (91-100)
Unspecified PCI	14	100 (78-100)	18	100 (82-100)	18	100 (82-100)
PCI with stent implantation	20	90 (70-97)	12	100 (76-100)	18	100 (82-100)
Cardiac pacemaker	29	100 (88-100)	41	100 (91-100)	30	100 (89-100)
ICD	36	100 (90-100)	30	100 (89-100)	34	100 (90-100)
Mitral valve surgery	34	100 (90-100)	34	100 (90-100)	32	100 (89-100)
Aortic valve surgery	38	100 (91-100)	32	100 (89-100)	30	97 (83-99)
CABG surgery	31	97 (84-99)	32	97 (84-99)	37	100 (91-100)
Heart transplantation	10	100 (72-100)	13	100 (77-100)	16	100 (81-100)

Abbreviations: CABG, coronary artery bypass graft surgery; CI, confidence interval. ICD, implantable cardiac defibrillator; PCI, percutaneous coronary intervention; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography

Study III

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Mortality Risk Among Heart Failure Patients With Depression: A Nationwide Population-Based Cohort Study

Kasper Adelborg, MD; Morten Schmidt, PhD; Jens Sundbøll, MD; Lars Pedersen, PhD; Poul Videbech, DMSc; Hans Erik Bøtker, DMSc; Kenneth Egstrup, DMSc; Henrik Toft Sørensen, DMSc

***Background*—**The prevalence of depression is 4- to 5-fold higher in heart failure patients than in the general population. We examined the influence of depression on all-cause mortality in patients with heart failure.

***Methods and Results*—**Using Danish medical registries, this nationwide population-based cohort study included all patients with a first-time hospitalization for heart failure (1995–2014). All-cause mortality risks and 19-year mortality rate ratios were estimated based on Cox regression analysis, adjusting for age, sex, time period, comorbidity, and socioeconomic status. The analysis included 9636 patients with and 194 887 patients without a diagnosis of depression. Compared with patients without a history of depression, those with depression had higher 1-year (36% versus 33%) and 5-year (68% versus 63%) mortality risks. Overall, the adjusted mortality rate ratio was 1.03 (95% CI 1.01–1.06). Compared with no depression, the adjusted mortality rate ratios for mild, moderate, and severe depression, as defined by diagnostic codes, were 1.06 (95% CI 1.00–1.13), 1.03 (95% CI 0.99–1.08), and 1.02 (95% CI 0.96–1.09), respectively. In a subcohort of patients, the mortality rate ratios were modified by left ventricular ejection fraction, with adjusted mortality rate ratios of 1.17 (95% CI, 1.05–1.31) for ≤35%, 0.98 (95% CI 0.81–1.18) for 36% to 49%, and 0.96 (95% CI 0.74–1.25) for ≥50%. Results were consistent after adjustment for alcohol abuse and smoking.

***Conclusions*—**A history of depression was an adverse prognostic factor for all-cause mortality in heart failure patients with left ventricular ejection fraction ≤35% but not for other heart failure patients. **(*J Am Heart Assoc*. 2016;5:e004137 doi: 10.1161/JAHA.116.004137)**

Key Words: cohort study • depression • heart failure • mortality

Heart failure is a major cause of hospitalization, morbidity, and mortality that affects >23 million people worldwide.[1] The prevalence of comorbid depression ranges between 9% and 60% and is highest among heart failure patients screened for depression, among women, and among those with advanced heart failure.[2]

From the Departments of Clinical Epidemiology (K.A., M.S., J.S., L.P., H.T.S.) and Cardiology (K.A., J.S., H.E.B.), Aarhus University Hospital, Aarhus N, Denmark; Mental Health Center Glostrup, Glostrup, Denmark (P.V.); Department of Medical Research, Odense University Hospital, Svendborg Hospital, Svendborg, Denmark (M.S., K.E.).

Accompanying Tables S1 through S5 and Figures S1 through S5 are available at http://jaha.ahajournals.org/content/5/9/e004137/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Kasper Adelborg, MD, Department of Clinical Epidemiology, Aarhus University Hospital, Skejby, Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark. E-mail: kade@clin.au.dk

Received June 30, 2016; accepted August 1, 2016.

Depression and heart failure share underlying biological mechanisms. Patients with depression have hyperactivity of the hypothalamic–pituitary–adrenal axis, higher levels of inflammatory markers, decreased heart rate variability, abnormalities in platelet function, lower compliance with medication and dietary guidelines, less social support, and a more sedentary lifestyle than patients without depression. These factors may aggravate cardiac dysfunction in heart failure patients.[3,4] Depressed heart failure patients appear to have a 1.5- to 2-fold higher risk of mortality than nondepressed heart failure patients.[2,5] Nevertheless, studies to date have been limited by inclusion of highly selected patients[6–11]; short follow-up periods (3 months to 3 years)[6,7,12–14]; use of self-reported symptoms or antidepressant prescriptions as proxies for depression[6,7,9,10,12–15]; limited control of confounding factors such as smoking, alcohol use, socioeconomic factors, and comorbidity[9,10,13–15]; and small sample size (<400 patients).[6,7,9,10,15]

Critical unanswered questions remain regarding the association between depression and mortality in subgroups of heart failure patients defined by sex, age group, left ventricular ejection fraction (LVEF) values, causes of heart failure, presence or absence of various comorbidities, and New York

Heart Association (NYHA) functional classes. We hypothesized that a history of depression is a prognostic factor for death in heart failure patients and examined long-term mortality among patients with and without a history of depression.

Methods

Setting and Design

This nationwide population-based cohort study, which used prospectively collected data, was conducted from July 1, 1995, to February 1, 2014. Using the unique personal identifiers assigned to all Danish residents at birth or at immigration, we linked individual-level data from Danish medical and administrative registries.[16] The Danish national health care system is government funded, ensuring equal and free access to all medical care services provided by hospitals and general practitioners.

Heart Failure Cohort

We identified all patients with a first-time hospitalization for heart failure (including primary and secondary diagnoses) from the Danish National Patient Registry (DNPR).[17] Admission date for the heart failure hospitalization defined the index date. The positive predictive value of heart failure diagnoses in the DNPR is 81% with clinical examination as the reference and 100% with information in medical records as the reference.[17]

Depression

Information on all recorded diagnoses of depression any time prior to the index date was obtained from the DNPR and the Danish Psychiatric Central Research Register (DPCR).[17,18] In addition, we retrieved information on severity of depression (mild, moderate, and severe) using codes from the *International Classification of Diseases, 10th Revision* (ICD-10). Patients with >1 depression diagnosis of any severity were classified as being in the group with the most severe depression. With an interview as the reference, the positive predictive value of a single severe or moderate depression episode in the DPCR is adequate (83% or 76%, respectively) but is lower for mild depression (65%).[19]

Because many patients receive treatment for depression in the primary care setting, depression may be underreported in Danish medical registries, which do not yet include primary care. To compensate for such underreporting, we obtained information on redeemed prescriptions for antidepressants. We divided patients into 6 categories: (1) no diagnosis of depression and ≤1 redeemed prescription for antidepressants before the index date (reference group); (2) no diagnosis of depression, >1 redeemed prescription before the index date, and previous use of antidepressants; (3) no diagnosis of depression, >1 redeemed prescription for antidepressants before the index date, and current use of antidepressants; (4) a depression diagnosis and ≤1 redeemed prescription for antidepressants; (5) a depression diagnosis, >1 redeemed prescription before the index date, and previous use of antidepressants; and (6) a depression diagnosis, >1 redeemed prescription before the index date, and current antidepressant use. We defined "current users" as having redeemed a prescription for antidepressants within 90 days before the index date. "Former users" redeemed their last prescription >90 days before the index date. Data on redeemed prescriptions of antidepressants were obtained from the Danish Register of Medicinal Product Statistics, which has recorded all dispensed prescriptions according to the Anatomical Therapeutical Chemical (ATC) classification system since 1995.[20]

Outcome

The study outcome was all-cause mortality. We used the Danish Civil Registration System to ascertain mortality during the years following the index date.[16] This registry has recorded dates of death and emigration, with daily updates since 1968.[16] We also examined immediate causes of deaths using data from the Danish Register of Causes of Death[21] (data available through December 31, 2012). We estimated cardiovascular and noncardiovascular mortality in patients with and without depression. For this analysis, depression was defined as any diagnosis or >1 prescription of antidepressant before the index date. Patients registered with only an underlying and no immediate cause of death were considered not to have an immediate cause of death; however, the results did not change if the underlying cause of death was considered as the immediate cause of death in these patients (data not shown). Moreover, we specifically examined deaths caused by arrhythmia, venous thromboembolism, stroke, myocardial infarction, and heart failure.

Covariates

We collected information on a range of comorbidities diagnosed from 1977 until the index date. These included myocardial infarction, hypertension, atrial fibrillation or atrial flutter, stroke, cancer, obesity, diabetes mellitus, chronic pulmonary disease, chronic kidney disease, peptic ulcer, illicit drug/alcohol/smoking abuse, dementia, anemia, and peripheral artery disease. Data on these diagnoses were obtained from the DNPR and the DPCR using ICD-8 codes until 1994 and ICD-10 codes thereafter.[17,18] We used all available diagnoses other than emergency room diagnoses, given the assumed low positive predictive value of the latter.[17]

Data on the following comedications used ≤90 and >90 days before the index date were retrieved from the Danish Register of Medicinal Product Statistics: antidepressants, selective serotonin reuptake inhibitors, tricyclic antidepressants, anxiolytics or hypnotics, antipsychotics, statins, low-dose aspirin, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers, diuretics, and nonsteroidal anti-inflammatory drugs.[20] Data on socioeconomic variables, including gross income, employment, and education, were obtained from the Integrated Database for Labor Market Research (for the index year or for previous years, depending on data availability).[22] For a subcohort of heart failure patients, we retrieved data from the Danish Heart Failure Registry on smoking status, alcohol habits, LVEF values, and NYHA functional class.[23] It has been mandatory for cardiologists to register all incident hospitalized heart failure cases in this nationwide registry since 2003. Patients with ICD-10 codes for heart failure are enrolled in the registry if they fulfill the European Society of Cardiology's definition of heart failure. Regular structured audits are conducted to ensure the high quality of the registry's data.[23] All ICD and ATC codes used in the study are provided in Table S1.

Statistical Analysis

All patients were followed from their admission date for heart failure (index date) until the date of death or emigration or September 1, 2014, whichever came first. We compiled descriptive data on the covariates described in the previous section. The Kaplan–Meier method was used to compute mortality risks at 1, 5, 10, and 15 years, and we generated survival curves for patients with and without previous depression. Crude and adjusted hazard ratios were computed using Cox proportional hazards regression analysis comparing heart failure patients with and without a history of depression. In multivariable analyses, we adjusted for age, sex, time periods, the comorbidities listed in Table 1, gross income, and employment.

In stratified analyses, we examined potential interactions on a relative scale according to time periods, age groups, sex, heart failure cause, LVEF, NYHA class, comorbidity, comedication use, and socioeconomic factors. The analyses stratified by LVEF group and NYHA class were restricted to patients with complete data on these variables. Because age was nonlinear, it was included in the models as the best-fitting second-degree fractional polynomial. We evaluated proportional hazards using log-log plots and found no violation of the assumption.

Sensitivity Analyses

To test the robustness of our estimates, we performed several sensitivity analyses. First, we analyzed patients whose first

Table 1. Characteristics of Heart Failure Patients With and Without Previous Depression

	No Depression	Previous Depression
Number	194 887 (95)	9636 (5)
Median age (25th to 75th percentiles), y	78 (68–84)	77 (67–84)
Women	89 671 (46)	6039 (63)
Time period		
1995–1999	49 498 (25)	1801 (19)
2000–2004	59 842 (31)	2850 (30)
2005–2009	48 796 (25)	2792 (29)
2010–2014	36 751 (19)	2193 (23)
Comorbidity		
Myocardial infarction	39 761 (20)	1770 (18)
Hypertension	50 303 (26)	3100 (32)
Atrial fibrillation/atrial flutter	38 175 (20)	1734 (18)
Stroke	21 968 (11)	1517 (16)
Cancer	31 198 (16)	1691 (18)
Obesity	10 728 (6)	827 (9)
Diabetes mellitus	26 724 (14)	1509 (16)
Chronic pulmonary disease	33 815 (17)	2369 (25)
Chronic kidney disease	9431 (5)	582 (6)
Peptic ulcer	17 751 (9)	1404 (15)
illicit drug/alcohol/ smoking abuse	9989 (5)	2358 (24)
Dementia	6483 (3)	1219 (13)
Anemia	17 345 (9)	1337 (14)
Peripheral artery disease	6077 (3)	369 (4)
Comedication in the prior 90 days		
Antidepressants	24 239 (12)	5814 (60)
SSRIs	16 358 (8)	3316 (34)
TCAs	4133 (2)	1104 (12)
Anxiolytics or hypnotics	50 070 (26)	4793 (50)
Antipsychotics	8238 (4)	2239 (23)
Statins	30 164 (15)	1578 (16)
Low-dose aspirin	60 214 (31)	3191 (33)
ACEI/ARB	55 582 (29)	2466 (26)
Beta blockers	46 395 (24)	2121 (22)
Diuretics	100 130 (51)	5143 (53)
NSAIDs	30 000 (15)	1586 (16)
Income		
Low	41 640 (21)	1654 (17)
Intermediate	52 031 (27)	2732 (28)
High	50 304 (26)	3082 (32)
Very high	50 912 (26)	2168 (23)

Continued

Table 1. Continued

	No Depression	Previous Depression
Employment		
Employed	25 618 (13)	557 (6)
Early retirement: receiving sickness, disability, or early retirement benefits	2649 (1)	145 (2)
Unemployed	20 163 (10)	1592 (17)
State pension	146 457 (75)	7342 (76)
Education		
Basic education, primary school	74 173 (38)	4288 (45)
Youth education, high school, or similar	43 145 (22)	2045 (22)
Higher education	15 199 (8)	827 (9)
Unknown	62 370 (32)	2476 (26)

Data are shown as number (percentage), except as otherwise indicated. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

diagnosis of depression was recorded in the DNPR separately from those whose first diagnosis was recorded in the DPCR. Second, we restricted our analysis to depression diagnoses occurring 1, 2, and 3 years before the index date. Third, we fitted 3 additional multivariable models, adjusted for education (omitted from the main model because data on education were missing for heart failure patients with a high age, and thus these data were missing not at random), use of anxiolytics or hypnotics, and use of antipsychotics. Fourth, we omitted myocardial infarction, stroke, hypertension, and diabetes mellitus because these covariates potentially could represent intermediate variables in the association between depression and all-cause mortality.[24–26] Finally, to increase the positive predictive value of the recorded diagnosis of heart failure, we repeated the main analysis restricted to patients included in the Danish Heart Failure Registry. In this subcohort, we also adjusted for smoking and alcohol habits as categorical variables in a complete-case analysis and used multiple imputation with chained equations to create 25 data sets with imputed values for smoking and alcohol.[27] We assumed that data were missing at random, and in the imputation model, we included the covariates from the main model and those presented in Table 1 (except for nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, and education), the outcome indicator, and the Nelson-Aalen cumulative baseline hazard. Finally, because depression can be difficult to assess in patients with illicit drug/alcohol/smoking abuse, or dementia, we repeated the analysis excluding these patients.

All analyses were performed using Stata version 14 (StataCorp LP). The study was approved by the Danish Data Protection Agency (record 1-16-02-268-14). No approval from an ethics committee or patient informed consent is required for registry-based studies conducted in Denmark.

Results

Overall, 205 719 patients with a first-time hospitalization for heart failure were eligible for analysis. We excluded 99 patients with negative follow-up time, 9 patients with missing data on age, and 1088 patients with missing data on gross income and employment. After these exclusions, 9636 heart failure patients with previous depression (5%) and 194 887 heart failure patients without depression (95%) were available for analysis. Median follow-up time was 844 days (25th to 75th percentiles: 164–2050 days) for patients without depression and 688 days (25th to 75th percentiles: 119–1737 days) for patients with previous depression. Median age was 78 years in patients without depression and 77 years in patients with depression. A higher proportion of patients with depression were women compared with patients without depression. Apart from hypertension, the groups were balanced in terms of cardiac comorbidities. Patients with a history of depression had a higher prevalence of noncardiac conditions than patients without depression (Table 1 and Table S2). We identified 29 854 heart failure patients from the Danish Heart Failure Registry. Descriptive data on these patients are provided in Table S3.

Mortality

Mortality risks among heart failure patients with depression were higher than among heart failure patients without depression (Table 2 and Figure S1). Compared with patients without depression, 19-year mortality rate ratios after multivariable adjustment were 1.03 (95% CI 1.01–1.06) overall, 1.06 (95% CI 1.00–1.13) for mild depression, 1.03 (95% CI 0.99–1.08) for moderate depression, and 1.02 (95% CI 0.96–1.09) for severe depression (Table 3). Slightly more positive associations were found with various combinations of depression diagnoses and antidepressant use (Table 4 and Table S2). Patients with previous depression had higher noncardiovascular mortality and slightly higher cardiovascular mortality than patients without previous depression (Table 5).

Age, Sex, Heart Failure Severity, Heart Failure Cause, and Comorbidity

No interactions were found by age, sex, NYHA class, and cause of heart failure (Figure and Figure S2). Among patients

Table 2. Mortality Risks (Percentage) Among Heart Failure Patients With and Without Previous Depression

	1 Year (95% CI)	5 Years (95% CI)	10 Years (95% CI)	15 Years (95% CI)
No depression	32.6 (32.4–32.9)	63.3 (63.0–63.5)	81.5 (81.3–81.8)	90.4 (90.2–90.6)
Depression	36.4 (35.4–37.3)	68.0 (67.0–69.0)	85.7 (84.8–86.5)	93.3 (92.3–94.1)

with LVEF values ≤35%, those with a history of depression had ≈20% higher mortality than those who never had depression (Figure). Stratified analyses among patients with various comorbidities and comedications and according to gross income, employment, and education showed no interactions (Figures S3 through S5).

Sensitivity Analyses

Separate analyses of the prognostic impact of depression based on cases registered in the DNPR and the DPCR agreed with the main results (all sensitivity analyses are reported in Table S4). When patients with depression diagnosed within 1, 2, and 3 years before the index date were excluded, the results remained similar to the overall estimates. Repeating the analyses restricted to heart failure patients included in the Danish Heart Failure Registry also did not change the overall estimates. The estimates remained unchanged among patients included in this subcohort when we extended the Cox model by adjusting for education, use of anxiolytics or hypnotics, and use of antipsychotics, as well as for smoking and alcohol use (in a complete case analysis and using multiple imputation). Similarly, the main results were unchanged when myocardial infarction, stroke, hypertension, and diabetes mellitus were omitted from the multivariable model and when we repeated the analysis excluding patients with illicit drug/alcohol/smoking abuse, or dementia from the cohort. Analyses stratified by time periods did not change the results appreciably (Table S5).

Table 3. The 19-Year MRRs in Heart Failure Patients With and Without Depression, Overall and by Depression Severity

	Crude MRR (95% CI)	Adjusted MRR (95% CI)*
No depression	Reference	Reference
Depression overall† (n=9636)	1.14 (1.12–1.17)	1.03 (1.01–1.06)
Mild depression‡ (n=1379)	1.27 (1.20–1.35)	1.06 (1.00–1.13)
Moderate depression‡ (n=2914)	1.16 (1.11–1.21)	1.03 (0.99–1.08)
Severe depression‡ (n=1305)	1.05 (0.99–1.12)	1.02 (0.96–1.09)

ICD indicates *International Classification of Diseases*; MRR, mortality rate ratio.
*Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation or atrial flutter, stroke, cancer, obesity, diabetes mellitus, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anemia, peripheral artery disease, gross income, and employment.
†Including all ICD codes for depression.
‡Specific ICD-10 codes are provided in Table S1.

Discussion

In this cohort study of patients with a first-time hospitalization for heart failure, depression was a prognostic factor for all-cause mortality in patients with LVEF ≤35%; however, in other heart failure patients, a history of depression was not associated with all-cause mortality. The prognostic effect of depression showed no interaction with age, sex, heart failure causes, NYHA class, cardiac comorbidities, and noncardiac comorbidities.

A meta-analysis of 8 studies demonstrated that comorbid depression was an adverse prognostic factor for all-cause mortality in heart failure patients (overall adjusted relative risk 2.10, 95% CI 1.71–2.58).[2] Consistent with this result, another meta-analysis of 9 studies including 4012 heart failure patients reported adjusted relative risk of all-cause mortality of 1.51 (95% CI 1.19–1.91) and adjusted relative risk of cardiovascular mortality of 2.19 (95% CI 1.46–3.29).[5] Severe depression was associated with increased mortality (relative risk 1.98, 95% CI 1.23–3.19) but not with mild depression (overall adjusted relative risk 1.04, 95% CI 0.75–1.45).[5]

The disparity between our results and those of the meta-analyses may have several explanations. Unlike our study, studies in the meta-analyses used self-reported symptoms to diagnose depression. Self-reported depression likely mimics somatic symptoms and could reflect increasing heart failure severity, which, if not sufficiently accounted for in the analyses, could explain the poor prognosis of patients with depression reported in previous studies.[2,5] In addition, some studies were not able to account for confounding factors such as socioeconomic factors, smoking, and alcohol use, which could have led to overestimation of the impact of depression on mortality.[9,10,13–15]

In contrast to previous studies investigating the prevalence of comorbid depression, we retrieved data on at least 15 years of depression history. Even so, the prevalence of depression was lower in our cohort (5%) than reported previously.[2] This may be attributed to our strict definition of

Table 4. The 19-Year MRRs in Heart Failure Patients According to Depression Diagnosis and Use of Antidepressants Before the Index Date

	Use of Antidepressants	Crude MRR (95% CI)	Adjusted MRR (95% CI)*
No depression	No use (n=156 168)	Reference	Reference
	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)
Depression	No use (n=1912)	1.07 (1.02–1.13)	1.00 (0.95–1.06)
	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)

MRR indicates mortality rate ratio.
*Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation or atrial flutter, stroke, cancer, obesity, diabetes mellitus, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anemia, peripheral arterial disease, gross income, and employment.

depression history, use of ICD codes, and restriction to patients with incident heart failure. When we defined previous depression using both diagnosed depression and use of antidepressants, the prevalence increased to 24% (Table 4), which is in accordance with the existing literature.[2]

Our results extend the results of previous studies. Supporting our findings, the US Cardiovascular Health Study demonstrated that patients with depression and elevated NT-proBNP had substantially increased all-cause mortality (hazard ratio 3.72, 95% CI 2.20–6.37) and cardiovascular mortality (hazard ratio 5.42, 95% CI 2.38–12.36) compared with patients without depression and with low NT-proBNP levels.[15] The prevalence of depression has been found to increase with severity of heart failure symptoms, from 11% among patients in NYHA class 1 to 20% in NYHA class 2, 38% in NYHA class 3, and 42% in NYHA class 4[2]; however, we did not find that depression was an adverse prognostic factor in different NYHA classes. Nevertheless, standardized diagnostic measures of depression could be particularly important for patients with LVEF ≤35%.

Several pathophysiological and psychosocial mechanisms in patients with depression and heart failure may underlie the higher mortality observed for patients with LVEF ≤35%.[3,4] Evidence suggests that patients with ongoing or remitted depression have disturbances in the hypothalamic–pituitary–adrenal axis, including higher cortisol levels than persons without depression. This may augment the sympathetic hyperactivity observed in advanced heart failure.[28] Cortisol has negative cardiovascular side effects, such as elevation of blood pressure, truncal obesity, hyperinsulinemia, hyperglycemia, insulin resistance, dyslipidemia, and increased plasma volume, which could worsen the prognosis of advanced heart failure patients.[29] Inflammatory cytokines such as tumor necrosis factor, interleukin 1, and interleukin 6 also are elevated in patients with heart failure, and these cytokines may be implicated in disease progression.[3] Elevation of these cytokines is also characteristic of depression

Table 5. Cardiovascular and Noncardiovascular Mortality in Patients With and Without Previous Depression, 1995–2012

	Rate Per 1000 Person-Years (95% CI)		
	No Depression (n=149 235)	Depression (n=45 224)	Adjusted MRR (95% CI)*
All-cause mortality	194.1 (193.0–195.2)	255.7 (253.1–258.3)	1.14 (1.12–1.15)
Cardiovascular mortality	70.3 (69.6–71.0)	86.0 (84.4–87.7)	1.09 (1.06–1.11)
Arrhythmia	7.6 (7.4–7.9)	8.9 (8.4–9.5)	1.08 (1.01–1.16)
Venous thromboembolism	1.7 (1.6–1.8)	2.3 (2.1–2.6)	1.15 (1.00–1.32)
Myocardial infarction	9.3 (9.0–9.6)	11.6 (11.0–12.3)	1.02 (0.97–1.09)
Stroke	6.5 (6.3–6.7)	9.2 (8.7–9.8)	1.12 (1.05–1.21)
Heart failure	23.4 (23.0–23.8)	29.8 (28.9–30.8)	1.08 (1.04–1.13)
Noncardiovascular mortality	108.9 (108.0–109.8)	160.2 (158.0–162.5)	1.19 (1.17–1.21)

MRR indicates mortality rate ratio.
*Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation or atrial flutter, stroke, cancer, obesity, diabetes mellitus, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anemia, peripheral artery disease, gross income, and employment.

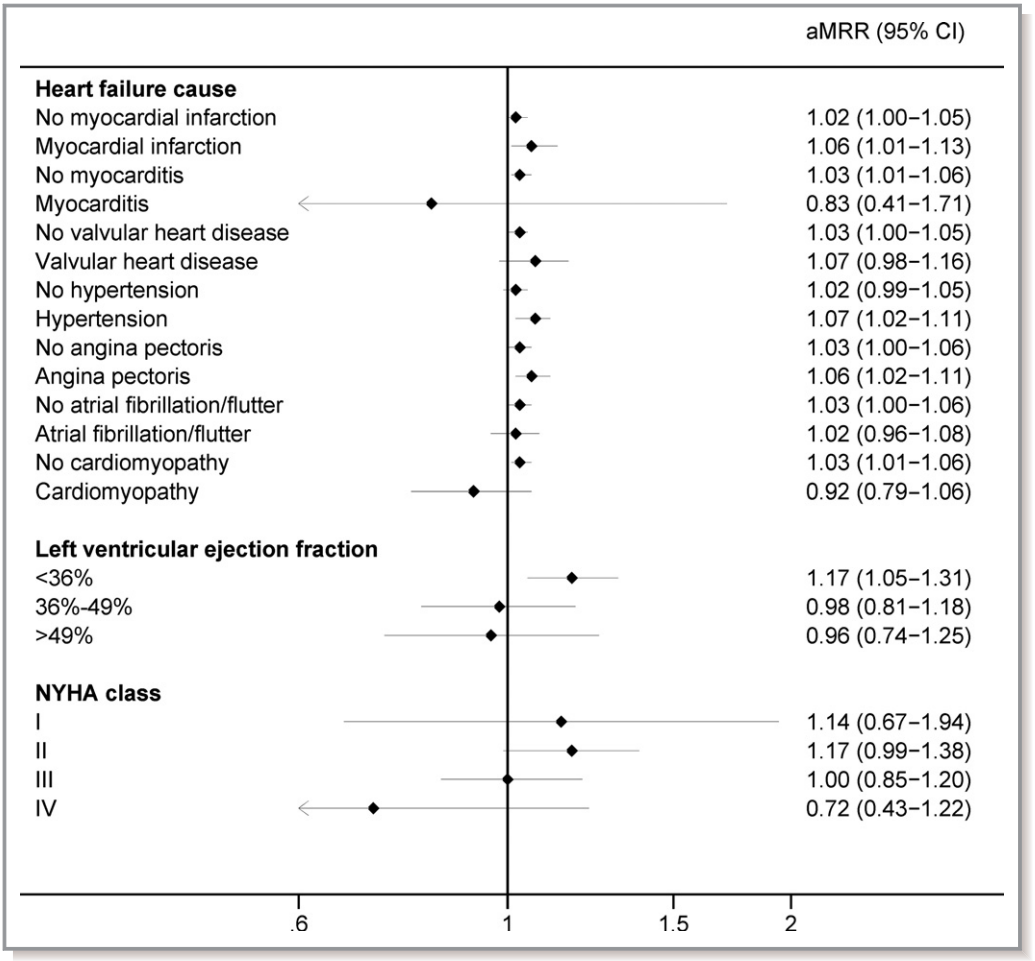


Figure. The aMRRs with 95% CIs in subgroups of heart failure patients with and without depression. The aMRRs were adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation or atrial flutter, stroke, cancer, obesity, diabetes mellitus, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anemia, peripheral artery disease, gross income, and employment (except for the stratifying variable). aMRR indicates adjusted mortality rate ratio; NYHA, New York Heart Association.

and may further adversely affect prognosis of heart failure patients with depression.[3] Studies to date, however, have found no association between depression severity and cytokine response, indicating that these cytokines may be trait markers for depression rather than markers of current depression.[3] Patients with depression also have decreased heart rate variability, which is a predictor of increased mortality and a prognostic factor for arrhythmias.[3] Finally, platelet abnormalities, noncompliance, poor social support, and suicide have been proposed as other mechanisms responsible for the adverse prognostic effect of depression in heart failure patients with low LVEF.[3]

Our study is the first nationwide population-based study to address the association between depression and all-cause mortality among heart failure patients. Strengths distinguishing this study from previous studies include the nationwide coverage and a sample size exceeding the combined number of patients included in the previous 2 meta-analyses.[2,5] This enabled us to study the prognostic impact of depression in several subgroups. We had no loss to follow-up, largely avoiding selection bias. Our study also has limitations. Because the validity of depression in the DNPR is unknown, misclassification of depression cannot be ruled out. We sought to address this potential limitation by showing that results were consistent when analyzed separately for cases identified in the DNPR and in the DPCR and by reclassifying depression using both diagnoses and antidepressant use; however, we had only a few years of prescription history for patients identified early in the study period. In addition, antidepressants are used for indications other than depression, a fact that we were unable to take into account. Consequently, some of the patients using an antidepressant without being diagnosed with depression may be misclassified as surrogates for a history of depression. Moreover, we had

data on depression severity for only about half of the patients, and positive predictive values for codes for mild, moderate, and severe depression were only moderate (65–83%). Another concern is that the observational nature of the study design did not permit us to exclude the risk of unmeasured confounding. Nevertheless, we were able to adjust for known prognostic comorbid conditions (anemia, chronic kidney disease, peripheral artery disease, atrial fibrillation, and diabetes mellitus).[30,31] Furthermore, we were able to adjust for smoking, alcohol use, and socioeconomic status.

Conclusions

We found that depression was an adverse prognostic factor for death in patients with LVEF ≤35%, but not in other heart failure patients. Consequently, clinical attention to depression seems particularly warranted for patients with advanced heart failure.

Sources of Funding

The study was supported by Aarhus University and grants from the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation. None of the funding sources had a role in the design, conduct, analysis, or reporting of the study.

Disclosures

None.

References

1. Roger VL. Epidemiology of heart failure. *Circ Res*. 2013;113:646–659.
2. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol*. 2006;48:1527–1537.
3. Joynt KE, Whellan DJ, O'connor CM. Why is depression bad for the failing heart? A review of the mechanistic relationship between depression and heart failure. *J Card Fail*. 2004;10:258–271.
4. York KM, Hassan M, Sheps DS. Psychobiology of depression/distress in congestive heart failure. *Heart Fail Rev*. 2009;14:35–50.
5. Fan H, Yu W, Zhang Q, Cao H, Li J, Wang J, Shao Y, Hu X. Depression after heart failure and risk of cardiovascular and all-cause mortality: a meta-analysis. *Prev Med*. 2014;63:36–42.
6. Kato N, Kinugawa K, Yao A, Hatano M, Shiga T, Kazuma K. Relationship of depressive symptoms with hospitalization and death in Japanese patients with heart failure. *J Card Fail*. 2009;15:912–919.
7. Vaccarino V, Kasl SV, Abramson J, Krumholz HM. Depressive symptoms and risk of functional decline and death in patients with heart failure. *J Am Coll Cardiol*. 2001;38:199–205.
8. Murberg TA, Furze G. Depressive symptoms and mortality in patients with congestive heart failure: a six-year follow-up study. *Med Sci Monit*. 2004;10:CR643–CR648.
9. Faller H, Stork S, Schowalter M, Steinbuchel T, Wollner V, Ertl G, Angermann CE. Depression and survival in chronic heart failure: does gender play a role? *Eur J Heart Fail*. 2007;9:1018–1023.
10. Junger J, Schellberg D, Muller-Tasch T, Raupp G, Zugck C, Haunstetter A, Zipfel S, Herzog W, Haass M. Depression increasingly predicts mortality in the course of congestive heart failure. *Eur J Heart Fail*. 2005;7:261–267.
11. O'Connor CM, Jiang W, Kuchibhatla M, Mehta RH, Clary GL, Cuffe MS, Christopher EJ, Alexander JD, Califf RM, Krishnan RR. Antidepressant use, depression, and survival in patients with heart failure. *Arch Intern Med*. 2008;168:2232–2237.
12. Macchia A, Monte S, Pellegrini F, Romero M, D'Ettorre A, Tavazzi L, Tognoni G, Maggioni AP. Depression worsens outcomes in elderly patients with heart failure: an analysis of 48,117 patients in a community setting. *Eur J Heart Fail*. 2008;10:714–721.
13. Moraska AR, Chamberlain AM, Shah ND, Vickers KS, Rummans TA, Dunlay SM, Spertus JA, Weston SA, McNallan SM, Redfield MM, Roger VL. Depression, healthcare utilization, and death in heart failure: a community study. *Circ Heart Fail*. 2013;6:387–394.
14. Lesman-Leegte I, van Veldhuisen DJ, Hillege HL, Moser D, Sanderman R, Jaarsma T. Depressive symptoms and outcomes in patients with heart failure: data from the COACH study. *Eur J Heart Fail*. 2009;11:1202–1207.
15. van den Broek KC, Defilippi CR, Christenson RH, Seliger SL, Gottdiener JS, Kop WJ. Predictive value of depressive symptoms and B-type natriuretic peptide for new-onset heart failure and mortality. *Am J Cardiol*. 2011;107:723–729.
16. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541–549.
17. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490.
18. Mors O, Perto GP, Mortensen PB. The Danish psychiatric central research register. *Scand J Public Health*. 2011;39:54–57.
19. Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV. Validity of the diagnosis of a single depressive episode in a case register. *Clin Pract Epidemiol Ment Health*. 2009;5:4.
20. Gaist D, Sorensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull*. 1997;44:445–448.
21. Helweg-Larsen K. The Danish register of causes of death. *Scand J Public Health*. 2011;39:26–29.
22. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health*. 2011;39:95–98.
23. Nakano A, Johnsen SP, Frederiksen BL, Svendsen ML, Agger C, Schjodt I, Egstrup K. Trends in quality of care among patients with incident heart failure in Denmark 2003–2010: a nationwide cohort study. *BMC Health Serv Res*. 2013;13:391.
24. Dong JY, Zhang YH, Tong J, Qin LQ. Depression and risk of stroke: a meta-analysis of prospective studies. *Stroke*. 2012;43:32–37.
25. Meng L, Chen D, Yang Y, Zheng Y, Hui R. Depression increases the risk of hypertension incidence: a meta-analysis of prospective cohort studies. *J Hypertens*. 2012;30:842–851.
26. Rugulies R. Depression as a predictor for coronary heart disease. A review and meta-analysis. *Am J Prev Med*. 2002;23:51–61.
27. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30:377–399.
28. Vreeburg SA, Hoogendijk WJ, van Pelt J, Derijk RH, Verhagen JC, van Dyck R, Smit JH, Zitman FG, Penninx BW. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Arch Gen Psychiatry*. 2009;66:617–626.
29. Whitworth JA, Williamson PM, Mangos G, Kelly JJ. Cardiovascular consequences of cortisol excess. *Vasc Health Risk Manag*. 2005;1:291–299.
30. Inglis SC, Hermis A, Shehab S, Newton PJ, Lal S, Davidson PM. Peripheral arterial disease and chronic heart failure: a dangerous mix. *Heart Fail Rev*. 2013;18:457–464.
31. Sridharan L, Klein L. Prognostic factors in patients hospitalized for heart failure. *Curr Heart Fail Rep*. 2013;10:380–386.

Mortality Risk among Heart Failure Patients with Depression: A Nationwide Population-Based Cohort Study

SUPPLEMENTAL MATERIAL

Table S1. *International Classification of Diseases* codes and Anatomical Therapeutic Classification codes used in the study.

	ICD-8	ICD-10	ATC codes
Heart failure	42709, 42710, 42711, 42719, 42899, 78249	I110, I130, I132, I420, I426, I427, I428, I429, I500, I501, I502, I503, I508, I509	N/A
Depression	29609, 29629, 29809, 30049	F32-F33	N/A
Mild depression	N/A	F320, F3200, F3201, F330, F3300, F3301	N/A
Moderate depression	N/A	F321, F3210, F3211, F331, F3310, F3311	N/A
Severe depression	N/A	F322, F323, F3230, F3231, F332, F333, F3330, F3331	N/A
Cardiac comorbidity			
Myocardial infarction	410	I21	N/A
Heart valve disease	394-397	I05-I08, I098, I34-I37	N/A
Myocarditis	422, 39129	I40-I41, I090, I514	N/A
Hypertension	400-404	I10-I15	N/A
Angina pectoris	411, 413	I20, I251, I259	N/A
Atrial fibrillation/atrial flutter	42793, 42794	I48	N/A
Cardiomyopathy	425	I42-I43	N/A
Non-cardiac comorbidities			
Stroke	430-434	I60-I61, I63-I64	N/A
Cancer	140-209	C00-C96	N/A
Obesity	277	E65-E66	N/A
Diabetes	24900-24909 (excluding 24902), 25000-25009 (excluding 25002)	E10 (excluding E102), E11 (excluding E112), E14 (excluding E142)	N/A
Chronic pulmonary disease	490-493, 515-518	J40-J47, J60-J67, J684, J701, J703, J841, J920, J961, J982-J983	N/A
Chronic kidney disease	24902, 25002, 75310-75319, 582-584, 59009, 59320, 792	E102, E112, E142, N03, N05, N110, N14, N16, N18-N19, N269, Q611-Q614	N/A
Peptic ulcer	53091, 53098, 531-534	K221, K25-K28	N/A
Illicit drug/alcohol/smoking abuse*	303-304	F10-F19	N/A
Dementia*	29009-29019, 29309	F00-F03, G30	N/A
Anaemia	280-281, 283-285	D50-55, D59, D61-D64	N/A
Peripheral arterial disease	44389-44399	I739	N/A
Comedication prescription <90 days			
Antidepressants	N/A	N/A	N06A
SSRIs	N/A	N/A	N06AB
TCAs	N/A	N/A	N06AA
Anxiolytics/hypnotics	N/A	N/A	N05B, N05C
Antipsychotics	N/A	N/A	N05A
Statins	N/A	N/A	C10AA, C10B
Low-dose aspirin	N/A	N/A	B01AC06, N02BA01
ACEI/ARBs	N/A	N/A	C09A, C09B, C09C, C09D
Betablockers	N/A	N/A	C07

Diuretics	N/A	N/A	C03
NSAIDs	N/A	N/A	M01A
Causes of death			
Cardiovascular mortality	N/A	I00-I99	N/A
Venous thromboembolism	N/A	I26, I80	N/A
Myocardial infarction	N/A	I21-I23	N/A
Stroke	N/A	I61, I63-I64	N/A
Heart failure	N/A	I50, I110, I130, I132	N/A
Arrhytmia	N/A	I44-I49	N/A
Non-cardiovascular mortality	N/A	All other codes than I00-I99	N/A

Abbreviations: SSRIs, Selective serotonin inhibitors; TCAs: Tricyclic antidepressants; ACEI/ARBs: Angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers; NSAIDs, Nonsteroidal anti-inflammatory drugs
*Data from the Danish National Patient Registry and the Danish Psychiatric Central Research Register.

Table S2. Descriptive data for patients with and without depression combining diagnoses and use of antidepressants.

	No depression			Depression		
	No use of antidepressants	**Former use of antidepressants**	**Current use of antidepressants**	**No use of antidepressants**	**Former use of antidepressants**	**Current use of antidepressants**
Median age (25th-75th percentiles)	77 (68-84)	77 (67-84)	79 (70-85)	75 (66-81)	74 (64-83)	78 (69-85)
Women	67,806 (43)	8954 (54)	12,911 (58)	1057 (55)	1166 (58)	3816 (67)
Time period						
1995-1999	43,912 (28)	1,820 (11)	3,766 (17)	649 (34)	239 (12)	913 (16)
2000-2004	48,178 (31)	4,606 (28)	7,058 (32)	603 (32)	551 (27)	1,696 (30)
2005-2009	37,111 (24)	5,181 (31)	6,504 (29)	427 (22)	626 (31)	1,739 (30)
2010-2014	26,967 (17)	4,850 (30)	4,934 (22)	233 (12)	591 (30)	1,369 (24)
Comorbidity						
Myocardial infarction	31,945 (21)	3524 (21)	4292 (19)	387 (20)	411 (21)	972 (17)
Hypertension	37,061 (24)	5869 (36)	7373 (33)	474 (25)	679 (34)	1947 (34)
Atrial fibrillation/atrial flutter	29,868 (19)	3623 (22)	4684 (21)	283 (15)	396 (20)	1055 (19)
Stroke	14,787 (9)	2681 (16)	4500 (20)	238 (12)	322 (16)	957 (16)
Cancer	24,083 (16)	3015 (18)	4100 (18)	275 (14)	366 (18)	1050 (18)
Obesity	7675 (5)	1383 (9)	1670 (8)	157 (8)	213 (11)	467 (8)
Diabetes	20,052 (13)	2883 (18)	3789 (17)	278 (15)	361 (18)	870 (15)
Chronic pulmonary disease	24,696 (16)	3845 (23)	5274 (24)	429 (22)	500 (25)	1440 (25)
Chronic kidney disease	7018 (4)	1094 (7)	1319 (6)	116 (6)	140 (7)	326 (6)
Peptic ulcer	12,868 (8)	1980 (12)	2903 (13)	271 (14)	306 (15)	827 (14)
Illicit drug/alcohol abuse	6147 (4)	1723 (11)	2119 (10)	509 (27)	570 (28)	1279 (22)
Dementia	3383 (2)	888 (5)	2212 (10)	136 (7)	244 (12)	839 (15)
Anaemia	12,437 (8)	1982 (12)	2926 (13)	190 (10)	287 (14)	860 (15)
Peripheral arterial disease	4267 (3)	862 (5)	948 (4)	59 (3)	94 (5)	216 (4)
Comedication < 90 days						
Antidepressants	1977 (1)	0 (0)	22,262 (100)	97 (5)	0 (0)	5717 (100)
SSRIs	1325 (0.9)	0 (0)	15,033 (68)	72 (4)	0 (0)	3244 (57)
TCAs	253 (0.2)	0 (0)	3880 (17)	6 (0.3)	0 (0)	1098 (19)
Anxiolytics/hypnotics	33,771 (22)	6281 (38)	10,018 (45)	705 (37)	887 (44)	3201 (56)

Antipsychotics	4599 (3)	1072 (7)	2567 (12)	338 (18)	347 (17)	1554 (27)
Statins	22,634 (14)	3362 (20)	4168 (19)	217 (11)	347 (17)	1014 (18)
Low-dose aspirin	46,153 (30)	5602 (34)	8459 (38)	536 (28)	620 (31)	2035 (36)
ACEI/ARBs	43,925 (28)	5167 (31)	6490 (29)	443 (23)	531 (26)	1492 (26)
Betablockers	36,578 (23)	4403 (27)	5414 (24)	361 (19)	477 (24)	1283 (23)
Diuretics	78,477 (50)	8401 (51)	13,252 (60)	914 (48)	888 (44)	3341 (58)
NSAIDs	23,122 (15)	2744 (17)	4134 (19)	296 (15)	308 (15)	982 (17)
Income						
Low	35,301 (23)	2345 (14)	3994 (18)	493 (26)	270 (13)	891 (16)
Intermediate	41,426 (27)	4209 (26)	6396 (29)	614 (32)	530 (26)	1588 (28)
High	38,271 (25)	5266 (32)	6767 (30)	497 (26)	689 (34)	1896 (33)
Very high	41,170 (26)	4637 (28)	5105 (23)	308 (16)	518 (26)	1342 (24)
Employment						
Employed	22,497 (14)	1601 (10)	1520 (7)	134 (7)	142 (7)	281 (5)
Early retirement, receiving sickness/incapacity/early retirement	2197 (1)	238 (1)	214 (1)	24 (1)	40 (2)	81 (1)
Unemployed	15,154 (10)	2426 (15)	2583 (12)	336 (18)	447 (22)	809 (14)
State pensioner	116,320 (75)	12,192 (74)	17,945 (81)	1418 (74)	1378 (69)	4546 (80)
Education						
Basic education, primary school	57,997 (37)	6916 (42)	9260 (42)	899 (47)	878 (44)	2511 (44)
Youth education, high school or similar	34,551 (22)	4042 (25)	4552 (21)	396 (21)	511 (25)	1138 (20)
Higher education	11,989 (8)	1548 (9)	1662 (7)	113 (6)	210 (11)	504 (9)
Missing	51,631 (33)	3951 (24)	6788 (30)	504 (26)	408 (20)	1564 (27)

Data are numbers (%).

Abbreviations: SSRIs, Selective serotonin inhibitors; TCAs, Tricyclic antidepressants; ACEI/ARBs: Angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers; NSAIDs, Nonsteroidal anti-inflammatory drugs

Table S3. Characteristics of heart failure patients with and without depression registered in the Danish Heart Failure Registry (1 January 2003–1 February 2014).

	No depression	Depression
Number of patients	28,602 (96)	1252 (4)
Left Ventricular Ejection Fraction		
>49%	1842 (6)	93 (7)
36%-49%	5509 (19)	270 (22)
<36%	17,948 (63)	714 (57)
Missing	3303 (12)	175 (14)
New York Heart Association (NYHA) classification		
NYHA Class I	2359 (8)	63 (5)
NYHA Class II	10,838 (38)	425 (34)
NYHA Class III	5798 (20)	299 (24)
NYHA Class IV	649 (2)	28 (2)
Missing	8958 (31)	437 (35)
Alcohol intake		
Maximum 14 drinks for women and 21 for men per week	20,491 (72)	827 (66)
More than 14 drinks for women and 21 for men per week	2075 (7)	125 (10)
Missing	6036 (21)	300 (24)
Smoking habits		
Smoker	7987 (28)	448 (36)
Former smoker	9741 (34)	376 (30)
Never smoker	6448 (23)	230 (18)
Missing	4426 (15)	198 (16)

Data are numbers (%).

Table S4. Sensitivity analyses: Mortality rate ratios comparing heart failure patients with and without depression. The number of patients with depression is reported in parentheses.

	Crude mortality rate ratio (95% confidence intervals)	Adjusted mortality rate ratio* (95% confidence intervals)
Registry with first diagnosis of depression		
National Patient Registry (n=2325)	1.28 (1.23-1.34)	1.01 (0.97-1.06)
Psychiatric Central Research Register (n=7311)	1.10 (1.07-1.13)	1.04 (1.01-1.06)
Years since first depression diagnosis		
Within 1 year (n=1253)	1.26 (1.19-1.34)	1.05 (0.99-1.12)
Within 2 years (n=1991)	1.23 (1.17-1.29)	1.05 (1.00-1.10)
Within 3 years (n=2578)	1.23 (1.18-1.29)	1.05 (1.00-1.10)
Danish Heart Failure Registry cohort		
Depression *vs.* no depression (n=1252)	1.24 (1.15-1.35)	1.07 (0.99-1.16)
+ adjustment for smoking† (n=1054)	1.24 (1.14-1.35)	1.07 (0.97-1.17)‡
+ adjustment for alcohol† (n=952)	1.20 (1.09-1.31)	1.06 (0.96-1.16)‡
Additional adjustments*		
+ education† (n=7160)	1.25 (1.22-1.29)	1.04 (1.01-1.07)
+ anxiolytics/hypnotics (n=9636)	1.14 (1.12-1.17)	1.00 (0.98-1.03)
+ antipsychotics (n=9636)	1.14 (1.12-1.17)	0.99 (0.96-1.01)
No adjustment for myocardial infarction, stroke, hypertension, and diabetes (n=9636)	1.14 (1.12-1.17)	1.04 (1.01-1.06)
Excluding patients with illicit drug/alcohol/smoking abuse or dementia		
Depression *vs.* no depression (n=6,331)	1.12 (1.09-1.16)	1.08 (1.05-1.11)

*Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anaemia, peripheral arterial disease, gross income, and employment.

†Analyses restricted to patients with complete data on all variables.

‡Using multiple imputation, the adjusted mortality rate ratio, including adjustment for smoking, was 1.09 (95% confidence interval: 1.00-1.18) and the adjusted mortality rate ratio, including adjustment for alcohol, was 1.09 (95% confidence interval: 1.01-1.18)

Table S5. Mortality rate ratios in heart failure patients according to depression diagnosis and use of antidepressants before the index date, by time periods.

Diagnosis	Use of antidepressants	Crude mortality rate ratio (95% confidence intervals)	Adjusted mortality ratio (95% confidence intervals)*
1995-1999			
No depression	-	Reference	Reference
Depression	-	1.13 (1.08-1.19)	1.07 (1.02-1.13)
	No use	Reference	Reference
No depression	Former use	1.17 (1.11-1.22)	1.09 (1.04-1.14)
	Current use	1.28 (1.24-1.33)	1.20 (1.16-1.24)
	No use	1.14 (1.05-1.23)	1.07 (0.99-1.16)
Depression	Former use	1.33 (1.17-1.52)	1.27 (1.11-1.44)
	Current use	1.14 (1.06-1.22)	1.06 (0-99-1.14)
2000-2004			
No depression	-	Reference	Reference
Depression	-	1.12 (1.08-1.17)	0.99 (0.95-1.03)
	No use	Reference	Reference
No depression	Former use	1.18 (1.14-1.22)	1.09 (1.06-1.13)
	Current use	1.37 (1.34-1.41)	1.18 (1.15-1.22)
	No use	1.00 (0.91-1.09)	0.96 (0.88-1.05)
Depression	Former use	1.13 (1.03-1.24)	0.94 (0.86-1.03)
	Current use	1.27 (1.21-1.34)	1.06 (1.01-1.12)
2005-2009			
No depression	-	Reference	Reference
Depression	-	1.19 (1.14-1.25)	1.02 (0.97-1.07)
	No use	Reference	Reference
No depression	Former use	1.14 (1.10-1.18)	1.05 (1.02-1.09)
	Current use	1.50 (1.45-1.54)	1.22 (1.18-1.26)
	No use	1.02 (0.90-1.14)	0.92 (0.82-1.04)
Depression	Former use	1.09 (0.99-1.20)	0.93 (0.85-1.03)
	Current use	1.43 (1.36-1.51)	1.11 (1.05-1.18)
2010-2014			
No depression	-	Reference	Reference
Depression	-	1.26 (1.19-1.34)	1.07 (1.00-1.14)
No depression	No use	Reference	Reference
	Former use	1.07 (1.02-1.12)	1.02 (0.97-1.07)
	Current use	1.52 (1.46-1.59)	1.22 (1.17-1.28)
Depression	No use	1.12 (0.92-1.36)	1.03 (0.85-1.26)
	Former use	1.06 (0.93-1.20)	1.02 (0.89-1.16)
	Current use	1.54 (1.43-1.66)	1.14 (1.06-1.24)

*Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anaemia, peripheral arterial disease, gross income, and employment.

Figure S1. Kaplan-Meier survival curve for heart failure patients with and without depression.

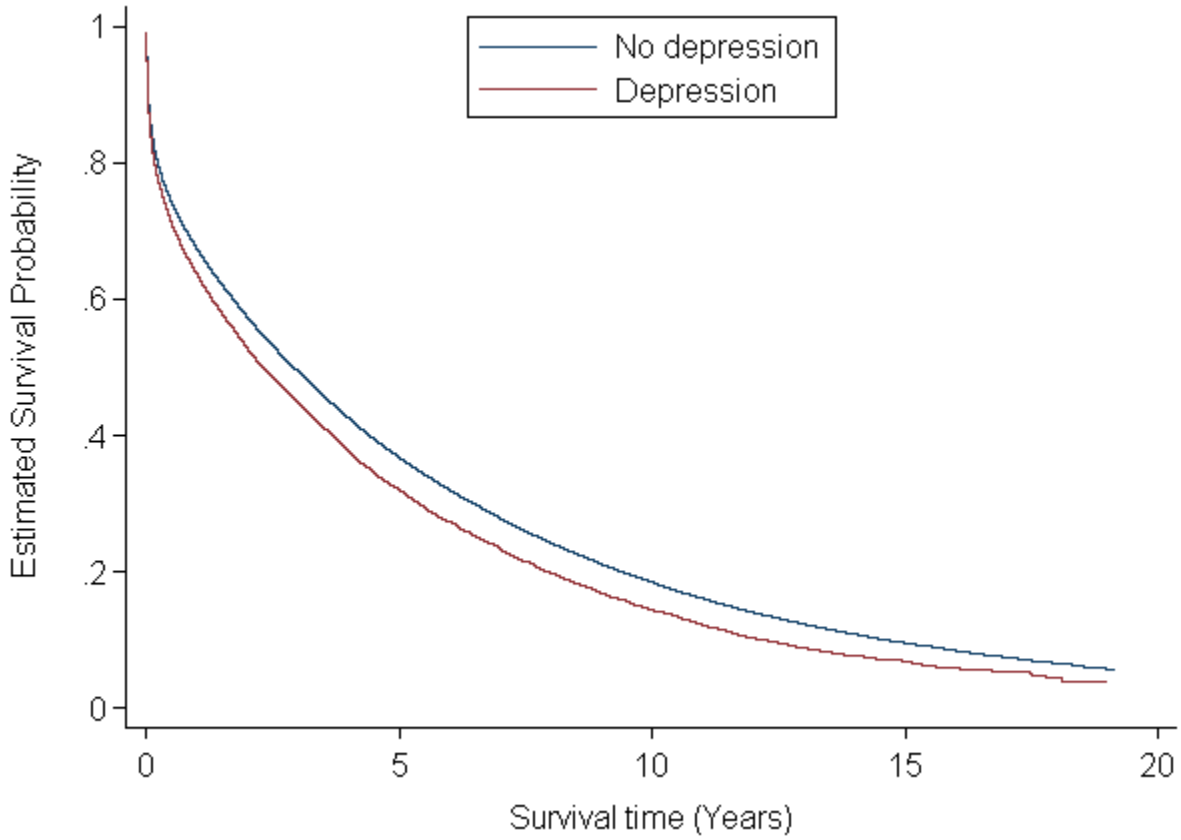
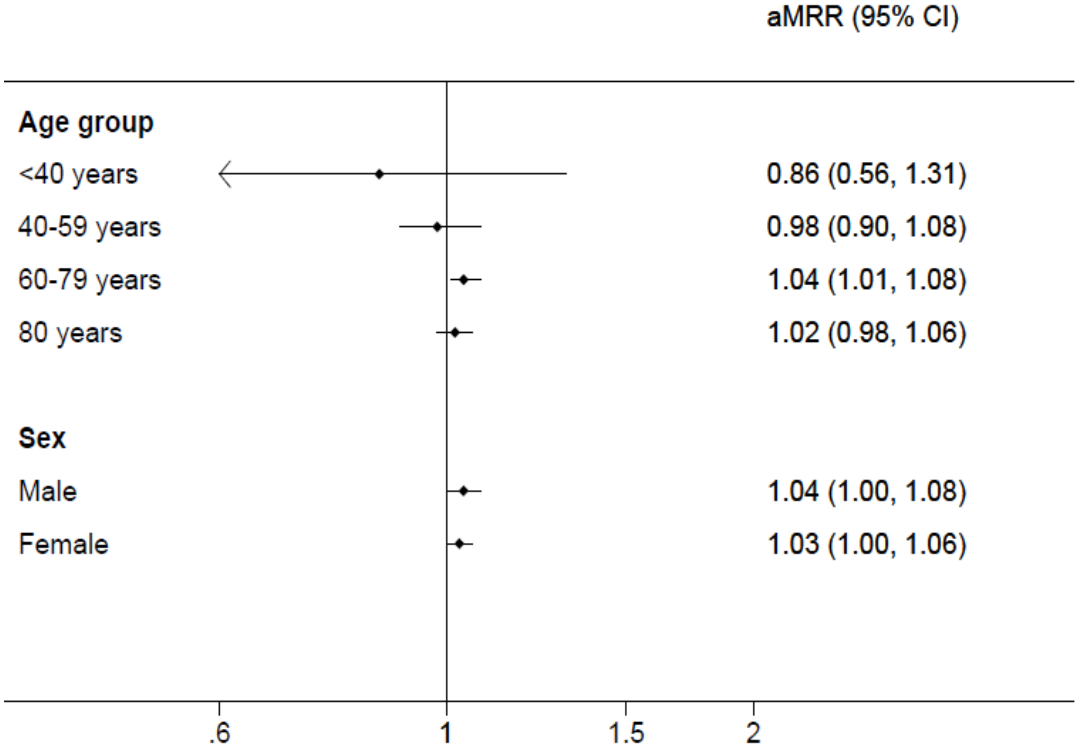
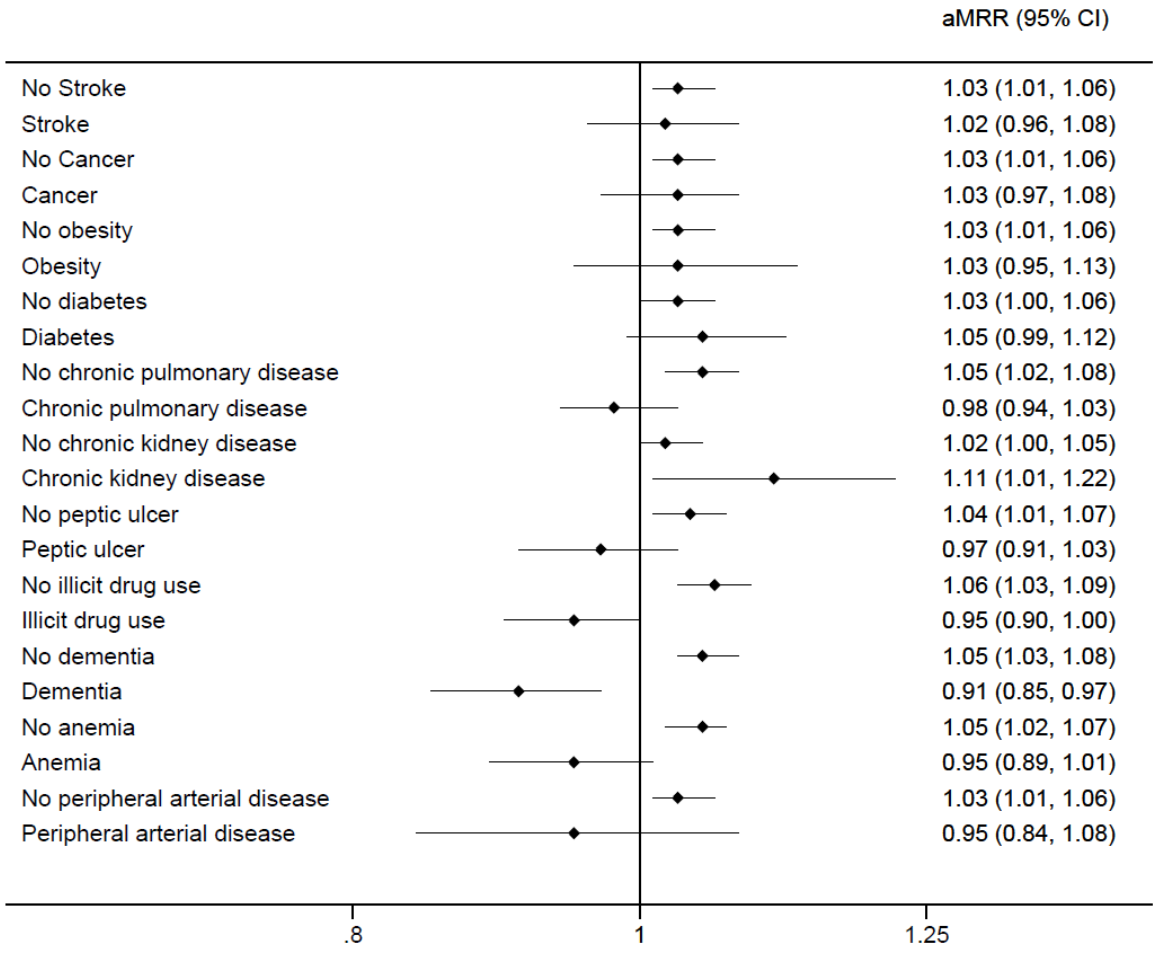


Figure S2. Adjusted mortality rate ratios with 95% confidence intervals by age and sex comparing heart failure patients with and without depression.



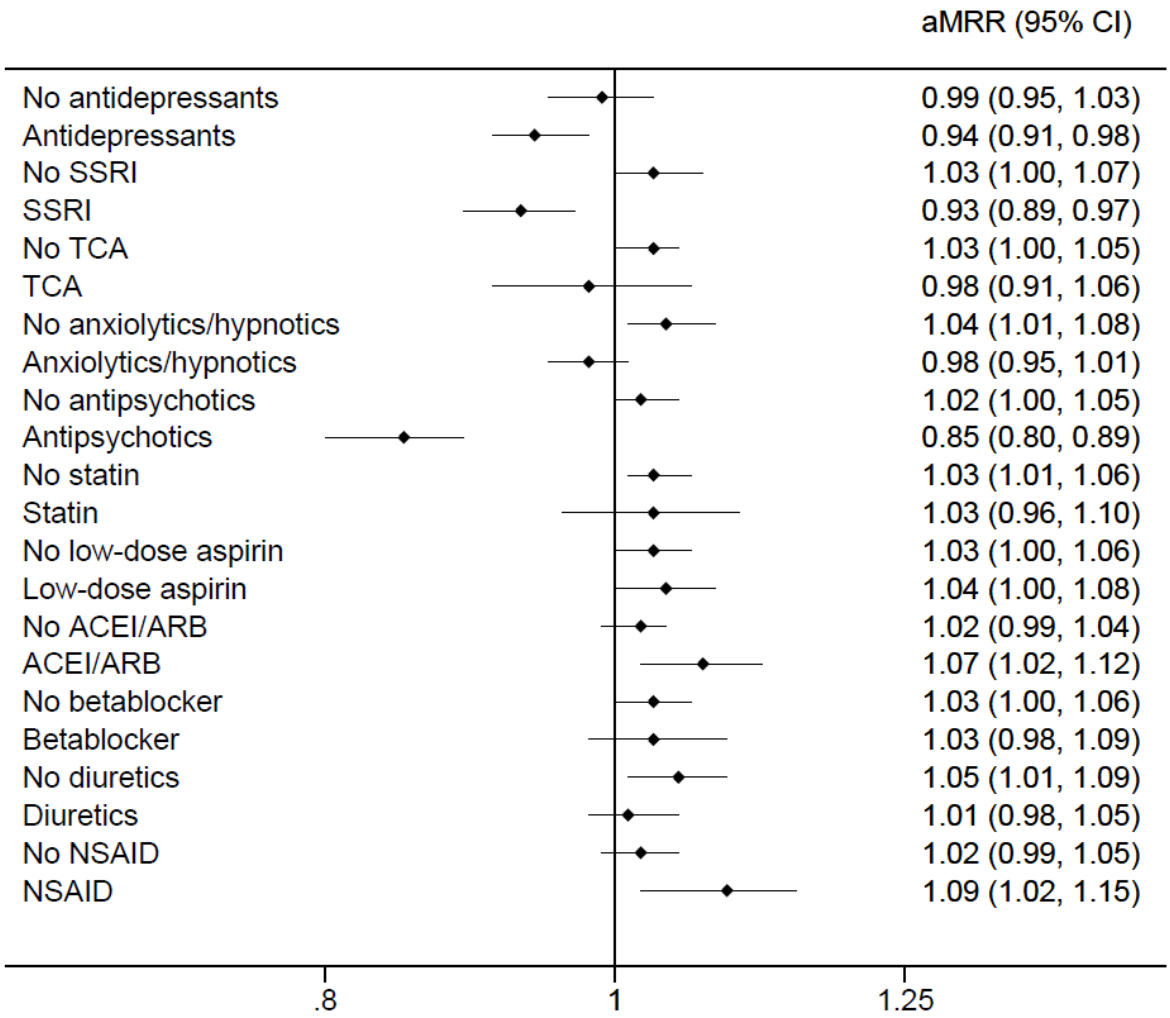
Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anaemia, peripheral arterial disease, gross income, and employment.
Abbreviations: aMRR, adjusted mortality rate ratio; CI, confidence interval

Figure S3. Comorbidity-stratified adjusted mortality rate ratios comparing heart failure patients with and without depression.



Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anaemia, peripheral arterial disease, gross income, and employment (except for the stratifying variable).
Abbreviations: aMRR, adjusted mortality rate ratio; CI, confidence interval

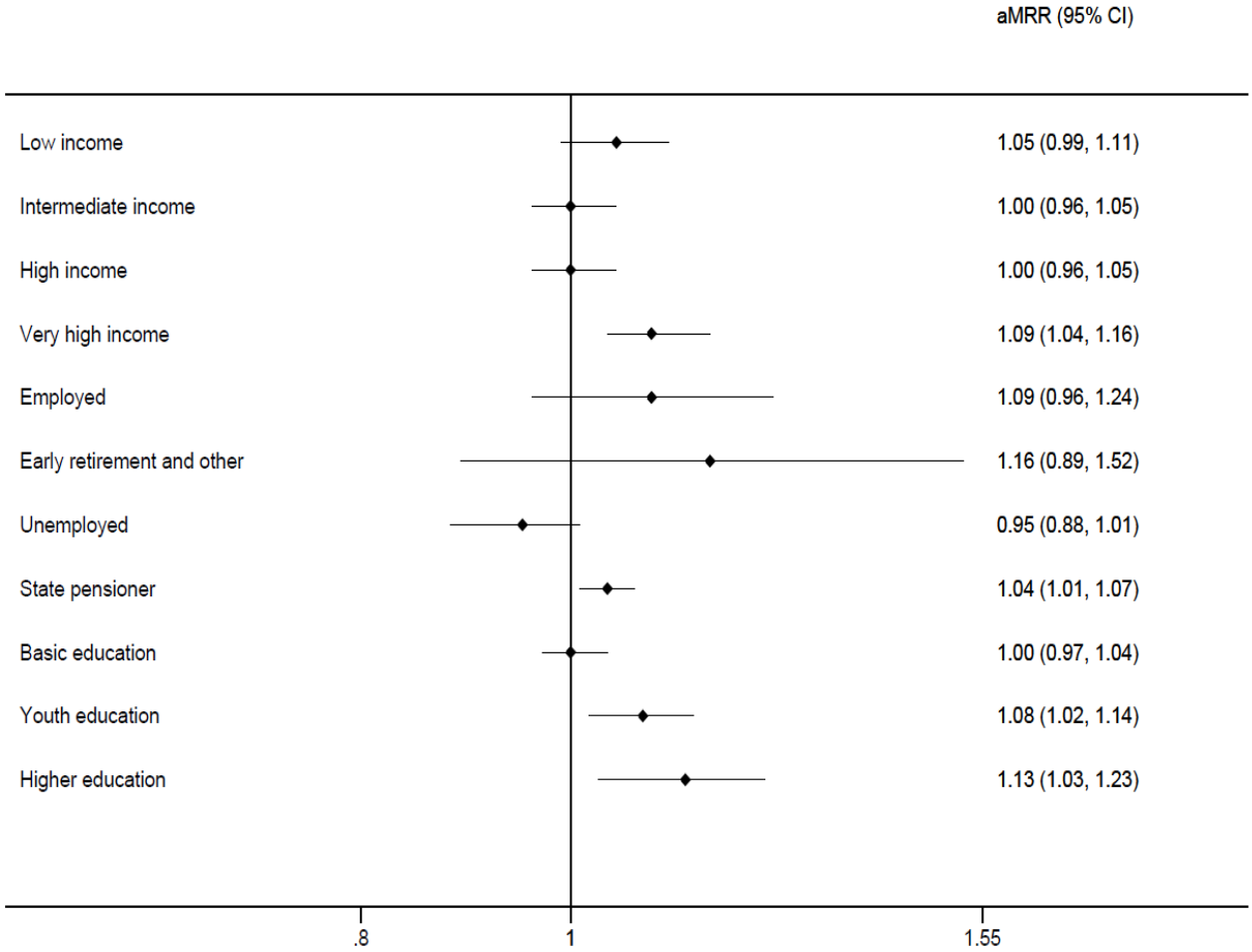
Figure S4. Adjusted mortality rate ratios comparing heart failure patients with and without depression according to use of comedications within 90 days prior to the index date.



Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anaemia, peripheral arterial disease, gross income, and employment.

Abbreviations: aMRR, adjusted mortality rate ratio; CI, confidence interval; SSRIs, Selective serotonin inhibitors; TCAs, Tricyclic antidepressants; ACEI/ARB, Angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers; NSAIDs, Nonsteroidal anti-inflammatory drugs

Figure S5. Adjusted mortality rate ratios comparing heart failure patients with and without depression according to socioeconomic status.



Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anaemia, peripheral arterial disease, gross income, and employment (except for the stratifying variable).
Abbreviations: aMRR, adjusted mortality rate ratio; CI, confidence interval

Mortality Risk Among Heart Failure Patients With Depression: A Nationwide Population–Based Cohort Study

Kasper Adelborg, Morten Schmidt, Jens Sundbøll, Lars Pedersen, Poul Videbech, Hans Erik Bøtker, Kenneth Egstrup and Henrik Toft Sørensen

J Am Heart Assoc. 2016;5:e004137; originally published September 7, 2016;
doi: 10.1161/JAHA.116.004137
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

Study IV

European Journal of Heart Failure (2017) **19**, 253–260
doi:10.1002/ejhf.631

RESEARCH ARTICLE

Heart failure and risk of dementia: a Danish nationwide population-based cohort study

Kasper Adelborg[1]*, Erzsébet Horváth-Puhó[1], Anne Ording[1], Lars Pedersen[1], Henrik Toft Sørensen[1,2], and Victor W. Henderson[1,2]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Skejby, Aarhus, Denmark; and [2]Departments of Health Research and Policy (Epidemiology) and of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA

Received 25 April 2016; revised 4 July 2016; accepted 11 July 2016; online publish-ahead-of-print 9 September 2016

Aims The association between heart failure and dementia remains unclear. We assessed the risk of dementia among patients with heart failure and members of a general population comparison cohort.

Methods and results Individual-level data from Danish medical registries were linked in this nationwide population-based cohort study comparing patients with a first-time hospitalization for heart failure between 1980 and 2012 and a year of birth-, sex-, and calendar year-matched comparison cohort from the general population. Stratified Cox regression analysis was used to compute 1–35-year hazard ratios (HRs) for the risk of all-cause dementia and, secondarily, Alzheimer's disease, vascular dementia, and other dementias. Analyses included 324 418 heart failure patients and 1 622 079 individuals from the general population (median age 77 years, 52% male). Compared with the general population cohort, risk of all-cause dementia was increased among heart failure patients [adjusted HR 1.21, 95% confidence interval (CI) 1.18–1.24]. The associations were stronger in men and in heart failure patients under age 70. Heart failure patients had higher risks of vascular dementia (adjusted HR 1.49, 95% CI 1.40–1.59) and other dementias (adjusted HR 1.30, 95% CI 1.26–1.34) than members of the general population cohort. Heart failure was not associated with Alzheimer's disease (adjusted HR 1.00, 95% CI 0.96–1.04).

Conclusion Heart failure was associated with an increased risk of all-cause dementia. Heart failure may represent a risk factor for dementia, but not necessarily for Alzheimer's disease.

Keywords Heart failure • Dementia • Morbidity • Epidemiology

Introduction

Dementia is one of the most burdensome health conditions in western countries.[1–3] The prevalence of dementia is increasing globally, with 4.6 million incident cases every year.[2] The societal and financial burdens are enormous. Identifying modifiable risk factors to prevent or delay dementia onset thus could have a major public health impact.[2,4]

While dementia and heart failure often co-exist, the relationship between these two common conditions is unclear.[5,6] A population-based Swedish cohort study found a 1.8-fold higher risk of dementia and Alzheimer's disease in heart failure patients aged 75 years and older compared with patients without heart failure.[7] In another small cohort study, late-life heart failure was associated with a doubled risk of dementia and Alzheimer's disease.[8] Putative mechanisms are unknown, but low cardiac output and neurohormonal effects of heart failure may lead to chronic cerebral hypoxia and potentially contribute directly to dementia pathogenesis[9] or may lower the threshold for the emergence of dementia symptoms in the presence of specific dementia pathologies.[10]

To examine potential associations between heart failure and dementia and to examine factors that might mediate this association, we used nationwide population registries to assess the risk of dementia in heart failure patients and in a matched general population comparison cohort.

*Corresponding author. Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43–45, DK-8200 Aarhus N, Denmark. Tel: +45 8716 8514, Fax: +45 8716 7215, Email: kade@clin.au.dk

Methods

This nationwide cohort study was conducted between 1 January 1980 and 1 September 2012 within a cumulative population of 8 262 736 Danish residents.[11] In Denmark all residents are assigned a unique personal identifier, which allows linkage of individual-level data across healthcare registries.[11]

Heart failure

We identified a cohort of patients with a first-time inpatient hospitalization for heart failure recorded in the Danish National Patient Registry (DNPR).[12] This registry has coded hospital admissions and outpatient clinic visits according to the International Classification of Diseases since 1977 [Eighth Revision (ICD-8) until 1994 and Tenth Revision (ICD-10) starting in 1994].[12] Each hospital contact is registered in the DNPR with one main diagnosis (primary) and appropriate secondary diagnoses. We used both primary and secondary diagnoses to identify heart failure patients. The positive predictive value of the heart failure diagnosis in the DNPR is between 81% and 100%.[12]

General population comparison cohort

We used the Danish Civil Registration System to construct a comparison cohort, consisting of up to five individuals randomly sampled from the general population for each heart failure patient, matched with replacement on year of birth, sex, and calendar year of heart failure diagnosis.[11] The Danish Civil Registration System has provided daily updates on vital statistics, including dates of birth, emigration, and death since 1968.[11] Heart failure patients and persons in the matched comparison cohort who were diagnosed with dementia before the index date were excluded. The index date was the date of heart failure diagnosis and the corresponding matching date for members of the general population cohort. If members of the general population cohort were diagnosed with heart failure after the index date, they were transferred to the heart failure group and new corresponding comparison cohort members were selected from the general population.

Incident dementia

The primary outcome was incident all-cause dementia diagnosed in hospital inpatient and outpatient settings. Secondary outcomes were dementia subtypes classified as Alzheimer's disease, vascular dementia, and other dementias (i.e. any specific or unspecified dementia other than Alzheimer's disease and vascular dementia). Information on dementia diagnoses was obtained from the DNPR and the Danish Central Psychiatric Registry.[12] In the DNPR, dementia diagnoses are available for hospital admissions since 1977 and for hospital-based outpatient clinics since 1995.[12] In the Danish Central Psychiatric Registry, dementia has been registered in the psychiatric hospital system since 1969.[13] The positive predictive value of all-cause dementia diagnosis in the two registries is 86% and that of Alzheimer's disease is 81%. Positive predictive values for other dementia subtypes are lower, and the diagnostic sensitivity is unknown.[14]

Covariates

We collected information on the following co-morbidities to include as covariates in our analyses: myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolaemia, hypertension, stroke, obesity, diabetes mellitus, chronic obstructive pulmonary disease (as an indicator of smoking exposure), myxoedema, alcoholism-related diseases, head trauma, osteoarthritis (as an indicator for use of non-steroidal anti-inflammatory drugs), anaemia, chronic kidney disease, and a modified Charlson Comorbidity Index (CCI) score (excluding congestive heart failure, myocardial infarction, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, diabetes, and chronic kidney disease) diagnosed up to the index date. Data on the above diagnoses (including all available primary and secondary diagnoses other than emergency room diagnoses) were retrieved from the DNPR from 1977 until the index date. ICD codes used in the study are provided in the Supplementary material online, *Tables S1* and *S2*.

Statistical analyses

All heart failure patients and members of the general population comparison cohort were followed from their index date until the date of an inpatient or outpatient hospital contact for any dementia diagnosis, emigration, death, or 1 September 2014, whichever came first. Descriptive data on sex, age groups (<60 years, 60–69 years, 70–79 years, and ≥80 years), index year calendar periods (1980–1989, 1990–1999, and 2000–2012), and co-morbidities are presented in *Table 1*. We excluded the first year of follow-up, since dementia diagnosed in this period is unlikely to be a consequence of heart failure. Using the cumulative incidence (risk) function accounting for death as a competing risk, we calculated dementia risks during 1–35 years, 1–10 years, 11–20 years, and 21–35 years of follow-up. We calculated standardized incidence ratios as the observed number of dementia cases among heart failure patients divided by the number expected if heart failure patients had the same dementia risk as the general population of Denmark. The expected number of dementia cases was calculated using national incidence rates for first-time dementia diagnoses, according to sex, age, and calendar 1-year intervals. The 95% confidence intervals (CIs) for the standardized incidence ratio estimates were computed assuming a Poisson distribution of the observed numbers of dementia cases in the different time periods.

Hazard ratios (HRs) and corresponding 95% CIs were computed with multivariable stratified Cox hazards regression models, comparing heart failure patients with members of the general population comparison cohort.[15] In the multivariable analyses, we controlled for age, sex, and calendar year by the matched study design and adjusted for co-morbidities in *Table 1* and the modified CCI score. We considered any potential interactions in stratified models, which we used to examine the risk of dementia by sex, age groups, and the following factors associated with heart failure: previous myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, myocarditis, hypertension, and cardiomyopathy. We also examined the risk of dementia in subgroups of heart failure patients with hypercholesterolaemia, stroke, obesity, diabetes mellitus, chronic obstructive pulmonary disease, myxoedema, alcoholism-related diseases, head trauma, osteoarthritis, anaemia, chronic kidney disease, and different CCI levels as potential underlying conditions that might modify associations between heart failure and dementia. We assessed the possibility of cohort effects due to lack of outpatient clinic records before 1995 and increasing dementia awareness by healthcare professionals, by stratifying analyses in two index periods (1980–1994 and 1995–2012). For this analysis, we restricted follow-up to 10 years, to ensure homogeneous follow-up between the index periods. We

Table 1 Characteristics of patients hospitalized with a first-time diagnosis of heart failure during 1980–2012 and members of the general population comparison cohort

	Heart failure cohort ($n = 324\,418$)	Comparison cohort ($n = 1\,622\,079$)
Male gender	168 564 (52)	842 810 (52)
Age, years		
<60	31 848 (10)	159 ,659 (10)
60–69	57 446 (18)	287 942 (18)
70–79	109 496 (34)	546 989 (34)
≥80	125 628 (39)	627 489 (39)
Median (interquartile range)	77 (69–84)	77 (69–84)
Decade of diagnosis		
1980 – 1989	96 020 (30)	480 096 (30)
1990 – 1999	109 866 (34)	549 327 (34)
2000 – 2012	118 532 (37)	592 656 (37)
Co-morbidities		
Myocardial infarction	51 802 (16)	69 041 (4)
Angina pectoris	53 484 (17)	89 915 (6)
Atrial fibrillation or flutter	39 005 (12)	61 464 (4)
Valvular heart disease	14 329 (4)	14 878 (0.9)
Hypercholesterolaemia	9 066 (3)	18 136 (1)
Hypertension	52 564 (16)	119 823 (7)
Stroke	20 625 (6)	57 244 (4)
Obesity	14 292 (4)	20 342 (1)
Diabetes mellitus	36 143 (11)	60 980 (4)
COPD	46 660 (14)	76 580 (5)
Myxoedema	4995 (2)	12 458 (0.8)
Alcoholism-related diseases	8480 (3)	16 852 (1)
Head trauma	43 632 (13)	183 321 (11)
Osteoartrhitis	38 387 (12)	146 389 (9)
Anaemia	19 575 (6)	42 714 (3)
Chronic kidney disease	10 095 (3)	12 900 (0.8)
Charlson Comorbidity Index[a]		
Normal	235 534 (73)	1 350 105 (83)
Moderate	45 406 (14)	118 649 (7)
Severe	31 105 (10)	123 189 (8)
Very severe	12 373 (4)	30 136 (2)

Values are given as *n* (%).
[a]Categories of co-morbidity were based on scores on the modified Charlson Comorbidity Index of 0 (normal), 1 (moderate), 2 (severe), and ≥3 (very severe).

assessed the proportionality of hazards graphically using log minus log plots, and found the assumption to be fulfilled in the analysed follow-up periods.

Sensitivity analyses

We performed three sensitivity analyses to assess the robustness of the study results. First, we redefined the cohort of heart failure patients to include patients diagnosed in outpatient as well as inpatient settings. Secondly, due to an assumed induction period in the development of dementia, we repeated the analyses sequentially excluding the initial 2, 3, 5, and 10 years of follow-up. Thirdly, we reclassified Alzheimer's disease to include the ICD code for unspecified dementia in the Alzheimer's disease definition.

All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). The study was approved by the Danish Data Protection Agency (record number: 1-16-02-268-14). No approval from an ethics committee or informed consent from patients is required for registry studies in Denmark.

Results

In total, 324 418 heart failure patients (median age, 77 years; male, 52%) and 1 622 079 individuals from the general population (median age, 77 years; male, 52%) were included in the analysis. Median follow-up time was 2 years (interquartile range 0.2–5.3 years) for patients with heart failure and 6.5 years (interquartile range 3.1–11.6 years) for members of the comparison cohort, due primarily to higher mortality in the heart failure cohort. Heart failure patients had a higher prevalence of co-morbidity than members of the general population cohort (*Table 1*).

Risk of dementia

During the 35-year follow-up period, 148 541 were diagnosed with dementia (51 412 with Alzheimer's disease, 18 624 with vascular dementia, and 78 505 with other dementias) (*Table 2*). Because of competing mortality, the absolute 1–35-year risk of all-cause dementia was substantially lower among heart failure patients (7.22%; 95% CI 7.08–7.36%) than among members of the general population comparison cohort (14.95%; 95% CI 14.84–15.06%) (*Table 2*). After adjustment for co-morbid diseases, the risk of all-cause dementia among heart failure patients was higher than that among the general population (1–35-year HR 1.21, 95% CI 1.18–1.24). There was no association with Alzheimer's disease (1–35-year HR 1.00, 95% CI 0.96–1.04), but the relative risks of vascular dementia (1–35-year HR 1.49, 95% CI 1.40–1.59) and other dementias (1–35-year HR 1.30, 95% CI 1.26–1.34) were higher in heart failure patients than in members of the general population (*Table 2*). The dementia incidence ratios standardized to the Danish population agreed with the unadjusted HRs (*Table 2*).

Age, sex, heart failure causes, and co-morbidity

Age-stratified analyses revealed that the magnitude of association between heart failure and all-cause dementia was higher in patients aged under 70 than in patients older than 70 (*Table 3*). The 1–35-year HRs were higher for men than women (*Table 3*). For men, the 1–35-year HR was 1.31 (95% CI 1.26–1.36), and for women it was 1.15 (95% CI 1.11–1.18). HRs for all-cause dementia were similar for heart failure patients with or without previous myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, and hypertension (*Table 4*). Results of analyses stratified by other co-morbidities are reported in the Supplementary material online, *Table S3*. The association between heart failure and all-cause dementia applied to patients in 1980–1994 as well as for patients in 1995–2012 (Supplementary material online, *Table S4*).

Table 2 Cumulative incidence risks and hazard ratios of dementia in heart failure patients and members of the general population comparison cohort

Years since diagnosis	Comparison cohort		Heart failure patients				
	Events/no. at risk	Cumulative incidence risk, % (95% CI)	Events /no. at risk	Cumulative incidence risk, % (95% CI)	Standardized incidence ratio (95% CI)	Hazard ratio controlled for matching factors[a] (95% CI)	Adjusted hazard ratio (95% CI)[b]
All-cause dementia							
1–10	92 228/1 492 102	7.18 (7.13–7.22)	9808/198 038	5.39 (5.29–5.49)	1.13 (1.10–1.15)	1.28 (1.25–1.31)	1.21 (1.18–1.24)
11–20	37 332/511 213	9.82 (9.72–9.92)	1534/29 655	6.96 (6.62–7.31)	1.13 (1.07–1.18)	1.26 (1.17–1.35)	1.19 (1.11–1.28)
21–35	7497/99 527	13.42 (13.00–13.86)	142/2906	7.60 (6.27–9.09)	1.20 (1.01–1.41)	1.47 (1.14–1.88)	1.38 (1.07–1.79)
1–35	137 057/1 492 102	14.95 (14.84–15.06)	11 484/198 038	7.22 (7.08–7.36)	1.13 (1.11–1.15)	1.28 (1.25–1.30)	1.21 (1.18–1.24)
Alzheimer's disease							
1–10	34 454/1 492 102	2.67 (2.65–2.70)	2921/198 038	1.59 (1.54–1.65)	0.90 (0.87–0.93)	1.02 (0.98–1.06)	1.02 (0.97–1.06)
11–20	11 170/511 213	2.95 (2.89–3.00)	356/29 655	1.62 (1.45–1.80)	0.82 (0.74–0.91)	0.79 (0.69–0.90)	0.80 (0.70–0.92)
21–35	2469/99 527	4.62 (4.37– 4.88)	42/2906	2.61 (1.74–3.75)	1.02 (0.74–1.38)	1.37 (0.88–2.12)	1.31 (0.83–2.07)
1–35	48 093/1 492 102	5.18 (5.11–5.25)	3319/198 038	2.07 (1.98–2.15)	0.89 (0.86–0.92)	1.00 (0.96–1.04)	1.00 (0.96–1.04)
Vascular dementia							
1–10	11 168/1 492 102	0.87 (0.86–0.89)	1546/198 038	0.85 (0.81–0.90)	1.43 (1.36–1.50)	1.66 (1.56–1.77)	1.47 (1.38–1.57)
11–20	4710/511 213	1.25 (1.22–1.29)	248/29 655	1.12 (0.98–1.27)	1.44 (1.26–1.63)	1.84 (1.54–2.20)	1.59 (1.32–1.93)
21–35	922/99 527	1.71 (1.56–1.87)	30/2906	1.53 (1.03–2.21)	2.04 (1.37–2.91)	2.64 (1.44–4.85)	2.29 (1.18–4.45)
1–35	16 800/1 492 102	1.90 (1.85–1.94)	1824/198 038	1.17 (1.11–1.23)	1.44 (1.37–1.50)	1.69 (1.59–1.79)	1.49 (1.40–1.59)
Other dementias							
1–10	46 606/1 492 102	3.67 (3.63–3.70)	5341/198 038	2.96 (2.88–3.03)	1.22 (1.19–1.25)	1.38 (1.33–1.43)	1.29 (1.25–1.34)
11–20	21 452/511 213	5.71 (5.63–5.79)	930/29 655	4.26 (3.99–4.54)	1.23 (1.15–1.31)	1.46 (1.33–1.60)	1.37 (1.24–1.51)
21–35	4106/99 527	7.37 (7.03–7.72)	70/2906	3.52 (2.71–4.49)	1.11 (0.87–1.41)	1.26 (0.89–1.79)	1.18 (0.82–1.70)
1–35	72 164/1 492 102	8.17 (8.08–8.26)	6341/198 038	4.03 (3.92–4.14)	1.22 (1.19–1.25)	1.39 (1.35–1.43)	1.30 (1.26–1.34)

CI, confidence interval.
[a] Age, sex, and calendar year.
[b] Controlled for matching factors by study design and adjusted for stroke, atrial fibrillation/atrial flutter, hypertension, hypercholesterolaemia, myocardial infarction, stable angina pectoris, valvular heart disease, diabetes, chronic obstructive pulmonary disease, obesity, myxoedema, alcoholism-related disease, head trauma, osteoarthritis, anaemia, chronic kidney disease, and a modified Charlson Comorbidity Index score.

Sensitivity analyses

Redefining the cohort to include both inpatient and outpatient diagnoses of heart failure did not change the overall results (Supplementary material online, *Table S5*). Excluding the first year of follow-up decreased the overall risk estimates of dementia, but HRs did not change by excluding more than the initial year of follow-up (Supplementary material online, *Table S6*). When ICD codes for unspecified dementia were reclassified as Alzheimer's disease, heart failure patients now had a higher risk of this diagnosis than members of the general population comparison cohort: 1–35-year adjusted HR of 1.16, 95% CI 1.14–1.20, with similar hazards for 1–10, 11–20, and 21–35 year categories (Supplementary material online, *Table S7*).

Discussion

In this nationwide cohort study, we found a clear association between heart failure and risk of all-cause dementia, driven by higher risks of vascular and other dementias, compared with members of the general population cohort over 35 years of follow-up. Dementia risk was increased for both men and women but was somewhat greater for men. Although causes and outcomes of heart failure can differ between men and women,[16] the basis of the sex difference in dementia risk is unclear. Heart failure was a less strong relative risk factor for dementia in elderly than in young patients.

Two small studies have evaluated the risk of dementia in heart failure patients.[7,8] A Finnish cohort study of 55 heart failure patients showed no association between midlife heart failure and dementia (25-year HR 0.84, 95% CI 0.33–2.13), but in 86 patients with late-life heart failure the risk of dementia was doubled (25-year HR 2.06, 95% CI, 1.00–4.27).[8] A Swedish population-based cohort study of 205 heart failure patients aged ≥75 years reported an adjusted 9-year HR of 1.84 (95% CI 1.35–2.51) for dementia.[7] In the Framingham Offspring Cohort Study, subjects with an impaired cardiac index ($n = 269$) had higher risks of all-cause dementia (adjusted HR 2.07, 95% CI 1.02–4.19) and Alzheimer's disease (adjusted HR 2.10, 95% CI 0.96–4.61) than patients with a normal cardiac index, after 7.7 years of follow-up.[17] Supporting a weak association between heart failure and dementia, the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study of 931 subjects showed an increased risk of mild cognitive impairment or dementia for each 10% decrease in LVEF (odds ratio 1.02, 95% CI 0.75–1.38), 10 mL decrease in LV stroke volume (odds ratio 1.24, 95% CI 0.99–1.57), and 1 L/min decrease in cardiac output (odds ratio 1.40, 95% CI 0.99–2.00).[18] Our results extend these findings within a large, nationwide cohort, indicating that heart failure is associated with ~20% elevated risk of all-cause dementia among patients surviving at least 1 year after their heart failure diagnosis.

Low cardiac output may directly reduce cerebral blood flow, contributing to cerebral hypoperfusion, impaired vascular autoregulation, and white matter injury. Moreover, neurohormonal

Table 3 Age- and sex-stratified analyses and cumulative incidence risks, %, and hazard ratio of dementia in heart failure patients and members of the general population comparison cohort

	1–10 years		11–35 years		1–35 years	
	Cumulative incidence risk, % (95% CI)	Adjusted hazard ratio (95% CI)[a]	Cumulative incidence risk, % (95% CI)	Adjusted hazard ratio (95% CI)[a]	Cumulative incidence risk, % (95% CI)	Adjusted hazard ratio (95% CI)[a]
All-cause dementia						
Male	4.60 (4.46–4.73)	1.31 (1.27–1.37)	7.69 (7.07–8.34)	1.26 (1.13–1.40)	6.29 (6.10–6.49)	1.31 (1.26–1.36)
Female	6.22 (6.07–6.39)	1.14 (1.11–1.18)	9.79 (9.07–10.54)	1.18 (1.07–1.29)	8.17 (7.95–8.38)	1.15 (1.11–1.18)
<60 years	1.05 (0.92–1.19)	2.50 (2.02–3.08)	4.90 (4.15–5.73)	1.56 (1.29–1.89)	3.77 (3.33–4.25)	1.93 (1.68–2.23)
60–69 years	3.03 (2.86–3.22)	1.71 (1.57–1.86)	10.77 (9.87–11.72)	1.31 (1.17–1.46)	6.52 (6.18–6.88)	1.56 (1.46–1.66)
70–79 years	6.25 (6.07–6.45)	1.24 (1.20–1.29)	10.88 (10.12–11.67)	1.06 (0.95–1.18)	8.13 (7.90–8.36)	1.22 (1.18–1.27)
≥80 years	7.51 (7.31–7.73)	1.06 (1.03–1.10)	6.33 (5.33–7.43)	0.80 (0.57–1.12)	7.85 (7.64–8.07)	1.06 (1.02–1.10)
Alzheimer's disease						
Male	1.32 (1.24–1.39)	1.13 (1.06–1.21)	1.82 (1.50–2.19)	0.80 (0.65–1.00)	1.72 (1.62–1.83)	1.09 (1.02–1.16)
Female	1.89 (1.80–1.98)	0.95 (0.90–1.01)	2.69 (2.20–3.24)	0.86 (0.73–1.02)	2.43 (2.29–2.57)	0.94 (0.89–0.99)
<60 years	0.13 (0.09–0.18)	2.73 (1.51–4.92)	1.40 (0.98–1.94)	1.07 (0.74–1.56)	0.90 (0.67–1.21)	1.35 (1.00–1.84)
60–69 years	0.76 (0.67–0.85)	1.22 (1.05–1.42)	2.78 (2.29–3.35)	0.98 (0.79–1.20)	1.66 (1.48–1.87)	1.14 (1.01–1.28)
70–79 years	2.05 (1.94–2.16)	1.05 (0.98–1.12)	2.68 (2.30–3.11)	0.69 (0.56–0.85)	2.52 (2.39–2.65)	1.01 (0.94–1.07)
≥80 years	2.17 (2.06–2.29)	0.94 (0.88–1.00)	0.86 (0.52–1.35)	0.35 (0.13–0.92)	2.22 (2.10–2.34)	0.93 (0.87–0.99)
Vascular dementia						
Male	0.83 (0.77–0.89)	1.47 (1.34–1.62)	1.47 (1.22–1.76)	1.70 (1.31–2.21)	1.16 (1.07–1.24)	1.50 (1.37–1.64)
Female	0.88 (0.82–0.94)	1.48 (1.35–1.62)	1.50 (1.23–1.81)	1.64 (1.28–2.11)	1.18 (1.10–1.27)	1.50 (1.38–1.64)
<60 years	0.25 (0.19–0.33)	4.43 (2.65–7.41)	1.11 (0.79–1.53)	2.41 (1.54–3.76)	0.87 (0.68–1.11)	3.27 (2.36–4.53)
60–69 years	0.71 (0.62–0.80)	2.48 (2.05–3.01)	2.21 (1.80–2.68)	1.91 (1.46–2.50)	1.43 (1.27–1.60)	2.24 (1.92–2.62)
70–79 years	1.07 (0.99–1.15)	1.54 (1.39–1.70)	1.36 (1.09–1.67)	1.23 (0.89–1.68)	1.31 (1.22–1.41)	1.50 (1.36–1.66)
≥80 years	0.94 (0.86–1.01)	1.13 (1.02–1.26)	0.62 (0.34–1.04)	0.53 (0.16–1.80)	0.97 (0.89–1.05)	1.13 (1.01–1.25)
Other dementias						
Male	2.46 (2.36–2.56)	1.41 (1.33–1.48)	4.47 (3.99–4.98)	1.43 (1.24–1.66)	3.45 (3.31–3.60)	1.41 (1.34–1.48)
Female	3.47 (3.35–3.60)	1.22 (1.17–1.28)	5.72 (5.25–6.22)	1.30 (1.15–1.47)	4.62 (4.47–4.78)	1.23 (1.18–1.29)
<60 years	0.67 (0.57–0.79)	2.24 (1.72–2.93)	2.44 (1.94–3.03)	1.63 (1.24–2.15)	2.02 (1.72–2.37)	1.93 (1.60–2.33)
60–69 years	1.58 (1.45–1.71)	1.92 (1.70–2.16)	5.94 (5.26–6.68)	1.39 (1.19–1.63)	3.51 (3.26–3.79)	1.70(1.55–1.87)
70–79 years	3.15 (3.02–3.29)	1.34 (1.26–1.42)	6.95 (6.33–7.60)	1.29 (1.13–1.48)	4.36 (4.19–4.54)	1.33 (1.26–1.41)
≥80 years	4.43 (4.27–4.60)	1.14 (1.08–1.19)	4.87 (4.00–5.86)	0.95 (0.63–1.42)	4.69 (4.52–4.87)	1.13 (1.08–1.19)

CI, confidence interval.
[a]Controlled for matching factors by study design and adjusted for stroke, atrial fibrillation/atrial flutter, hypertension, hypercholesterolaemia, myocardial infarction, stable angina pectoris, valvular heart disease, diabetes, chronic obstructive pulmonary disease, obesity, myxoedema, alcoholism-related disease, head trauma, osteoarthritis, anaemia, chronic kidney disease, and a modified Charlson Comorbidity Index score.

activation related to heart failure may cause inflammation and cerebral microvascular dysfunction.[9] These mechanisms may lead to chronic cerebral hypoxia and contribute directly to dementia pathogenesis[9] or lower the threshold for the emergence of dementia symptoms in the presence of dementia pathology.[10]

Dementia risk was elevated for vascular dementia and other dementias, but heart failure was not associated with registry diagnoses of Alzheimer's disease. However, relatively large numbers of patients were classified as having unspecified dementia (ICD-10), suggesting substantial misclassification of specific dementia subtypes into this less specific category. Patients with heart failure have multiple vascular risk factors that may explain their observed increased risk of vascular dementia.[19,20] Heart failure has been suggested to increase the risk of stroke.[21] Similarly, heart failure is associated with atrial fibrillation, diabetes, and hypertension, all of which are strongly associated with stroke or vascular dementia,[22] but also with Alzheimer's disease.[23] Although heart failure was not associated with Alzheimer's disease *per se*, our sensitivity analysis, in which unspecified dementia was reclassified as Alzheimer's disease, implied that heart failure patients might in fact be at higher risk of Alzheimer's disease than members of the general population comparison cohort.

Due to the dramatic increase in ageing populations of Western countries in the coming years, the number of patients with dementia is expected to increase.[2] More assiduous management of heart failure might reduce the burden of dementia. Since cognitive impairment and dementia in heart failure patients predict mortality,[24] clinicians should remain vigilant to these conditions, and more research on prevention and intervention strategies is warranted.

Strengths and limitations

This is the largest cohort study to date on the association between heart failure and dementia. Study strengths include its nationwide

Table 4 Risk of dementia in selected subgroups of heart failure patients: adjusted hazard ratios (reference group: general population)

	1–10 year adjusted hazard ratio (95% CI)[a]				11–35 year adjusted hazard ratio (95% CI)[a]			
	Alzheimer's disease	Vascular dementia	Other dementias	All-cause dementia	Alzheimer's disease	Vascular dementia	Other dementias	All-cause dementia
Myocardial infarction								
Yes	1.01 (0.90–1.15)	1.23 (1.05–1.44)	1.14 (1.04–1.24)	1.11 (1.04–1.19)	0.88 (0.65–1.20)	1.15 (0.79–1.69)	1.18 (0.95–1.46)	1.08 (0.92–1.27)
No	0.99 (0.95–1.03)	1.39 (1.31–1.48)	1.26 (1.22–1.30)	1.18 (1.15–1.20)	0.85 (0.76–0.95)	1.43 (1.25–1.64)	1.24 (1.15–1.33)	1.14 (1.08–1.21)
Angina pectoris								
Yes	0.77 (0.69–0.86)	1.35 (1.18–1.54)	1.17 (1.09–1.26)	1.07 (1.01–1.13)	0.74 (0.55–1.00)	1.47 (1.01–2.14)	1.03 (0.84–1.26)	0.99 (0.86–1.16)
No	1.02 (0.98–1.07)	1.36 (1.28–1.45)	1.26 (1.22–1.30)	1.19 (1.16–1.22)	0.87 (0.78–0.97)	1.38 (1.20–1.58)	1.26 (1.18–1.35)	1.16 (1.10–1.22)
Atrial fibrillation or flutter								
Yes	0.94 (0.83–1.06)	1.12 (0.96–1.31)	1.18 (1.08–1.28)	1.10 (1.03–1.17)	0.94 (0.61–1.43)	1.07 (0.66–1.72)	1.10 (0.84–1.43)	1.05 (0.86–1.30)
No	0.99 (0.95–1.03)	1.40 (1.32–1.49)	1.25 (1.22–1.29)	1.18 (1.15–1.20)	0.84 (0.75–0.93)	1.42 (1.25–1.62)	1.24 (1.16–1.33)	1.14 (1.08–1.20)
Valvular heart disease								
Yes	0.78 (0.62–0.98)	1.17 (0.86–1.61)	1.29 (1.09–1.53)	1.08 (0.96–1.22)	1.01 (0.46–2.23)	2.24 (0.79–6.37)	2.04 (1.21–3.46)	1.71 (1.14–2.54)
No	1.00 (0.96–1.04)	1.37 (1.30–1.45)	1.25 (1.21–1.28)	1.17 (1.15–1.20)	0.85 (0.76–0.94)	1.38 (1.22–1.57)	1.22 (1.14–1.31)	1.13 (1.07–1.19)
Hypertension								
Yes	0.96 (0.86–1.06)	1.27 (1.12–1.44)	1.31 (1.22–1.40)	1.19 (1.13–1.26)	0.63 (0.42–0.93)	1.39 (0.90–2.16)	1.13 (0.89–1.44)	1.01 (0.84–1.22)
No	0.99 (0.95–1.03)	1.38 (1.29–1.47)	1.23 (1.19–1.27)	1.16 (1.13–1.19)	0.86 (0.78–0.96)	1.39 (1.22–1.59)	1.24 (1.15–1.32)	1.14 (1.08–1.20)
Myocarditis								
Yes	(.–.)	(.–.)	3.72 (1.02–13.59)	0.99 (0.37–2.67)	(.–.)	(.–.)	(.–.)	(.–.)
No	0.99 (0.95–1.03)	1.37 (1.30–1.45)	1.25 (1.21–1.29)	1.17 (1.15–1.20)	0.85 (0.76–0.94)	1.39 (1.23–1.58)	1.23 (1.15–1.31)	1.13 (1.08–1.19)
Cardiomyopathy								
Yes	0.86 (0.41–1.78)	1.47 (0.63–3.46)	1.18 (0.73–1.93)	1.15 (0.80–1.65)	1.12 (0.07–18.41)	(.–.)	1.06 (0.15–7.30)	1.85 (0.51–6.70)
No	0.99 (0.95–1.03)	1.37 (1.29–1.45)	1.25 (1.21–1.29)	1.17 (1.15–1.20)	0.85 (0.76–0.94)	1.39 (1.23–1.58)	1.23 (1.15–1.32)	1.13 (1.08–1.19)

CI, confidence interval.

(.–.) Insufficient for estimates.

[a]Adjusted for age, sex, calendar year, stroke, atrial fibrillation/atrial flutter, hypertension, hypercholesterolaemia, myocardial infarction, stable angina pectoris, valvular heart disease, diabetes, chronic obstructive pulmonary disease, obesity, myxoedema, alcoholism-related disease, head trauma, osteoarthritis, anaemia, chronic kidney disease, and a modified Charlson Comorbidity Index score (except the stratified variable).

population coverage and complete long-term follow-up, virtually eliminating the risk of selection bias. However, our study is subject to the limitations inherent to dementia registration in the Danish medical registries. The diagnosis of dementia has a high positive predictive value,[14] but the sensitivity of this diagnosis is unknown. Low sensitivity would be expected to underestimate associations with dementia. Heart failure patients are more frequently in contact with the healthcare system than members of the general population. Therefore, registration of dementia may be higher for heart failure patients than for members of the general population, and surveillance bias could have overestimated the associations observed with dementia.[25] We lacked results of diagnostic brain imaging; data on drug treatment, socio-economic status, marital status, and other potential confounders; and objective measures of cognitive function. Also, due to vascular risk factors in heart failure patients, diagnostic bias may contribute to findings on our initial analysis of increased risk of vascular dementia but the null association with Alzheimer's disease. In addition, while we adjusted for previous cardiovascular co-morbidities, we did not include incident cardiovascular conditions occurring during follow-up, because these conditions could represent factors that mediate the association between heart failure and dementia. Because data on heart failure severity are not registered in the DNPR, we could not investigate the risk of dementia in subgroups of patients with more advanced heart failure. However, dementia risks were similar in heart failure patients with shorter and longer follow-up intervals. The Danish population is relatively homogeneous, consisting mostly of Caucasians, and the generalizability of our study results to other populations is unknown.

Conclusion

Heart failure was associated with an increased risk of all-cause dementia, with stronger associations for men than for women.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. International Classification of Diseases codes used in the study.

Table S2. Charlson Comorbidity Index conditions.

Table S3. Selected subgroups of heart failure patients and corresponding hazard ratios for dementia comparing heart failure patients with members of the general population comparison cohort.

Table S4. Cumulative incidence 1–10 year risks and hazard ratios of dementia in heart failure patients and members of the general population comparison cohort, stratified by index periods.

Table S5. Cumulative incidence risks and hazard ratio of dementia in heart failure patients (defined as a first-time inpatient and/or outpatient diagnosis) and members of the general population comparison cohort.

Table S6. Cumulative incidence risks and hazard ratios of dementia in heart failure patients and members of the general population comparison cohort, excluding the initial follow-up periods.

Table S7. Cumulative incidence risks and hazard ratio of Alzheimer's disease including ICD code F03 in heart failure patients and members of the general population comparison cohort.

Funding

The work was supported by the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation, and by the Aarhus University Research Foundation. None of the funding sources had a role in the design, conduct, analysis, or reporting of the study.

Conflict of interest: none declared.

Author contributions: K.A., A.O., H.T.S., and V.W.H. conceived the study idea and designed the study. L.P. and H.T.S. established and designed the cohort. K.A. reviewed the literature, and E.H.P. carried out the analysis under supervision from L.P. All authors participated in the discussion and interpretation of the results. K.A. organized the writing and wrote initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version. H.T.S. is the guarantor.

References

1. Burns A, Iliffe S. Dementia. *BMJ* 2009;**338**:b75.
2. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M, Alzheimer's Disease International. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005;**366**:2112–2117.
3. Kelley AS, McGarry K, Gorges R, Skinner JS. The burden of health care costs for patients with dementia in the last 5 years of life. *Ann Intern Med* 2015;**163**:729–736.
4. Hurd MD, Martorell P, Langa KM. Monetary costs of dementia in the United States. *N Engl J Med* 2013;**369**:489–490.
5. Poblador-Plou B, Calderon-Larranaga A, Marta-Moreno J, Hancco-Saavedra J, Sicras-Mainar A, Soljak M, Prados-Torres A. Comorbidity of dementia: a cross-sectional study of primary care older patients. *BMC Psychiatry* 2014;**14**:84.
6. Blecker S, Paul M, Taksler G, Ogedegbe G, Katz S. Heart failure-associated hospitalizations in the United States. *J Am Coll Cardiol* 2013;**61**:1259–1267.
7. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. *Arch Intern Med* 2006;**166**:1003–1008.
8. Rusanen M, Kivipelto M, Levalahti E, Laatikainen T, Tuomilehto J, Soininen H, Ngandu T. Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE study. *J Alzheimers Dis* 2014;**42**:183–191.
9. Cermakova P, Eriksdotter M, Lund LH, Winblad B, Religa P, Religa D. Heart failure and Alzheimer's disease. *J Intern Med* 2015;**277**:406–425.
10. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol* 2012;**11**:1006–1012.
11. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;**29**:541–549.
12. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449–490.
13. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health* 2011;**39**:54–57.
14. Phung TK, Andersen BB, Hogh P, Kessing LV, Mortensen PB, Waldemar G. Validity of dementia diagnoses in the Danish hospital registers. *Dement Geriatr Cogn Disord* 2007;**24**:220–228.
15. Therneau T. *Modeling Survival Data: Extending the Cox Model.* Springer Science & Business Media; 2000. p44–48.
16. Taylor AL. Heart failure in women. *Curr Heart Fail Rep* 2015;**12**:187–195.
17. Jefferson AL, Beiser AS, Himali JJ, Seshadri S, O'Donnell CJ, Manning WJ, Wolf PA, Au R, Benjamin EJ. Low cardiac index is associated with incident dementia and Alzheimer disease: the Framingham Heart Study. *Circulation* 2015;**131**:1333–1339.

18. Sabayan B, van Buchem MA, Sigurdsson S, Zhang Q, Harris TB, Gudnason V, Arai AE, Launer LJ. Cardiac hemodynamics are linked with structural and functional features of brain aging: the age, gene/environment susceptibility (AGES)-Reykjavik Study. *J Am Heart Assoc* 2015;**4**:e001294.
19. Taylor J, Stott DJ. Chronic heart failure and cognitive impairment: co-existence of conditions or true association? *Eur J Heart Fail* 2002;**4**:7–9.
20. Cermakova P, Lund LH, Fereshtehnejad SM, Johnell K, Winblad B, Dahlstrom U, Eriksdotter M, Religa D. Heart failure and dementia: survival in relation to types of heart failure and different dementia disorders. *Eur J Heart Fail* 2015;**17**:612–619.
21. Haeusler KG, Laufs U, Endres M. Chronic heart failure and ischemic stroke. *Stroke* 2011;**42**:2977–2982.
22. Korczyn AD, Vakhapova V, Grinberg LT. Vascular dementia. *J Neurol Sci* 2012;**322**:2–10.
23. Stampfer MJ. Cardiovascular disease and Alzheimer's disease: common links. *J Intern Med* 2006;**260**:211–223.
24. Pilotto A, Addante F, Franceschi M, Leandro G, Rengo G, D'Ambrosio P, Longo MG, Rengo F, Pellegrini F, Dallapiccola B, Ferrucci L. Multidimensional Prognostic Index based on a comprehensive geriatric assessment predicts short-term mortality in older patients with heart failure. *Circ Heart Fail* 2010;**3**:14–20.
25. Copeland KT, Checkoway H, McMichael AJ, Holbrook RH. Bias due to misclassification in the estimation of relative risk. *Am J Epidemiol* 1977;**105**:488–495.

Supplementary Online Material

Table S1. *International Classification of Diseases* codes used in the study.

	ICD-8	ICD-10
Heart failure	42709, 42710, 42711, 42719, 42899,78249	I50, I11.0, I13.0, I13.2
Myocardial infarction	410	I21
Angina pectoris	413	I20 (except I20.0), I25.1, I25.9
Atrial fibrillation or flutter	42793, 42794	I48
Valvular heart disease	394-398	I05, I06, I07, I08.0, I09.8, I34-I37, I39.0, I39.3, I51.1A, Q22
Hypercholesterolemia	27200	E780
Hypertension	400-404	DI10-DI15, I67.4
Stroke	431, 433-434	I61, I63-I64
Myocarditis	422	I40, I41, I090, I514
Cardiomyopathy	425	I42-I43 (exluding I42.6)
Obesity	277	E65-E68
Diabetes mellitus	249, 250 (excluding 24902, 25002)	E10 (excluding E10.2), E11 (excluding E11.2), H36.0
Chronic obstructive pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Myxedema	244	E00, E03, E890
Alcoholism-related diseases	980, 29109-29199, 30309-30399, 57109-57111, 57710	F10 (except F10.0), G31.2, G62.1, G72.1, I 42.6, K29.2, K86.0, Z72.1
Head trauma	800-803, 850-854, 810-874	S00-S09
Osteoarthritis (patients often use NSAIDs which therefore may modify the risk of dementia). Other connective tissue diseases associated with use of NSAIDs are included in the CCI index	713	M15-M19
Anemia	280-281, 283-285	D50-55, D59, D61-D64
Chronic kidney disease	24902, 25002, 75310-75319, 582-584, 59009, 59320, 792	E102, E112, E142, N03, N05, N110, N14, N16, N18-N19, N269, Q611-Q614
Outcomes		
Alzheimer's disease	29010, 29009	F00 series (includes F00.0x, F00.1x, F00.2x, and F00.9x); G30 (includes G30, G30.0, 30.1, 30.8, 30.9)

Vascular dementia	29309, 29319	F01 series (includes F01.0x, F01.1x, F01.2x, F01.3x, F01.8x, & F01.9x)
Other dementia	09419 and 29209, 29011, 29018, 29019, 29209	F02 series; F03 series; F1x.73 series (F10.73 through F19.73); G23.1; G31.0, G31.1, G31.8B, G31.8E, G31.85

Table S2. Charlton comorbidity index conditions.

Diseases	**Weights**	
Peripheral vascular disease	1	ICD-8: 440, 441, 442, 443, 444, 445; ICD-10: I70, I71, I72, I73, I74, I77
Connective tissue disease		ICD-8: 712, 716, 734, 446, 135.99; ICD-10: M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Ulcer disease		ICD-8: 530.91, 530.98, 531-534; ICD-10: K22.1, K25-K28
Mild liver disease		ICD-8: 571, 57301, 57304; ICD-10:B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0
Hemiplegia	2	ICD-8: 344; ICD-10: G81, G82
Non-metastatic solid tumor		ICD-8: 140-194; ICD-10: C00-C75
Leukemia		ICD-8: 204-207; ICD-10: C91-C95
Lymphoma		ICD-8: 200-203, 275.59; ICD-10: C81-C85, C88, C90, C96
Moderate to severe liver disease	3	ICD-8: 070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09; ICD-10: B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Metastatic cancer	6	ICD-8: 195-198, 199; ICD-10: C76-C80
AIDS		ICD-8: 079.83; ICD-10: B21-B24

Table S3. Selected subgroups of heart failure patients and corresponding hazard ratios for dementia comparing heart failure patients with members of the general population.

	1-10 year adjusted hazard ratio (95% CI)*				11-35 year adjusted hazard ratio (95% CI)*			
	Alzheimer's disease	**Vascular dementia**	**Other dementias**	**All-cause dementia**	**Alzheimer's disease**	**Vascular dementia**	**Other dementias**	**All-cause dementia**
Hypercholesterolemia								
Yes	1.00 (0.79–1.27)	1.39 (1.01–1.90)	1.53 (1.27–1.86)	1.30 (1.13–1.48)	0.87 (0.39–1.97)	0.46 (0.09–2.26)	1.74 (0.70–4.30)	0.96 (0.55–1.67)
No	0.99 (0.95–1.03)	1.37 (1.30–1.45)	1.24 (1.21–1.28)	1.17 (1.14–1.20)	0.85 (0.76–0.94)	1.41 (1.24–1.60)	1.23 (1.15–1.31)	1.13 (1.08–1.19)
Stroke								
Yes	0.98 (0.81–1.18)	0.98 (0.84–1.15)	1.14 (1.02–1.27)	1.07 (0.98–1.16)	1.16 (0.47–2.84)	1.17 (0.58–2.38)	1.54 (0.98–2.43)	1.34 (0.94–1.91)
No	0.99 (0.95–1.03)	1.42 (1.34–1.51)	1.25 (1.22–1.29)	1.18 (1.15–1.20)	0.84 (0.76–0.94)	1.40 (1.23–1.59)	1.22 (1.14–1.31)	1.13 (1.07–1.19)
Obesity								
Yes	1.26 (1.01–1.58)	1.17 (0.87–1.56)	1.35 (1.15–1.60)	1.29 (1.14–1.46)	0.76 (0.43–1.36)	1.82 (0.83–4.01)	1.53 (1.07–2.19)	1.30 (0.98–1.73)
No	0.98 (0.95–1.02)	1.38 (1.30–1.46)	1.24 (1.21–1.28)	1.17 (1.14–1.19)	0.85 (0.76–0.94)	1.38 (1.21–1.57)	1.22 (1.14–1.30)	1.12 (1.07–1.18)
Diabetes mellitus								
Yes	0.84 (0.73–0.98)	1.15 (0.96–1.38)	1.18 (1.07–1.30)	1.07 (1.00–1.16)	0.70 (0.41–1.21)	1.39 (0.77–2.52)	1.18 (0.87–1.60)	1.09 (0.85–1.39)
No	1.00 (0.96–1.04)	1.39 (1.31–1.47)	1.25 (1.21–1.29)	1.18 (1.15–1.20)	0.85 (0.77–0.95)	1.39 (1.22–1.58)	1.23 (1.15–1.31)	1.13 (1.07–1.19)
Chronic pulmonary disease								
Yes	0.90 (0.79–1.04)	1.07 (0.89–1.30)	1.15 (1.05–1.27)	1.06 (0.99–1.14)	1.00 (0.66–1.49)	1.80 (1.09–2.98)	1.40 (1.06–1.84)	1.33 (1.08–1.63)
No	1.00 (0.96–1.04)	1.40 (1.32–1.49)	1.26 (1.22–1.30)	1.18 (1.16–1.21)	0.84 (0.75–0.93)	1.36 (1.20–1.56)	1.22 (1.14–1.30)	1.12 (1.06–1.18)
Myxedema								
Yes	0.86 (0.61–1.20)	1.34 (0.83–2.16)	1.19 (0.96–1.49)	1.10 (0.93–1.31)	0.65 (0.15–2.81)	1.13 (0.24–5.33)	0.81 (0.36–1.85)	0.80 (0.42–1.52)
No	0.99 (0.95–1.03)	1.37 (1.29–1.45)	1.25 (1.21–1.29)	1.17 (1.15–1.20)	0.85 (0.76–0.94)	1.39 (1.22–1.58)	1.23 (1.15–1.32)	1.13 (1.08–1.19)
Alcoholism-related disease								
Yes	0.90 (0.62–1.31)	1.18 (0.79–1.78)	1.13 (0.94–1.35)	1.10 (0.94–1.28)	1.58 (0.58–4.33)	1.44 (0.44–4.70)	1.33 (0.85–2.08)	1.34 (0.91–1.97)
No	0.99 (0.96–1.03)	1.37 (1.30–1.45)	1.25 (1.21–1.29)	1.17 (1.15–1.20)	0.85 (0.76–0.94)	1.39 (1.23–1.58)	1.22 (1.15–1.31)	1.13 (1.07–1.19)
Head trauma								
Yes	0.88 (0.78–0.98)	1.37 (1.17–1.59)	1.12 (1.04–1.21)	1.07 (1.01–1.14)	0.68 (0.47–1.00)	1.45 (0.97–2.16)	1.31 (1.08–1.59)	1.16 (0.99–1.35)
No	1.01 (0.97–1.05)	1.37 (1.29–1.46)	1.27 (1.23–1.32)	1.19 (1.16–1.22)	0.86 (0.78–0.96)	1.39 (1.22–1.59)	1.22 (1.14–1.31)	1.13 (1.07–1.19)
Osteoarthritis								
Yes	0.94 (0.85–1.05)	1.24 (1.06–1.44)	1.17 (1.09–1.26)	1.11 (1.05–1.17)	0.77 (0.54–1.09)	1.69 (1.12–2.54)	0.91 (0.72–1.15)	0.96 (0.80–1.14)
No	1.00 (0.96–1.04)	1.39 (1.31–1.48)	1.26 (1.22–1.31)	1.18 (1.16–1.21)	0.85 (0.77–0.95)	1.36 (1.19–1.56)	1.26 (1.18–1.35)	1.15 (1.09–1.21)
Anemia								
Yes	0.65 (0.52–0.82)	1.20 (0.91–1.57)	1.11 (0.98–1.25)	0.99 (0.90–1.10)	1.31 (0.61–2.81)	1.63 (0.48–5.56)	0.99 (0.58–1.69)	1.12 (0.74–1.70)
No	1.00 (0.96–1.04)	1.37 (1.30–1.46)	1.25 (1.21–1.29)	1.18 (1.15–1.20)	0.84 (0.76–0.93)	1.39 (1.23–1.58)	1.23 (1.15–1.32)	1.13 (1.08–1.19)
Chronic kidney disease								
Yes	1.04 (0.74–1.47)	1.21 (0.79–1.85)	1.27 (1.00–1.61)	1.20 (1.00–1.43)	0.52 (0.13–2.15)	1.18 (0.11–12.79)	1.89 (0.89–4.00)	1.35 (0.71–2.56)
No	0.99 (0.95–1.03)	1.37 (1.30–1.45)	1.25 (1.21–1.28)	1.17 (1.15–1.20)	0.85 (0.76–0.94)	1.40 (1.23–1.59)	1.23 (1.15–1.31)	1.13 (1.07–1.19)
Charlson Comorbidity Index score								
Normal	1.02 (0.98–1.07)	1.40 (1.31–1.49)	1.24 (1.20–1.28)	1.18 (1.15–1.21)	0.83 (0.74–0.93)	1.42 (1.24–1.63)	1.19 (1.10–1.27)	1.11 (1.05–1.17)

Moderate	0.88 (0.78–1.00)	1.25 (1.07–1.46)	1.22 (1.12–1.32)	1.11 (1.04–1.18)	0.92 (0.63–1.34)	1.09 (0.68–1.74)	1.70 (1.37–2.12)	1.38 (1.16–1.64)
Severe	0.78 (0.67–0.91)	1.22 (1.01–1.49)	1.30 (1.18–1.43)	1.14 (1.06–1.23)	0.89 (0.56–1.41)	1.29 (0.66–2.51)	1.29 (0.955–1.75)	1.15 (0.91–1.46)
Very severe	0.87 (0.65–1.16)	1.32 (0.90–1.94)	1.29 (1.08–1.53)	1.17 (1.04–1.33)	1.30 (0.51–3.32)	0.57 (0.06–5.12)	0.91 (0.41–2.01)	0.99 (0.56–1.77)

*Adjusted for age, sex, calendar year, stroke, atrial fibrillation/atrial flutter, hypertension, hypercholesterolemia, myocardial infarction, stable angina pectoris, valvular heart disease, diabetes, chronic obstructive pulmonary disease, obesity, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, and a modified CCI score (except the stratified variable).

CI, confidence interval

Table S4. Cumulative incidence 1-10 year risks and hazard ratios of dementia in heart failure patients and members of the general population cohort, stratified by index periods.

	Comparison Cohort		Heart Failure Patients			
	Events /No. at risk	**Cumulative incidence risk, % (95% CI)**	**Events /No. at risk**	**Cumulative incidence risk, % (95% CI)**	**Hazard ratio controlled for matching factors* (95% CI)**	**Adjusted hazard ratio (95% CI)†**
1980-1994						
All-cause dementia	33,059/704,336	5.03 (4.98 - 5.09)	3,063/85,496	3.58 (3.46 - 3.71)	1.38 (1.32–1.44)	1.31 (1.26–1.37)
Alzheimer's disease	16,553/704,336	2.49 (2.46 - 2.53)	1,508/85,496	1.76 (1.68 - 1.85)	1.28 (1.20–1.36)	1.24 (1.17–1.32)
Vascular dementia	3,678/704,336	0.56 (0.54 - 0.58)	438/85,496	0.51 (0.47 - 0.56)	1.92 (1.70–2.17)	1.69 (1.49–1.92)
Other dementias	12,828/704,336	1.98 (1.95 - 2.02)	1,117/85,496	1.31 (1.23 - 1.38)	1.39 (1.29–1.49)	1.31 (1.21–1.41)
1995-2012						
All-cause dementia	59,169/787,766	9.43 (9.36 - 9.50)	6,745/112,542	6.95 (6.78 - 7.11)	1.23 (1.20–1.27)	1.17 (1.13–1.20)
Alzheimer's disease	17,901/787,766	2.91 (2.87 - 2.96)	1,413/112,542	1.48 (1.41 - 1.56)	0.84 (0.79–0.89)	0.84 (0.79–0.89)
Vascular dementia	7,490/787,766	1.20 (1.17 - 1.23)	1,108/112,542	1.14 (1.08 - 1.21)	1.58 (1.47–1.70)	1.39 (1.29–1.51)
Other dementias	33,778/787,766	5.40 (5.34 - 5.46)	4,224/112,542	4.35 (4.22 - 4.48)	1.38 (1.33–1.43)	1.29 (1.24–1.34)

*Age, sex, and calendar year

†Controlled for matching factors by study design and adjusted for stroke, atrial fibrillation/atrial flutter, hypertension, hypercholesterolemia, myocardial infarction, stable angina pectoris, valvular heart disease, diabetes, chronic obstructive pulmonary disease, obesity, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, and a modified CCI score. CI, confidence interval

Table S5. Cumulative incidence risks and hazard ratio of dementia in heart failure patients (defined as a first-time inpatient and/or outpatient diagnosis) and members of the general population.

Years since Diagnosis	Events /No. at risk	Cumulative incidence risk, % (95% CI)	Events /No. at risk	Cumulative incidence risk, % (95% CI)	Hazard ratio controlled for matching factors* (95% CI)	Adjusted hazard ratio (95% CI)†
All-cause dementia						
1-10	100,211/1,665,527	7.12 (7.08 - 7.17)	11,199/231,360	5.42 (5.32 - 5.52)	1.25 (1.22–1.28)	1.19 (1.16–1.22)
11-20	39,216/558,822	9.75 (9.65 - 9.84)	1,790/36,414	6.98 (6.66 - 7.31)	1.26 (1.18–1.34)	1.19 (1.11–1.27)
21-35	7,575/102,213	13.40 (12.98 - 13.83)	150/3,209	7.52 (6.22 - 8.97)	1.42 (1.12–1.81)	1.35 (1.06–1.73)
1-35	147,002/1,665,527	15.13 (15.01 - 15.24)	13,139/231,360	7.55 (7.40 - 7.70)	1.25 (1.22–1.28)	1.19 (1.16–1.21)
Alzheimer's disease						
1-10	37,154/1,665,527	2.63 (2.61 - 2.66)	3,290/231,360	1.58 (1.53 - 1.64)	0.99 (0.95–1.03)	0.99 (0.95–1.03)
11-20	11,909/558,822	2.97 (2.91 - 3.02)	443/36,414	1.73 (1.57 - 1.90)	0.84 (0.74–0.95)	0.85 (0.75–0.97)
21-35	2,496/102,213	4.61 (4.36 - 4.87)	43/3,209	2.57 (1.72 - 3.70)	1.27 (0.83–1.94)	1.22 (0.78–1.91)
1-35	51,559/1,665,527	5.24 (5.17 - 5.31)	3,776/231,360	2.16 (2.07 - 2.25)	0.98 (0.94–1.01)	0.98 (0.94–1.02)
Vascular dementia						
1-10	12,289/1,665,527	0.88 (0.86 - 0.89)	1,798/231,360	0.88 (0.84 - 0.92)	1.63 (1.54–1.72)	1.44 (1.35–1.53)
11-20	4,951/558,822	1.24 (1.21 - 1.28)	289/36,414	1.11 (0.98 - 1.25)	1.81 (1.53–2.13)	1.55 (1.30–1.85)
21-35	929/102,213	1.70 (1.55 - 1.86)	32/3,209	1.52 (1.04 - 2.17)	2.80 (1.53–5.10)	2.58 (1.32–4.91)
1-35	18,169/1,665,527	1.93 (1.89 - 1.97)	2,119/231,360	1.24 (1.18 - 1.30)	1.65 (1.57–1.75)	1.46 (1.38–1.54)
Other dementias						
1-10	50,768/1,665,527	3.65 (3.62 - 3.68)	6,111/231,360	2.98 (2.91 - 3.06)	1.35 (1.30–1.39)	1.27 (1.23–1.31)
11-20	22,356/558,822	5.63 (5.56 - 5.70)	1,058/36,414	4.19 (3.94 - 4.45)	1.43 (1.31–1.56)	1.34 (1.22–1.46)
21-35	4,150/102,213	7.36 (7.02 - 7.72)	75/3,209	3.49 (2.71 - 4.42)	1.25 (0.89–1.74)	1.17 (0.83–1.66)
1-35	77,274/1,665,527	8.27 (8.18 - 8.37)	7,244/231,360	4.21 (4.10 - 4.32)	1.35 (1.32–1.39)	1.28 1.24–1.31)

*Age, sex, and calendar year

†Controlled for matching factors by study design and adjusted for stroke, atrial fibrillation/atrial flutter, hypertension, hypercholesterolemia, myocardial infarction, stable angina pectoris, valvular heart disease, diabetes, chronic obstructive pulmonary disease, obesity, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, and a modified CCI score. CI, confidence interval

Table S6. Cumulative incidence risks and hazard ratios of dementia in heart failure patients and members of the general population comparison cohort, excluding the initial follow-up periods.

	Comparison cohort		Heart failure patients			
Years since diagnosis	**Events /No. at risk**	**Cumulative incidence risk, % (95% CI)**	**Events /No. at risk**	**Cumulative incidence risk, % (95% CI)**	**Hazard ratio controlled for matching factors* (95% CI)**	**Adjusted hazard ratio (95% CI)†**
All-cause dementia						
1-35	137,057/1,492,102	14.95 (14.84 - 15.06)	11,484/198,038	7.22 (7.08 - 7.36)	1.28 (1.25–1.30)	1.21 (1.18–1.24)
2-35	123,074/1,370,234	15.01 (14.90 - 15.13)	9,409/162,228	7.53 (7.37 - 7.70)	1.27 (1.24–1.30)	1.20 (1.17–1.24)
3-35	110,204/1,226,987	15.09 (14.96 - 15.21)	7,631/131,192	7.72 (7.53 - 7.91)	1.26 (1.23–1.30)	1.19 (1.16–1.23)
5-35	87,270/974,261	15.23 (15.09 - 15.37)	5,051/85,962	8.14 (7.89 - 8.40)	1.27 (1.23–1.32)	1.20 (1.15–1.24)
10-35	44,829/511,213	15.37 (15.17 - 15.58)	1,676/29,655	8.73 (8.26 - 9.21)	1.27 (1.19–1.36)	1.21 (1.12–1.29)
Alzheimer's disease						
1-35	48,093/1,492,102	5.18 (5.11 - 5.25)	3,319/198,038	2.07 (1.98 - 2.15)	1.00 (0.96–1.04)	1.00 (0.96–1.04)
2-35	42,331/1,370,234	5.13 (5.06 - 5.20)	2,654/162,228	2.11 (2.01 - 2.21)	0.98 (0.94–1.03)	0.99 (0.94–1.03)
3-35	37,278/1,226,987	5.10 (5.02 - 5.17)	2,064/131,192	2.09 (1.98 - 2.21)	0.94 (0.89–0.99)	0.95 (0.90–1.00)
5-35	28,545/974,261	5.04 (4.95 - 5.12)	1,302/85,962	2.14 (1.99 - 2.29)	0.91 (0.85–0.98)	0.92 (0.86–0.98)
10-35	13,639/511,213	4.90 (4.78 - 5.02)	398/29,655	2.24 (1.96 - 2.54)	0.82 (0.72–0.93)	0.83 (0.73–0.95)
Vascular dementia						
1-35	16,800/1,492,102	1.90 (1.85 - 1.94)	1,824/198,038	1.17 (1.11 - 1.23)	1.69 (1.59–1.79)	1.49 (1.40–1.59)
2-35	15,099/1,370,234	1.91 (1.86 - 1.95)	1,504/162,228	1.23 (1.16 - 1.30)	1.69 (1.58–1.80)	1.49 (1.39–1.59)
3-35	13,490/1,226,987	1.91 (1.87 - 1.96)	1247/131,192	1.28 (1.20 - 1.36)	1.75 (1.63–1.89)	1.53 (1.42–1.66)
5-35	10,718/974,261	1.94 (1.88 - 1.99)	811/85,962	1.34 (1.24 - 1.45)	1.80 (1.64–1.98)	1.58 (1.43–1.74)
10-35	5,632/511,213	1.98 (1.91 - 2.06)	278/29,655	1.48 (1.29 - 1.69)	1.89 (1.60–2.24)	1.66 (1.38–1.99)
Other dementia						
1-35	72,164/1,492,102	8.17 (8.08 - 8.26)	6,341/198,038	4.03 (3.92 - 4.14)	1.39 (1.35–1.43)	1.30 (1.26–1.34)
2-35	65,644/1,370,234	8.28 (8.19 - 8.38)	5,251/162,228	4.24 (4.12 - 4.37)	1.38 (1.34–1.43)	1.29 (1.25–1.34)
3-35	59,436/1,226,987	8.39 (8.28 - 8.49)	4,320/131,192	4.40 (4.26 - 4.54)	1.38 (1.33–1.44)	1.29 (1.24–1.34)
5-35	48,007/974,261	8.57 (8.46 - 8.69)	2,938/85,962	4.73 (4.55 - 4.92)	1.41 (1.34–1.48)	1.30 (1.24–1.37)
10-35	25,558/511,213	8.82 (8.66 - 8.99)	1,000/29,655	5.09 (4.76 - 5.45)	1.45 (1.32–1.58)	1.35 (1.23–1.48)

*Age, sex, and calendar year.

†Controlled for matching factors by study design and adjusted for stroke, atrial fibrillation/atrial flutter, hypertension, hypercholesterolemia, myocardial infarction, stable angina pectoris, valvular heart disease, diabetes, chronic obstructive pulmonary disease, obesity, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, and a modified CCI score. CI, confidence interval

Table S7. Cumulative incidence risks and hazard ratio of Alzheimer's disease using including ICD code F03 in heart failure patients and members of the general population comparison cohort.

	Comparison Cohort		Heart Failure Patients			
Years since Diagnosis	**Events /No. at risk**	**Cumulative incidence risk, % (95% CI)**	**Events /No. at risk**	**Cumulative incidence risk, % (95% CI)**	**Hazard ratio controlled for matching factors* (95% CI)**	**Adjusted hazard ratio (95% CI)†**
1-10	77,905/1,492,102	6.07 (6.03 - 6.12)	7,871/198,038	4.33 (4.24 - 4.42)	1.21 (1.18–1.25)	1.17 (1.14–1.20)
11-20	31,290/511,213	8.25 (8.16 - 8.34)	1,229/29,655	5.60 (5.29 - 5.92)	1.19 (1.10–1.28)	1.14 (1.06–1.24)
21-35	6,334/99,527	11.35 (10.95 - 11.76)	104/2,906	5.72 (4.53 - 7.09)	1.24 (0.93–1.65)	1.16 (0.87–1.56)
1-35	115,529/1,492,102	12.65 (12.55 - 12.76)	9,204/198,038	5.79 (5.66 - 5.92)	1.21 (1.18–1.24)	1.16 (1.14–1.20)

*Age, sex, and calendar year.

†Controlled for matching factors by study design and adjusted for stroke, atrial fibrillation/atrial flutter, hypertension, hypercholesterolemia, myocardial infarction, stable angina pectoris, valvular heart disease, diabetes, chronic obstructive pulmonary disease, obesity, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, and a modified CCI score. CI, confidence interval

Study V

Original Contribution

Risk of Stroke in Patients With Heart Failure
A Population-Based 30-Year Cohort Study

Kasper Adelborg, MD; Szimonetta Szépligeti, MSc; Jens Sundbøll, MD; Erzsébet Horváth-Puhó, PhD; Victor W. Henderson, MD, MS; Anne Ording, PhD; Lars Pedersen, PhD; Henrik Toft Sørensen, MD, PhD, DMSc

Background and Purpose—The long-term risk of specific stroke subtypes among heart failure patients is largely unknown. We examined short-term and long-term risk of ischemic stroke, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH) in heart failure patients and in a general population comparison cohort.

Methods—In this nationwide cohort study (1980–2012), we used Danish population-based medical registries to identify and follow (1) all patients hospitalized for the first time with heart failure and (2) a birth year–, sex-, and calendar year–matched general population comparison cohort. Age-, sex-, and comorbidity-adjusted stroke rate ratios were computed based on Cox regression analysis.

Results—We included 289 353 patients with heart failure and 1 446 765 individuals from the general population in the analysis. One- and 5-year risks among heart failure patients were 1.4% and 3.9% for ischemic stroke, 0.2% and 0.5% for ICH, and 0.03% and 0.07% for SAH. The 30-day adjusted stroke rate ratio was increased markedly for ischemic stroke (5.08; 95% confidence interval, 4.58–5.63] and was also elevated for ICH (2.13; 95% confidence interval, 1.53–2.97) and SAH (3.52; 95% confidence interval, 1.54–8.08). Between 31 days and 30 years, risk of all stroke subtypes remained positively associated with heart failure (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) in comparison with the general population cohort.

Conclusions—Heart failure was associated with increased short-term and long-term risk of all stroke subtypes, suggesting that heart failure is a potent and persistent risk factor for ischemic stroke, ICH, and SAH. (***Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.016022.)**

Key Words: cerebral hemorrhage ■ heart failure ■ hemorrhagic ■ risk factor ■ stroke, ischemic

Heart failure, affecting >23 million people per year worldwide, is a leading cause of death.[1] Comorbidities associated with heart failure have substantial implications for its prognosis.[2] Heart failure may increase the risk of ischemic stroke because of thromboembolic complications and increased activity of procoagulant factors. At the same time, heart failure is associated with low blood pressure, which may protect against stroke.[3] Well-known stroke risk factors include disorders associated with heart disease, such as hypertension, coronary artery disease, atrial fibrillation, diabetes mellitus, and obesity.[4] However, the role of heart failure as a risk factor for stroke remains less clear.[5–15]

A few studies have compared stroke risk among heart failure patients with that of the general population. However, these were limited by relatively small sample sizes (<1500 patients)[5–8] and relatively short follow-up periods (<5 years).[5–7] As well, they were conducted in the era before routine use of angiotensin-converting enzyme inhibitors and beta blockers,[8] did not separately examine ischemic and hemorrhagic stroke,[6–8] and did not adjust or stratify for atrial fibrillation.[7,8] They found that heart failure patients had a higher 30-day ischemic stroke rate than persons in the general population,[5,6,15] but data after this initial follow-up period were sparse and equivocal.[5,15]

We, therefore, examined short-term (0–1 year) and long-term (1–30 year) risks and temporal trends in risk of ischemic stroke, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH) in a large cohort of heart failure patients and in a general population comparison cohort. We also assessed how comorbidity affected the relation between heart failure and stroke risk. An understanding of this association could have important implications for future prevention strategies in patients with heart failure.

Received November 9, 2016; final revision received February 2, 2017; accepted February 10, 2017.

From the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark (K.A., S.S., J.S., E.H.-P., V.W.H., A.O., L.P., H.T.S.); and Department of Health Research and Policy (Epidemiology) (V.W.H., H.T.S.) and Department of Neurology and Neurological Sciences (V.W.H.), Stanford University, Stanford, CA.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.116.016022/-/DC1.

Correspondence to Kasper Adelborg, MD, Department of Clinical Epidemiology, Aarhus University Hospital, Skejby, Olof Palmes Allé 43–45, DK-8200, Aarhus N, Denmark. E-mail kade@clin.au.dk

Methods

Setting and Design

We conducted a population-based nationwide cohort study of Danish-born residents (7 107 236 people cumulatively during the study period).[16] In Denmark, all residents have equal access to universal tax-supported health care, including unfettered access to general practitioners and hospitals, and partial reimbursement for prescribed medications. All residents are assigned a unique central personal registry number at birth or on immigration, allowing linkage of data among administrative and medical registries.[16]

Heart Failure Patients

Patients with a first-time hospitalization for heart failure between January 1, 1980, and November 30, 2012, were identified from the Danish National Patient Registry (DNPR).[17] Since 1977, this registry has maintained records on hospital admissions and discharges, including dates and diagnoses coded according to the *International Classification of Diseases*, *8th Revision* through 1993 and *10th Revision* thereafter.[17] Hospital outpatient clinic and emergency room visits were added in 1995. We used both primary and secondary diagnoses (eg, heart failure diagnosed secondary to myocardial infarction) to identify patients with heart failure. To examine first-time stroke events in our study population, we excluded patients with an inpatient, emergency room, or outpatient clinic diagnosis of transient ischemic attack or stroke before the heart failure admission date. *International Classification of Diseases* codes used in the study are provided in Table I in the online-only Data Supplement.

General Population Comparison Cohort

We used the Danish Civil Registration System, which has maintained a registry with dates of birth, emigration, and death with daily updates since 1968, to form a general population comparison cohort. We matched each heart failure patient on birth year, sex, and calendar year of heart failure diagnosis with ≤5 individuals drawn from the general population without heart failure.[16] We used matching with replacement (ie, individuals from the general population comparison cohort could be matched with >1 heart failure patient).[18] We excluded individuals with a previous inpatient or outpatient diagnosis of transient ischemic attack or stroke. Individuals diagnosed with heart failure after the index date were sustained in the general population comparison cohort (to avoid informative censoring). The index date was defined as the inpatient hospital admission date for persons diagnosed with heart failure and the corresponding date of matching for members of the general population cohort.

Stroke

The study outcome was defined as all inpatient hospitalizations for stroke recorded in the DNPR after the index date.[17] Stroke included first-time ischemic stroke, ICH, or SAH. In primary analyses, unspecified stroke diagnoses were included in the definition of ischemic stroke because more than 2 thirds of unspecified strokes in the DNPR are ischemic in origin.[19]

Covariables

We retrieved information from the DNPR on factors associated with heart failure and comorbidities between 1977 and the index date, using all available primary and secondary hospital-based diagnoses except for those made in an emergency room.[17] We obtained data on previous myocardial infarction, angina pectoris, atrial fibrillation or flutter, valvular heart disease, hypertension, intermittent claudication, venous thromboembolism, hypercholesterolemia, hypertriglyceridemia, obesity, diabetes mellitus, chronic kidney disease, cancer, chronic pulmonary disease (as an indicator of chronic cigarette exposure), alcoholism-related disease, and dementia.

Statistical Analysis

All heart failure patients and members of the general population comparison cohort were followed from the index date until the hospital admission date for any stroke, emigration, death, November 30, 2013, or 30 years of follow-up, whichever came first. We characterized the cohorts by sex, age categories (<60, 60–69, 70–79, and ≥80 years), index year calendar periods (1980–1989, 1990–1999, and 2000–2012), and the covariables described earlier. Age and person-years of follow-up were reported as medians with interquartile ranges. Characteristics of the cohorts were compared using Chi-square test for categorical variables and 2-sample *t* test for continuous variables. Cumulative stroke risks were calculated using cumulative incidence curves/risks, accounting for death as a competing risk. We computed standardized incidence ratios as the observed number of stroke cases among heart failure patients divided by the expected number of cases in the general Danish population (assuming that heart failure patients had the same stroke risk as the general population).[20] The expected number of stroke cases was calculated using national incidence rates for first-time stroke diagnoses, by sex, age, and 1-year intervals. The 95% confidence intervals (CIs) for the standardized incidence ratio estimates were computed assuming a Poisson distribution of the observed number of stroke cases in the different time periods. Stratified Cox regression analysis was used to calculate unadjusted (controlled only for matching factors by study design) and adjusted stroke rate ratios (aSRRs, specifically hazard ratios) with corresponding 95% CIs, comparing heart failure patients with the general population cohort.[21] We adjusted for the variables presented in Table 1 in the regression analysis.

To investigate associations between heart failure and stroke independent of atrial fibrillation or atrial flutter, we repeated the analyses in heart failure patients and individuals from the general population with and without atrial fibrillation or atrial flutter. To assess temporal changes in stroke risk, we stratified the analyses by calendar periods, and we provided statistics for temporal changes using the statistical basis of meta-analyses.[22] We also considered potential interactions in stratified analyses, which we used to examine the risk of stroke by sex, age groups, and in subgroups of heart failure patients. The proportional hazards assumption was assessed graphically in the pooled data set by means of log–log plots and found to be satisfied for the time periods analyzed.

Sensitivity Analyses

We conducted 7 sensitivity analyses. First, to improve the specificity of the stroke diagnosis, we limited an analysis to patients who were diagnosed with stroke and underwent a computed tomography scan or magnetic resonance imaging scan of the brain during the same admission (restricted to patients diagnosed from January 1, 2000, onwards, when these data were available). Second, we separately analyzed patients with unspecified stroke and specified ischemic stroke. Third, since antithrombotic drugs, angiotensin-converting enzyme inhibitors, and beta blockers may be important risk reduction mediators between heart failure and ischemic stroke, we repeated the analyses adjusting for their use within 90 days before the index date, using data from the National Health Service Prescription Database (data available from July 2004 onwards).[23] Because the validity of recurrent stroke diagnoses in the DNPR is unknown, in the main analysis, we followed patients only until their first stroke diagnosis. However, to test the sensitivity of this approach, in our fourth sensitivity analysis, we allowed individuals to be at risk of other stroke subtypes after their initial stroke diagnosis. Fifth, we repeated the analyses for patients with first-time outpatient heart failure diagnoses (data available from January 1, 1995, onwards). Sixth, to exclude reverse causality (ie, stroke patients admitted with heart failure), we restricted the analyses to patients with primary heart failure inpatient diagnoses. Finally, because data on heart failure severity (ie, left ventricular ejection fraction) were not available, we stratified our heart failure cohort by intensive care unit admission and length of hospital stay (≤7 days and >7 days) as proxy measures of severity. To avoid conditioning on the future and potential immortal time bias, we changed the index date to 30 days after the admission date, with subsequent

Table 1. Characteristics of Patients Hospitalized With First-Time Heart Failure and Members of the General Population Comparison Cohort, Denmark, 1980–2012

	Heart Failure Cohort (n=289 353), n (%)	Comparison Cohort (n=1 446 765), n (%)	*P* Value
Male	150 349 (52.0)	751 745 (52.0)	1
Age			
<60 y	28 760 (9.9)	144 113 (10.0)	0.723
60–69 y	51 260 (17.7)	256 959 (17.8)	0.558
70–79 y	96 894 (33.5)	484 451 (33.5)	0.989
≥80 y	112 439 (38.9)	561 242 (38.8)	0.507
Median (interquartile range)	77 (69–84)	77 (69–83)	0.618
Decade of diagnosis			
1980–1989	92 148 (31.8)	460 740 (31.8)	1
1990–1999	97 377 (33.7)	486 885 (33.7)	1
2000–2012	99 828 (34.5)	499 140 (34.5)	1
Comorbidities			
Myocardial infarction	43 985 (15.2)	58 177 (4.0)	<0.001
Angina pectoris	42 939 (14.8)	72 278 (5.0)	<0.001
Atrial fibrillation or flutter	31 001 (10.7)	47 136 (3.3)	<0.001
Valvular heart disease	11 480 (4.0)	11 558 (0.8)	<0.001
Hypertension	38 251 (13.2)	86 932 (6.0)	<0.001
Intermittent claudication	4570 (1.6)	7342 (0.5)	<0.001
Venous thromboembolism	9291 (3.2)	23 728 (1.6)	<0.001
Hypercholesterolemia	6041 (2.1)	11 656 (0.8)	<0.001
Hypertriglyceridemia	1820 (0.6)	2667 (0.2)	<0.001
Obesity	11 989 (4.1)	17 018 (1.2)	<0.001
Diabetes mellitus	29 147 (10.1)	49 177 (3.4)	<0.001
Chronic kidney disease	8191 (2.8)	10 505 (0.7)	<0.001
Cancer	31 942 (11.0)	122 368 (8.5)	<0.001
Chronic pulmonary disease	40 766 (14.1)	66 023 (4.6)	<0.001
Alcoholism-related disease	7609 (2.6)	15 827 (1.1)	<0.001
Dementia	4808 (1.7)	23 003 (1.6)	0.005

new matching at this point in time. We excluded patients who died or had stroke within 30 days in this analysis.

In all sensitivity analyses, a 1- to 5-year instead of a 1- to 30-year follow-up period was applied for long-term risk assessment.

All statistical analyses were performed using SAS version 9.2. According to Danish law, no approval from an ethics committee or informed consent from patients was required for this registry-based study. The study was approved by the Danish Data Protection Agency (record numbers: 1-16-02-1-08 and 2011-41-5755).

Results

The study comprised 289 353 heart failure patients and 1 446 765 individuals from the general population (Table 1). Because of the study design, the distribution of age, sex, and calendar year of the index date was the same for both cohorts. The median follow-up was 1.9 years (interquartile range, 0.2–5.1 years) for the heart failure cohort and 6.7 years (interquartile range, 3.2–11.9 years) for the general population comparison cohort. Competing mortality largely explains the difference in median follow-up. Heart failure patients had a higher prevalence of cardiac and noncardiac comorbidity than people from the general population (Table 1).

Ischemic Stroke

Cumulative incidence curves for the heart failure and general population cohorts are shown in Figure 1. During the first 5 years, patients with heart failure had a slightly higher absolute risk of ischemic stroke than individuals from the general population (Table 2 and Figure 1; and Table II in the online-only Data Supplement). After 5 years, the absolute risk of ischemic stroke was somewhat lower for heart failure patients than for the general population cohort because of competing mortality. In the Cox regression analysis, the 30-day aSRR was 5.08 (95% CI, 4.58–5.63). It declined but remained elevated during

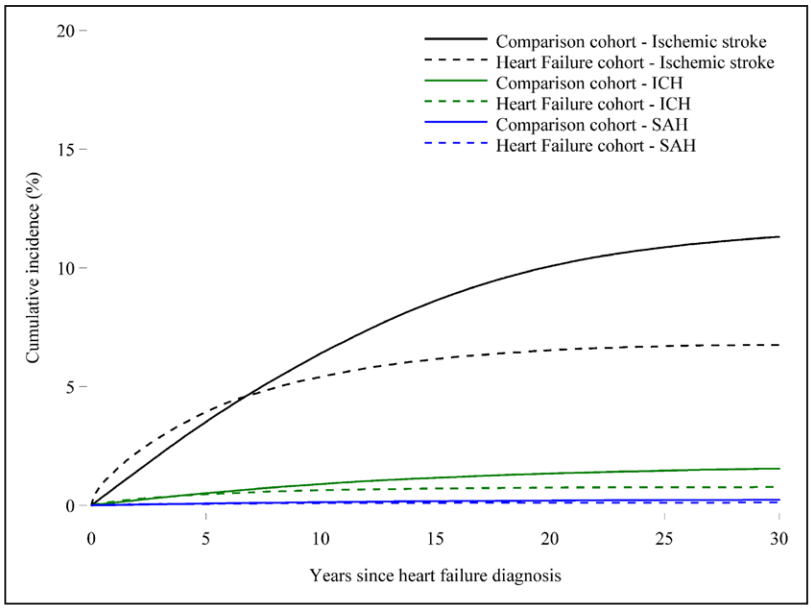


Figure 1. Cumulative 30-year incidence curve for ischemic stroke, ICH, and SAH in patients with incident heart failure compared with the general population comparison cohort. ICH indicates intracerebral hemorrhage; and SAH, subarachnoid hemorrhage.

31 to 365 days of follow-up (aSRR=2.08; 95% CI, 1.99–2.18) and during 1 to 30 years of follow-up (aSRR=1.54; 95% CI, 1.51–1.58; Table 2). Standardized incidence ratio estimates agreed closely with unadjusted stroke rate ratios (Table 2), and the associations between heart failure and ischemic stroke persisted in patients without atrial fibrillation or atrial flutter (Table 3).

Hemorrhagic Stroke

During the first 5 years of follow-up, absolute risks of ICH and SAH were similar for heart failure patients and the general population comparison cohort. After 5 years, absolute risks decreased for the heart failure cohort because of competing mortality (Figure 1). The 30-day aSRRs of ICH and SAH were increased (2.13 [95% CI, 1.53–2.97] and 3.52 [95% CI, 1.54–8.08], respectively) and remained 1.1- to 1.8- fold increased from 31 days to 30 years of follow-up (Table 2).

Stroke Risk Over Time

Temporal changes in stroke risk are illustrated in Figure 2. For ischemic stroke, a slight increase was seen in the 30-day aSRR over the 3 decades. In contrast, the aSRR slightly decreased for the 31- to 365-day and 1- to 5-year follow-up periods. For ICH, the aSRR remained stable during the 3 decades.

Subgroup and Sensitivity Analyses

Analyses stratified by age, sex, and cardiac comorbidity are presented in Table III in the online-only Data Supplement. For ischemic stroke, the aSRRs were similar for men and women. Although the aSRR for ischemic stroke decreased with age, the age-stratified results were consistent with the pattern reported for the main analysis (Table III the online-only Data Supplement).

The results were not appreciably different in any of the sensitivity analyses (Tables IV–X in the online-only Data Supplement). Within the first year of follow-up, the association between heart failure and ischemic stroke was stronger for patients admitted than for those not admitted to the intensive care unit and for those with length of stay >7 days than for those with length of stay ≤7 days (Table X in the online-only Data Supplement).

Discussion

In this nationwide cohort study, heart failure was associated with increased risks of ischemic stroke, ICH, and SAH over both the short and long term, and risks did not differ over 3 decades of follow-up. The associations persisted in patients without atrial fibrillation or flutter, across age groups, and sex, and remained robust in sensitivity analyses.

In accordance with previous studies, we found that heart failure is a strong risk factor for ischemic stroke, especially over the short term. A US cohort study of 630 heart failure patients reported a 17-fold elevated 30-day ischemic stroke risk compared with the general population, which persisted over 5 years.[6] These findings were supported by a UK study reporting 2- to 3-fold higher odds for prevalent stroke in heart failure patients compared with the general population.[7] Similar to these results, a Danish study of 1239 heart failure patients in the Diet, Cancer and Health Cohort reported an ischemic stroke rate ratio of 2.3 (95% CI, 1.8–3.0) and a 30-day relative risk for the composite outcome of death and all strokes of 35.7 (95% CI, 27.5–46.4). Although the association leveled out, it persisted over time (6 months to 14 years).[15] Similarly, a Dutch cohort study of 1247 heart failure patients found that the rate of ischemic strokes was elevated in the first 6 months after a heart failure diagnosis. In contrast to our findings, the risk then converged to or became even lower than the risk of the general population.[5] The Danish Diet, Cancer and Health Cohort study also reported elevated hemorrhagic stroke risk (adjusted hazard ratio, 1.8; 95% CI, 1.0–3.3) in heart failure patients,[15] while another study found a decreased hemorrhagic stroke risk (hazard ratio, 0.80; 95% CI, 0.37–1.76)[5] among heart failure patients relative to the general population. Our

Table 2. Risk of Stroke in Heart Failure Patients and Members of the General Population Comparison Cohort, by Type of Stroke and Follow-Up Time

	Number at Risk/ No. of Events	Risk, % (95% CI)	SIR (95% CI)	Stroke Rate Ratio Controlled for Matching Factors* (95% CI)	*P* Value	Fully Adjusted Stroke Rate Ratio† (95% CI)	*P* Value
Ischemic stroke							
0–30 days							
CC cohort	1 446 765/886	0.06 (0.06–0.07)	Reference	Reference		Reference	
HF cohort	289 353/883	0.31 (0.29–0.33)	5.30 (4.96–5.67)	5.68 (5.16–6.26)	<0.001	5.08 (4.58–5.63)	<0.001
31–365 days							
CC cohort	1 438 164/9677	0.67 (0.66–0.69)	Reference	Reference		Reference	
HF cohort	238 274/3227	1.36 (1.31–1.40)	2.19 (2.12–2.27)	2.39 (2.29–2.49)	<0.001	2.08 (1.99–2.18)	<0.001
1–30 y							
CC cohort	1 345 483/112 000	11.35 (11.29–11.42)	Reference	Reference		Reference	
HF cohort	176 288/12 218	8.73 (8.57–8.89)	1.64 (1.61–1.67)	1.74 (1.70–1.78)	<0.001	1.54 (1.51–1.58)	<0.001
Intracerebral hemorrhage							
0–30 days							
CC cohort	1 446 765/153	0.01 (0.01–0.01)	Reference	Reference		Reference	
HF cohort	289 353/62	0.02 (0.02–0.03)	2.45 (1.87–3.14)	2.18 (1.62–2.94)	<0.001	2.13 (1.53–2.97)	<0.001
31–365 days							
CC cohort	1 438 164/1476	0.10 (0.10–0.11)	Reference	Reference		Reference	
HF cohort	238 274/395	0.17 (0.15–0.18)	1.81 (1.64–2.00)	1.97 (1.75–2.22)	<0.001	1.83 (1.62–2.07)	<0.001
1–30 y							
CC cohort	1 345 483/14 024	1.53 (1.50–1.56)	Reference	Reference		Reference	
HF cohort	176 288/1327	0.98 (0.93–1.04)	1.38 (1.30–1.45)	1.45 (1.35–1.54)	<0.001	1.37 (1.28–1.46)	<0.001
Subarachnoid hemorrhage							
0–30 days							
CC cohort	1 446 765/23	0.00 (0.00–0.00)	Reference	Reference		Reference	
HF cohort	289 353/15	0.01 (0.00–0.01)	4.24 (2.37–7.00)	3.55 (1.83–6.89)	<0.001	3.52 (1.54–8.08)	0.003
31–365 days							
CC cohort	1 438 164/219	0.02 (0.01–0.02)	Reference	Reference		Reference	
HF cohort	238 274/63	0.03 (0.02–0.03)	2.01 (1.54–2.57)	1.90 (1.42–2.55)	<0.001	1.70 (1.24–2.34)	0.001
1–30 y							
CC cohort	1 345 483/2080	0.23 (0.22–0.24)	Reference	Reference		Reference	
HF cohort	176 288/185	0.14 (0.12–0.17)	1.23 (1.06–1.42)	1.18 (1.00–1.39)	0.056	1.13 (0.95–1.35)	0.178

CC indicates comparison cohort; CI, confidence interval; HF, heart failure; and SIR, standardized incidence ratio.

*Adjusted for matching factors (age, sex, calendar decade of heart failure diagnosis).

†Adjusted for matching factors, myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, intermittent claudication, venous thromboembolism, hypercholesterolemia, hypertriglyceridemia, hypertension, obesity, diabetes, chronic kidney disease, cancer, chronic pulmonary disease, alcoholism-related disorders, and dementia.

study complements and extends knowledge about long-term stroke risk and risk of stroke subtypes among patients with heart failure.

Several mechanisms are thought to underlie the increased risk of ischemic stroke in heart failure patients. One is formation of thrombi in the dilated, hypokinetic left ventricle because of wall-motion abnormalities and in the left atrium because of atrial fibrillation. In addition to shared stroke risk factors, heart failure is also associated with increased activity of procoagulant factors, aggregation of thrombocytes, and endothelial dysfunction.[3] Changes in cardiovascular risk factors over time could be a part of the causal pathway to a subsequent stroke, and thus, they were not adjusted for in the analyses. Clinical pathways leading to the increased risk of hemorrhagic stroke are less well characterized and likely multifactorial, but may in part reflect a higher use of

Table 3. Risk of Stroke Among Heart Failure Patients With and Without Atrial Fibrillation or Flutter, by Stroke Subtype

	Risk, % (95% CI)	Fully Adjusted Stroke Rate Ratio* (95% CI)	*P* Value
No atrial fibrillation or atrial flutter			
Ischemic stroke			
0–30 days	0.29 (0.27–0.31)	5.49 (4.95–6.10)	<0.001
31–365 days	1.26 (1.21–1.31)	2.18 (2.09–2.28)	<0.001
1–30 y	8.48 (8.31–8.64)	1.52 (1.49–1.55)	<0.001
Intracerebral hemorrhage			
0–30 days	0.02 (0.02–0.03)	2.57 (1.86–3.55)	<0.001
31–365 days	0.16 (0.14–0.18)	1.78 (1.58–2.02)	<0.001
1–30 y	0.95 (0.89–1.01)	1.33 (1.25–1.41)	<0.001
Subarachnoid hemorrhage			
0–30 days	0.01 (0.00–0.01)	4.09 (1.99–8.38)	<0.001
31–365 days	0.03 (0.02–0.03)	1.95 (1.42–2.66)	<0.001
1–30 y	0.14 (0.11–0.16)	1.08 (0.92–1.28)	0.343
Atrial fibrillation or atrial flutter			
Ischemic stroke			
0–30 days	0.41 (0.35–0.49)	2.84 (2.13–3.78)	<0.001
31–365 days	2.13 (1.96–2.31)	1.40 (1.26–1.57)	<0.001
1–30 y	11.11 (10.48–11.77)	1.07 (1.00–1.13)	0.041
Intracerebral hemorrhage			
0–30 days	0.02 (0.01–0.04)	0.66 (0.23–1.90)	0.442
31–365 days	0.22 (0.17–0.28)	1.24 (0.88–1.74)	0.216
1–30 y	1.39 (1.13–1.70)	1.05 (0.87–1.27)	0.584
Subarachnoid hemorrhage			
0–30 days	0.01 (0.00–0.02)	0.75 (0.09–6.54)	0.798
31–365 days	0.03 (0.02–0.06)	1.27 (0.51–3.14)	0.606
1–30 y	0.19 (0.12–0.30)	1.55 (0.93–2.59)	0.095

CI indicates confidence interval.

*Adjusted for matching factors, myocardial infarction, angina pectoris, valvular heart disease, intermittent claudication, venous thromboembolism, hypercholesterolemia, hypertriglyceridemia, hypertension, obesity, diabetes mellitus, chronic kidney disease, cancer, chronic pulmonary disease, alcoholism-related disorders, and dementia.

antithrombotic drugs in the heart failure cohort than in the general population comparison cohort during follow-up.

Use of antithrombotic agents to reduce ischemic stroke risk among heart failure patients in sinus rhythm has been debated during recent years.[2] Because of null findings in randomized trials, anticoagulants have not been included in international treatment recommendations for heart failure patients without atrial fibrillation.[2] However, the WARCEF substudy (Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction) of heart failure patients in sinus rhythm reported that longer time in the therapeutic range among patients allocated to warfarin reduced the risk of the primary outcome (ischemic stroke, ICH, or death) and death alone and also improved net clinical benefit.[24] Heart failure patients with particularly high stroke risk include those with severely impaired left ventricular ejection fraction[9,12,13] and with high risk scores for atrial fibrillation.[25] The potential benefit of ischemic stroke prevention, including use of anticoagulants in heart failure patients without atrial fibrillation who are at high risk of stroke, and the role of non–vitamin K oral antagonists remains to be elucidated.

Our study benefitted from a large sample size, nationwide coverage, and virtually complete follow-up for 30 years. The risk of selection bias was, thus, minimized. The positive predictive value of diagnoses of ischemic stroke in the DNPR is 97% (using medical records as reference).[17] However, the positive predictive values are somewhat lower for heart failure (~80%–100%),[26] ICH (74%), and SAH (67%).[17] Because recording of stroke subtypes is likely independent of the presence or absence of heart failure, any misclassification would be nondifferential and, thus, would bias our results toward

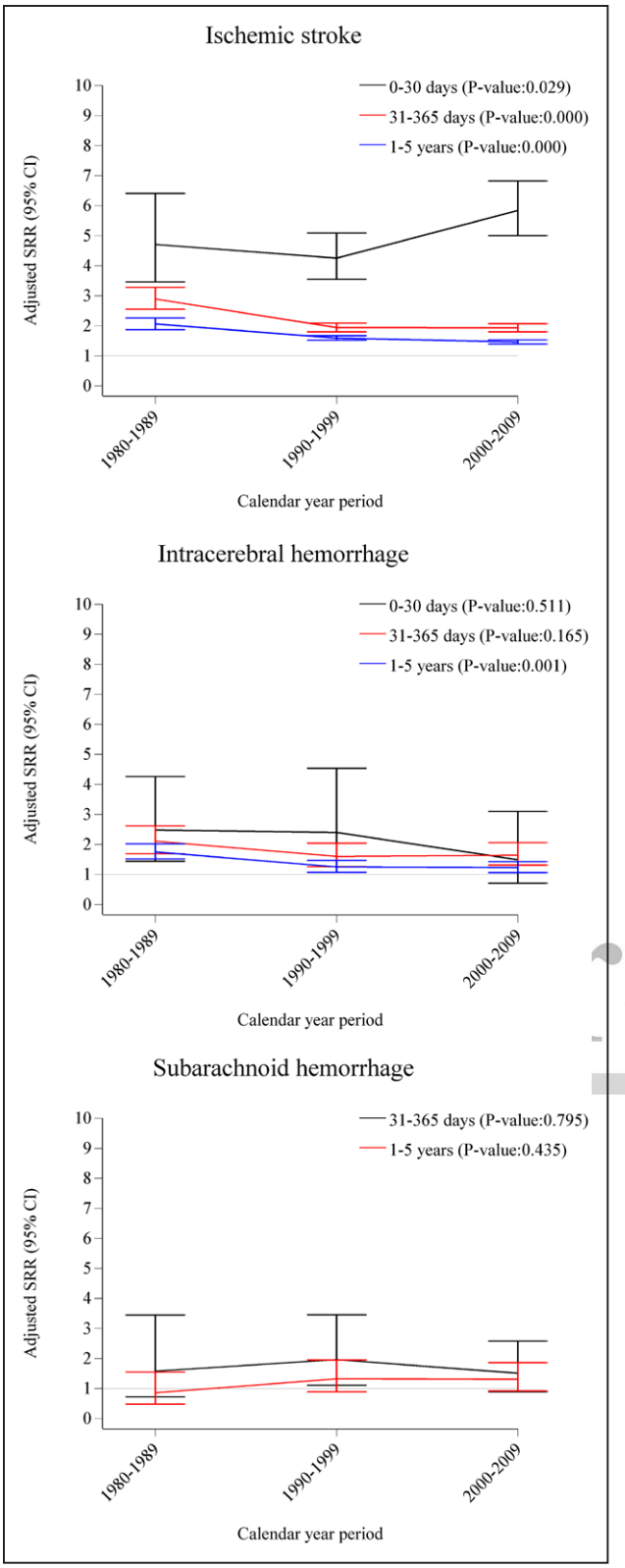


Figure 2. Short- and long-term temporal trends in the adjusted stroke rate ratio (SRR) for heart failure patients compared with the general population during 1980 to 2009, with 95% confidence intervals (CIs). Adjusted SRR for 0 to 30 days omitted for subarachnoid hemorrhage because of insufficient numbers.

the null.[20] We adjusted for a range of confounders, but cannot exclude unmeasured confounders, such as physical activity. We lacked data on left ventricular ejection fraction. We could, therefore, not separately assess the potential differences in stroke risk among heart failure patients with reduced left ventricular ejection fraction and in those with preserved ventricular ejection fraction. However, analyses stratified by proxy measures of heart failure severity—intensive care unit admission and length of hospital stay—suggested that stroke risk may indeed be greater among patients whose left ventricular ejection fractions are reduced.

Conclusions

In this nationwide cohort study, heart failure was associated with increased hazard of ischemic stroke, ICH, and SAH, especially in the short term but also in the long term, suggesting that heart failure is an important risk factor for all types of stroke. This finding highlights the importance of clinical attention to stroke risk among heart failure patients. Further studies on potential prevention strategies are warranted.

Sources of Funding

The study was supported by Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation.

Disclosures

None.

References

1. Roger VL. Epidemiology of heart failure. *Circ Res*. 2013;113:646–659. doi: 10.1161/CIRCRESAHA.113.300268.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:e147–e239. doi: 10.1016/j.jacc.2013.05.019.
3. Haeusler KG, Laufs U, Endres M. Chronic heart failure and ischemic stroke. *Stroke*. 2011;42:2977–2982. doi: 10.1161/STROKEAHA.111.628479.
4. Sacco RL, Benjamin EJ, Broderick JP, Dyken M, Easton JD, Feinberg WM, et al. American Heart Association Prevention Conference. IV. Prevention and Rehabilitation of Stroke. Risk factors. *Stroke*. 1997;28:1507–1517.
5. Alberts VP, Bos MJ, Koudstaal P, Hofman A, Witteman JC, Stricker B, et al. Heart failure and the risk of stroke: the Rotterdam Study. *Eur J Epidemiol*. 2010;25:807–812. doi: 10.1007/s10654-010-9520-y.
6. Witt BJ, Brown RD Jr, Jacobsen SJ, Weston SA, Ballman KV, Meverden RA, et al. Ischemic stroke after heart failure: a community-based study. *Am Heart J*. 2006;152:102–109. doi: 10.1016/j.ahj.2005.10.018.
7. Pullicino PM, McClure LA, Wadley VG, Ahmed A, Howard VJ, Howard G, et al. Blood pressure and stroke in heart failure in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Stroke*. 2009;40:3706–3710. doi: 10.1161/STROKEAHA.109.561670.
8. Kannel WB, Wolf PA, Verter J. Manifestations of coronary disease predisposing to stroke. The Framingham study. *JAMA*. 1983;250:2942–2946.
9. Freudenberger RS, Hellkamp AS, Halperin JL, Poole J, Anderson J, Johnson G, et al; SCD-HeFT Investigators. Risk of thromboembolism in heart failure: an analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation*. 2007;115:2637–2641. doi: 10.1161/CIRCULATIONAHA.106.661397.
10. Szummer KE, Solomon SD, Velazquez EJ, Kilaru R, McMurray J, Rouleau JL, et al; VALIANT Registry. Heart failure on admission and the risk of stroke following acute myocardial infarction: the VALIANT

registry. *Eur Heart J*. 2005;26:2114–2119. doi: 10.1093/eurheartj/ehi352.
11. Mahaffey KW, Harrington RA, Simoons ML, Granger CB, Graffagnino C, Alberts MJ, et al. Stroke in patients with acute coronary syndromes: incidence and outcomes in the platelet glycoprotein IIb/IIIa in unstable angina. Receptor suppression using integrilin therapy (PURSUIT) trial. The PURSUIT Investigators. *Circulation*. 1999;99:2371–2377.
12. Loh E, Sutton MS, Wun CC, Rouleau JL, Flaker GC, Gottlieb SS, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. *N Engl J Med*. 1997;336:251–257. doi: 10.1056/NEJM199701233360403.
13. Dries DL, Rosenberg YD, Waclawiw MA, Domanski MJ. Ejection fraction and risk of thromboembolic events in patients with systolic dysfunction and sinus rhythm: evidence for gender differences in the studies of left ventricular dysfunction trials. *J Am Coll Cardiol*. 1997;29:1074–1080.
14. Sampson UK, Pfeffer MA, McMurray JJ, Lokhnygina Y, White HD, Solomon SD; VALIANT Trial Investigators. Predictors of stroke in high-risk patients after acute myocardial infarction: insights from the VALIANT Trial. *Eur Heart J*. 2007;28:685–691. doi: 10.1093/eurheartj/ehl197.
15. Lip GY, Rasmussen LH, Skjoth F, Overvad K, Larsen TB. Stroke and mortality in patients with incident heart failure: the Diet, Cancer and Health (DCH) cohort study. *BMJ Open*. 2012;2:pii: E000975. doi: 10.1136/bmjopen-2012-000975.
16. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541–549. doi: 10.1007/s10654-014-9930-3.
17. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490. doi: 10.2147/CLEP.S91125.
18. Stuart EA. Matching methods for causal inference: a review and a look forward. *Stat Sci*. 2010;25:1–21. doi: 10.1214/09-STS313.
19. Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology*. 2007;28:150–154. doi: 10.1159/000102143.
20. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
21. Therneau T. The Cox Model. In: Dietz K, Gail M, Krickeberg K, Samet J, Tsiatis A, eds. *Modeling Survival Data: Extending the Cox Model*. New York: Springer-Verlag; 2000:44–48.
22. Ken Rothman's Episheet, Modern Epidemiology [online]. http://www.krothman.org/episheet.xls. Accessed January 30, 2017.
23. Johannesdottir SA, Horváth-Puhó E, Ehrenstein V, Schmidt M, Pedersen L, Sørensen HT. Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. *Clin Epidemiol*. 2012;4:303–313. doi: 10.2147/CLEP.S37587.
24. Homma S, Thompson JL, Qian M, Ye S, Di Tullio MR, Lip GY, et al; WARCEF Investigators. Quality of anticoagulation control in preventing adverse events in patients with heart failure in sinus rhythm: Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction trial substudy. *Circ Heart Fail*. 2015;8:504–509. doi: 10.1161/CIRCHEARTFAILURE.114.001725.
25. Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GY. Assessment of the CHA2DS2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. *JAMA*. 2015;314:1030–1038. doi: 10.1001/jama.2015.10725.
26. Adelborg K, Sundbøll J, Munch T, Frøslev T, Sørensen HT, Bøtker HE, et al. Positive predictive value of cardiac examination, procedure and surgery codes in the Danish National Patient Registry: a population-based validation study. *BMJ Open*. 2016;6:e012817. doi: 10.1136/bmjopen-2016-012817.

Risk of Stroke in Patients With Heart Failure: A Population-Based 30-Year Cohort Study

Kasper Adelborg, Szimonetta Szépligeti, Jens Sundbøll, Erzsébet Horváth-Puhó, Victor W. Henderson, Anne Ording, Lars Pedersen and Henrik Toft Sørensen

Stroke. published online April 4, 2017;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

SUPPLEMENTAL MATERIAL

Risk of Stroke in Patients with Heart Failure:

A Population-Based 30-Year Cohort Study

Kasper Adelborg, MD[1]; Szimonetta Szépligeti, MSc[1]; Jens Sundbøll, MD[1]; Erzsébet Horváth-Puhó, PhD[1]; Victor W. Henderson, MD, MS[1,2,3]; Anne Ording, PhD[1]; Lars Pedersen, PhD[1]; Henrik Toft Sørensen, MD, PhD, DMSc[1,2]

Contents

Supplemental Table I. *International Classification of Diseases* (ICD) codes.

	ICD-8 codes	ICD-10 codes
Heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Stroke		
Ischemic stroke	433-434	I63-I64
Specified ischemic stroke	433-434	I63
Unspecified ischemic stroke		I64
Intracerebral hemorrhage	431	I61
SAH	430	I60
Transient ischemic attack	435	G45.9
Computed tomography (CT) scan*	N/A	UXCA
Magnetic resonance imaging (MRI)*	N/A	UXMA
Comorbidities		
Myocardial infarction	410	I21
Angina pectoris	413	I20 (except I20.0), I25.1, og I25.9
Atrial fibrillation or flutter	427.93, 427.94	I48
Valvular heart disease	394-398	I05, I06, I07, I08.0, I09.8, I34-I37, I39.0, I39.3, I51.1A, Q22
Hypertension	400-404	DI10-DI15, I67.4
Intermittent claudication	443.89-443.99	I73.9
Venous thromboembolism	450.99, 451.00	I26, I80.1-3
Hypercholesterolemia	27200	E780
Hypertriglyceridemia	27201	E781-785
Other diseases		
Obesity	277	E65-E68
Diabetes mellitus	249, 250 (excluding 249.02, 250.02)	E10, E11, H36.0 (excluding E10.2 and E11.2)
Chronic kidney disease	249.02, 250.02, 753.10-	E10.2, E11.2, E14.2, N03, N05,

	753.19, 582, 583, 584, 590.09, 593.20, 792	N11.0, N14; N16, N18-N19, N26.9, Q61.1-Q61.4
Cancer	140-209, 28710	C00-C99, D45, D473
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Alcoholism-related diseases	291, 303, 456, 571.09, 571.10, 577.10	F10.1-9, G31.2, G62.1, G72.1, I 42.6, K29.2, K86.0, Z72.1;
Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30

Antithrombotic drugs: B01A
Angiotensin converting enzyme inhibitors: C09A, C09B
Betablockers: C07
*Codes for these examinations, not ICD-10 codes.

Supplemental Table II. Risk of stroke in patients with heart failure and the general population comparison cohort, by stroke type and follow-up period.

	0-1 year risk, % (95% CI)		**0-3 year risk, % (95% CI)**		**0-5 year risk, % (95% CI)**	
	Heart failure cohort	**General population comparison cohort**	**Heart failure cohort**	**General population comparison cohort**	**Heart failure cohort**	**General population comparison cohort**
Ishemic stroke	1.42 (1.38–1.47)	0.73 (0.72–0.74)	2.88 (2.82–2.94)	2.16 (2.14–2.18)	3.94 (3.86–4.01)	3.52 (3.49–3.55)
ICH	0.16 (0.15–0.17)	0.11 (0.11–0.12)	0.34 (0.32–0.36)	0.32 (0.32–0.33)	0.47 (0.45–0.50)	0.51 (0.50–0.53)
SAH	0.03 (0.02–0.03)	0.02 (0.01–0.02)	0.05 (0.05–0.06)	0.05 (0.04–0.05)	0.07 (0.06–0.08)	0.08 (0.07–0.08)

Abbreviations: CI: confidence interval, ICH: intracerebral hemorrhagic, SAH: subarachnoid hemorrhage

Supplemental Table III. Risk of stroke in patients with heart failure compared with a general population comparison cohort, by selected subgroups of heart failure patients.

	0-30 days		31-365 days		1-30 years	
	Risk among heart failure patients, % (95% CI)	**Fully-adjusted stroke rate ratio (95% CI)***	**Risk among heart failure patients, % (95% CI)**	**Fully-adjusted stroke rate ratio (95% CI)***	**Risk among heart failure patients, % (95% CI)**	**Fully-adjusted stroke rate ratio (95% CI)***
Ischemic stroke						
Sex						
Female	0.32 (0.29–0.35)	5.15 (4.47–5.94)	1.44 (1.38–1.52)	2.08 (1.96–2.20)	8.99 (8.77–9.22)	1.52 (1.48–1. 56)
Male	0.29 (0.26–0.32)	4.69 (4.08–5.39)	1.27 (1.21–1.34)	1.92 (1.81–2.04)	8.47 (8.25–8.70)	1.43 (1.39–1.47)
Age						
<60 years	0.25 (0.20–0.32)	24.05 (13.62–42.44)	0.83 (0.72–0.94)	7.11 (5.58–9.04)	11.06 (10.43–11.71)	1.92 (1.79–2.06)
60-69 years	0.32 (0.27–0.37)	15.64 (11.17–21.90)	1.02 (0.93–1.11)	2.92 (2.54–3.34)	10.38 (9.99–10.79)	1.69 (1.61–1.77)
70-79 years	0.30 (0.26–0.33)	5.68 (4.71–6.84)	1.41 (1.33–1.49)	2.13 (1.97–2.30)	9.00 (8.75–9.26)	1.42 (1.38–1.47)
≥80 years	0.32 (0.29–0.36)	3.28 (2.86–3.75)	1.64 (1.55–1.72)	1.63 (1.54–1.73)	(.–.)	1.24 (1.20–1.29)
Comorbidities						
No myocardial infarction	0.29 (0.27–0.31)	5.12 (4.61–5.69)	1.33 (1.28–1.39)	2.11 (2.02–2.21)	8.64 (8.47–8.81)	1.50 (1.47–1.53)
Previous myocardial infarction	0.39 (0.34–0.46)	4.77 (3.51–6.49)	1.47 (1.35–1.60)	1.56 (1.39–1.76)	9.30 (8.86–9.76)	1.17 (1.10–1.24)
No angina	0.29 (0.27–0.31)	5.25 (4.72–5.84)	1.28 (1.23–1.33)	2.12 (2.02–2.22)	8.39 (8.22–8.55)	1.50 (1.47–1.53)
Previous angina	0.41 (0.35–0.47)	4.03 (3.08–5.26)	1.75 (1.62–1.89)	1.63 (1.46–1.81)	10.92 (10.37–11.48)	1.22 (1.16–1.29)
No valvular heart disease	0.30 (0.28–0.32)	5.15 (4.66–5.70)	1.33 (1.29–1.38)	2.06 (1. 98–2.15)	8.66 (8.50–8.82)	1.48 (1.45–1.51)
Valvular heart disease	0.52 (0.40–0.67)	5.16 (2.89–9.19)	1.85 (1.60–2.14)	1.61 (1.29–2.00)	10.73 (9.76–11.76)	1.14 (1.01–1.28)
No hypertension	0.28 (0.26–0.30)	5.35 (4.81–5.97)	1.23 (1.19–1.28)	2.09 (2.00–2.19)	8.34 (8.18–8.51)	1.49 (1.46–1.52)
Hypertension	0.48 (0.42–0.55)	3.98 (3.12–5.08	2.12 (1.97–2.28)	1.76 (1.59–1. 95)	11.69 (11.10–12.30)	1.28 (1.21–1.35)
Intracerebral hemorrhagic						
Sex						
Female	0.02 (0.01–0.02)	1.42 (0.86–2.34)	0.15 (0.13–0.18)	1.52 (1.28–1.81)	0.95 (0.87–1.03)	1.32 (1.22–1.44)
Male	0.03 (0.02–0.04)	3.18 (2.12–4.76)	0.18 (0.16–0.21)	1.94 (1.65–2. 28)	1.02 (0.94–1.11)	1.29 (1.19–1.40)

Age						
<60 years	0.04 (0.02–0.07)	47.50 (10.27–219.61)	0.15 (0.11–0.20)	3.87 (2.24–6.69)	1.27 (1.04–1.52)	1.59 (1.30–1.94)
60-69 years	0.02 (0.01–0.04)	5.48 (2.30–13.01)	0.17 (0.13–0.21)	3.07 (2.24–4.22)	1.26 (1.11–1.42)	1.58 (1.40–1.80)
70-79 years	0.02 (0.01–0.03)	1.81 (0.99–3.31)	0.19 (0.16–0.22)	1.81 (1.48–2.21)	1.03 (0.94–1.12)	1.21 (1.10–1.33)
≥80 years	0.02 (0.01–0.03)	1.41 (0.88–2.26)	0.15 (0.13–0.18)	1.25 (1.04–1.50)	(.–.)	1.09 (0.98–1.22)
Comorbidities						
No myocardial infarction	0.02 (0.02–0.03)	2.17 (1.57–3.01)	0.17 (0.16–0.19)	1.75 (1.54–1.97)	1.01 (0.94–1.07)	1.33 (1.25–1.41)
Previous myocardial infarction	0.02 (0.01–0.04)	2.62 (0.82–8.32)	0.12 (0.09–0.17)	1.37 (0.91–2.05)	0.86 (0.72–1.01)	1.07 (0.89–1. 30)
No angina	0.02 (0.02–0.03)	2.30 (1.67–3.18)	0.17 (0.15–0.19)	1.75 (1.55–1.98)	0.97 (0.91–1.04)	1.33 (1.24–1.41)
Previous angina	0.01 (0.00–0.03)	1.28 (0.40–4.05)	0.15 (0.12–0.20)	1.40 (0.98–1.99)	1.05 (0.89–1.24)	1.13 (0.95–1.34)
No valvular heart disease	0.02 (0.02–0.03)	2.18 (1.59–2.99)	0.16 (0.15–0.18)	1.70 (1.51–1.91)	0.96 (0.90–1.02)	1.30 (1.23–1. 39)
Valvular heart disease	0.02 (0.00–0.06)	4.37 (0.39–49.50)	0.26 (0.18–0.38)	2.07 (1.10–3.91)	1.71 (1.29–2.23)	1.21 (0.88–1.68)
No hypertension	0.02 (0.02–0.03)	2.14 (1.52–3.00)	0.16 (0.14–0.18)	1.83 (1.61–2.07)	0.94 (0.88–1.00)	1.29 (1.21–1.38)
Hypertension	0.03 (0.02–0.05)	2.61 (1.13–6.02)	0.21 (0.17–0.27)	1.14 (0. 85–1.53)	1.39 (1.16–1.66)	1.29 (1. 10–1.52)
Subarachnoid hemorrhage						
Sex						
Female	0.00 (0.00–0.01)	2.55 (0.87–7.47)	0.02 (0.01–0.03)	1.32 (0.83–2.12)	0.16 (0.13–0.19)	1.17 (0.94–1.46)
Male	0.01 (0.00–0.01)	3.72 (1.49–9.29)	0.03 (0.02–0.04)	2.23 (1.51–3.31)	0.13 (0.10–0.16)	1.07 (0.85–1. 35)
Age						
<60 years	0.01 (0.00–0.03)	21.31 (1.93–235.04)	0.03 (0.02–0.07)	2.06 (0.81–5.24)	0.29 (0.20–0.42)	1.10 (0.75–1.62)
60-69 years	0.00 (0.00–0.01)	0.91 (0.10–8.68)	0.02 (0.01–0.04)	1.53 (0.73–3.23)	0.18 (0.13–0.24)	1.07 (0.77–1.50)
70-79 years	0.01 (0.00–0.01)	3.44 (1.18–10.03)	0.03 (0.02–0.04)	2.28 (1.36–3.82)	0.12 (0.09–0.15)	1.11 (0.85–1.46)
≥80 years	0.00 (0.00–0.01)	3.40 (1.01–11.47)	0.02 (0.02–0.04)	1.49 (0.91–2.43)	(.–.)	1.16 (0.85–1.60)
Comorbidities						
No myocardial infarction	0.01 (0.00–0.01)	3.33 (1.67–6.66)	0.03 (0.02–0.03)	1.90 (1.38–2.62)	0.14 (0.12–0.17)	1.10 (0.93–1.30)

Previous myocardial infarction	(.–.)	(.–.)	0.03 (0.02–0.06)	1.62 (0.71–3.72)	0.14 (0.09–0.21)	1.42 (0.86–2.32)
No angina	0.00 (0.00–0.01)	3.29 (1.55–6.98)	0.03 (0.02–0.03)	2.01 (1.47–2.77)	0.14 (0.12–0.16)	1.15 (0.97–1.36)
Previous angina	0.01 (0.00–0.02)	5.52 (0.56–54.30)	0.03 (0.01–0.05)	1.08 (0.48–2.42)	0.20 (0.11–0.35)	0.98 (0.63–1.53)
No valvular heart disease	0.01 (0.00–0.01)	3.44 (1.71–6.92)	0.03 (0.02–0.03)	1.84 (1.35–2.50)	0.14 (0.12–0.16)	1.12 (0.95–1.32)
Valvular heart disease	0.01 (0.00–0.05)	(.–.)	0.05 (0.02–0.12)	1.06 (0.24–4.76)	0.21 (0.11–0.39)	1.00 (0.45–2.26)
No hypertension	0.00 (0.00–0.01)	3.10 (1.44–6. 70)	0.02 (0.02–0.03)	1.78 (1.28–2.47)	0.13 (0.11–0.16)	1.10 (0.93–1.31)
Hypertension	0.01 (0.00–0.03)	4.86 (0.81–29. 01)	0.04 (0.02–0.06)	1.70 (0.79–3. 64)	0.17 (0.12–0.25)	1.15 (0.76–1. 74)

*Adjusted for age, sex, calendar year, myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, intermittent claudication, venous thromboembolism, hypercholesterolemia, hypertriglyceridemia, hypertension, obesity, diabetes, chronic kidney disease, cancer, chronic pulmonary disease, alcoholism-related disorders, and dementia (except as a stratifying variable).
Abbreviation: CI: confidence interval.
(.-.) Insufficient number for estimates.

Supplemental Table IV. Risk of stroke in heart failure patients and the general population comparison cohort. Computed tomography or magnetic resonance imaging of the brain was obtained during the stroke admission (available for patients after year 2000).

	Number at risk/no. events	Risk, % (95% CI)	Stroke rate ratio controlled for matching factors* (95% CI)	Fully-adjusted stroke rate ratio (95% CI)†
Ischemic stroke				
0-30 days				
CC cohort	416,144/271	0.07 (0.06–0.07)	Reference	Reference
HF cohort	182,824/513	0.28 (0.26–0.31)	6.25 (5.34–7.31)	5.66 (4.77–6.72)
31-365 days				
CC cohort	413,644/3043	0.74 (0.71–0.76)	Reference	Reference
HF cohort	156,531/1945	1.25 (1.19–1.30)	2.45 (2.30–2.61)	2.13 (1.99–2.28)
1-5 years				
CC cohort	386,839/10,893	3.21 (3.15–3.27)	Reference	Reference
HF cohort	121,650/4154	3.90 (3.79–4.02)	1.84 (1.76–1.92)	1.64 (1.56–1.71)
Intracerebral hemorrhage				
0-30 days				
CC cohort	416,144/30	0.01 (0.01–0.01)	Reference	Reference
HF cohort	182,824/28	0.02 (0.01–0.02)	2.65 (1.55–4.51)	1.47 (0.71–3.03)
31-365 days				
CC cohort	413,644/371	0.09 (0.08–0.10)	Reference	Reference
HF cohort	156,531/201	0.13 (0.11–0.15)	1.99 (1.64–2.40)	1.89 (1.54–2.30)
1-5 years				
CC cohort	386,839/1331	0.40 (0.38–0.42)	Reference	Reference
HF cohort	121,650/436	0.41 (0.38–0.45)	1.52 (1.34–1.73)	1.37 (1.19–1.57)
Subarachnoid hemorrhage				
0-30 days				
CC cohort	416,144/8	0.00 (0.00–0.00)	Reference	Reference
HF cohort	182,824/7	0.00 (0.00–0.01)	2.86 (0.98–8.35)	1.25 (0.20–7.89)
31-365 days				
CC cohort	413,644/70	0.02 (0.01–0.02)	Reference	Reference
HF cohort	156,531/39	0.03 (0.02–0.03)	1.87 (1.23–2.86)	1.58 (0.97–2.56)
1-5 years				
CC cohort	386,839/251	0.08 (0.07–0.09)	Reference	Reference
HF cohort	121,650/64	0.06 (0.05–0.08)	1.10 (0.81–1.50)	1.01 (0.72–1.43)

* Controlled for matching factors (age, sex, calendar decade of heart failure diagnosis).
† Adjusted for matching factors, myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, intermittent claudication, venous thromboembolism, hypercholesterolemia, hypertriglyceridemia, hypertension, obesity, diabetes, chronic kidney disease, cancer, chronic pulmonary disease, alcoholism-related disorders, and dementia.
Abbreviations: CC: comparison cohort, CI: confidence interval, HF: heart failure.

Supplemental Table V. Risk of specified ischemic stroke and unspecified stroke in heart failure patients and the general population comparison cohort.

	Number at risk/no. events	Risk, % (95% CI)	Stroke rate ratio controlled for matching factors* (95% CI)	Fully-adjusted stroke rate ratio (95% CI)†
Specified ischemic stroke				
0-30 days				
CC cohort	604,940/241	0.04 (0.04–0.05)	Reference	Reference
HF cohort	265,618/518	0.20 (0.18–0.21)	6.94 (5.90–8.15)	6.23 (5.22–7.43)
31-365 days				
CC cohort	601,193/2622	0.44 (0.42–0.45)	Reference	Reference
HF cohort	226,095/1746	0.78 (0.74–0.81)	2.50 (2.34–2.67)	2.21 (2.05–2.38)
1-5 years				
CC cohort	561,223/10,137	2.00 (1.96–2.04)	Reference	Reference
HF cohort	173,549/3831	2.46 (2.38–2.54)	1.85 (1.77–1.94)	1.65 (1.57–1.73)
Unspecified stroke				
0-30 days				
CC cohort	604,940/317	0.05 (0.05–0.06)	Reference	Reference
HF cohort	265,618/764	0.29 (0.27–0.31)	8.25 (7.17–9.50)	7.35 (6.30–8.56)
31-365 days				
CC cohort	601,193/3592	0.60 (0.58–0.62)	Reference	Reference
HF cohort	226,095/2619	1.16 (1.12–1.21)	2.81 (2.66–2.98)	2.42 (2.28–2.57)
1-5 years				
CC cohort	561,223/11,741	2.30 (2.26–2.34)	Reference	Reference
HF cohort	173,549/4812	3.06 (2.97–3.15)	2.08 (2.00–2.17)	1.85 (1.77–1.93)

* Controlled for matching factors (age, sex, calendar decade of heart failure diagnosis).
† Adjusted for matching factors, myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, intermittent claudication, venous thromboembolism, hypercholesterolemia, hypertriglyceridemia, hypertension, obesity, diabetes, chronic kidney disease, cancer, chronic pulmonary disease, alcoholism-related disorders, and dementia.
Abbreviations: CI: confidence interval, CC: comparison cohort, HF: heart failure.

Supplemental Table VI. Risk of stroke in heart failure patients and the general population comparison cohort. Analyses adjusted for use of antithrombotic drugs, use of angiotensin converting enzyme inhibitors, and beta blockers (for patients included after 2004).

	Number at risk no. events	Fully-adjusted stroke rate ratio (95% CI)*	Fully*- adjusted stroke rate ratio and adjustment for antithrombotic drugs (95% CI)	Fully*-adjusted stroke rate ratio and adjustment for ACE-I and beta blockers (95% CI)
Ischemic stroke				
0-30 days				
CC cohort	245,630/206	Reference	Reference	Reference
HF cohort	49,126/258	6.23 (5.05–7.69)	6.22 (5.04–7.68)	6.29 (5.08–7.78)
31-365 days				
CC cohort	244,227/2187	Reference	Reference	Reference
HF cohort	42,172/723	2.08 (1.89–2.29)	2.07 (1.88–2.28)	2.07 (1.88–2.28)
1-5 years				
CC cohort	229,084/6111	Reference	Reference	Reference
HF cohort	33,123/1161	1.50 (1.39–1.61)	1.49 (1.39–1.61)	1.49 (1.38–1.60)
Intracerebral hemorrhage				
0-30 days				
CC cohort	245,630/27	Reference	Reference	Reference
HF cohort	49,126/11	1.49 (0.54–4.14)	1.46 (0.53–4.06)	1.39 (0.49–3.98)
31-365 days				
CC cohort	244,227/259	Reference	Reference	Reference
HF cohort	42,172/83	1.98 (1.50–2.61)	1.94 (1.47–2.57)	1.99 (1.50–2.63)
1-5 years				
CC cohort	229,084/800	Reference	Reference	Reference
HF cohort	33,123/128	1.13 (0.91–1.40)	1.12 (0.90–1.39)	1.13 (0.91–1.41)
Subarachnoid hemorrhage				
0-30 days				
CC cohort	245,630/7	Reference	Reference	Reference
HF cohort	49,126/10	33.30 (2.57–431.13)	34.08 (2.31–503.21)	25.41 (1.71–376.87)
31-365 days				
CC cohort	244,227/65	Reference	Reference	Reference
HF cohort	42,172/16	1.47 (0.75–2.89)	1.50 (0.76–2.97)	1.46 (0.74–2.88)
1-5 years				
CC cohort	229,084/158	Reference	Reference	Reference
HF cohort	33,123/30	1.49 (0.93–2.39)	1.47 (0.92–2.37)	1.51 (0.94–2.44)

* Controlled for matching factors (age, sex, calendar decade of heart failure diagnosis) and adjusted for matching factors, myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, intermittent claudication, venous thromboembolism, hypercholesterolemia, hypertriglyceridemia, hypertension, obesity, diabetes, chronic kidney disease, cancer, chronic pulmonary disease, alcoholism-related disorders, and dementia.

Abbreviations: ACE-I: angiotensin converting enzyme inhibitors, CC: comparison cohort, CI: confidence interval, HF: heart failure.

Supplemental Table VII. Risk of stroke in heart failure patients and the general population comparison cohort. Person-time counted separately for each outcome.

	Number at risk/no. events	Risk, % (95% CI)	Stroke rate ratio controlled for matching factors* (95% CI)	Fully-adjusted stroke rate ratio† (95% CI)
Ischemic stroke				
0-30 days				
CC cohort	1,446,765/892	0.06 (0.06–0.07)	Reference	Reference
HF cohort	289,353/884	0.31 (0.29–0.33)	5.65 (5.13–6.22)	5.04 (4.54–5.59)
31-365 days				
CC cohort	1,438,276/9768	0.68 (0.67–0.69)	Reference	Reference
HF cohort	238,314/3245	1.36 (1.32–1.41)	2.38 (2.28–2.48)	2.07 (1.98–2.17)
1-5 years				
CC cohort	1,346,257/38,912	3.02 (2.99–3.05)	Reference	Reference
HF cohort	176,473/6973	4.13 (4.04–4.23)	1.78 (1.73–1.83)	1.57 (1.53–1.62)
Intracerebral hemorrhage				
0-30 days				
CC cohort	1,446,765/167	0.01 (0.01–0.01)	Reference	Reference
HF cohort	289,353/63	0.02 (0.02–0.03)	2.04 (1.52–2.74)	2.03 (1.47–2.81)
31-365 days				
CC cohort	1,438,965/1596	0.11 (0.11–0.12)	Reference	Reference
HF cohort	238,978/425	0.18 (0.16–0.20)	1.95 (1.74–2.18)	1.81 (1.61–2.04)
1-5 years				
CC cohort	1,353,065/6211	0.48 (0.47–0.49)	Reference	Reference
HF cohort	178,594/927	0.54 (0.51–0.58)	1.47 (1.36–1.58)	1.37 (1.27–1.49)
Subarachnoid hemorrhage				
0-30 days				
CC cohort	1,446,765/24	0.00 (0.00–0.00)	Reference	Reference
HF cohort	289,353/16	0.01 (0.00–0.01)	3.61 (1.90–6.88)	3.60 (1.60–8.07)
31-365 days				
CC cohort	1,439,064/270	0.02 (0.02–0.02)	Reference	Reference
HF cohort	239,000/73	0.03 (0.02–0.04)	1.80 (1.37–2.35)	1.58 (1.18–2.11)
1-5 years				
CC cohort	1,353,718/978	0.08 (0.07–0.08)	Reference	Reference
HF cohort	178,718/146	0.09 (0.07–0.10)	1.36 (1.13–1.65)	1.23 (1.01–1.50)

* Adjusted for matching factors (age, sex, calendar decade of heart failure diagnosis).
† Adjusted for matching factors, myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, intermittent claudication, venous thromboembolism, hypercholesterolemia, hypertriglyceridemia, hypertension, obesity, diabetes, chronic kidney disease, cancer, chronic pulmonary disease, alcoholism-related disorders, and dementia.
Abbreviations: CC: comparison cohort, CI: confidence interval, HF: heart failure.

Supplemental Table VIII. Risk of stroke in first-time outpatient heart failure patients and the general population comparison cohort.

	Number at risk/no. events	Risk, % (95% CI)	Stroke rate ratio controlled for matching factors* (95% CI)	Fully-adjusted stroke rate ratio† (95% CI)
Ischemic stroke				
0-30 days				
CC cohort	169,930/121	0.07 (0.06–0.08)	Reference	Reference
HF cohort	33,986/76	0.22 (0.18–0.28)	3.14 (2.35–4.18)	3.21 (2.33–4.43)
31-365 days				
CC cohort	169,346/1207	0.71 (0.67–0.75)	Reference	Reference
HF cohort	33,585/486	1.45 (1.32–1.58)	2.12 (1.91–2.36)	1.84 (1.63–2.07)
1-5 years				
CC cohort	162,527/4425	3.18 (3.09–3.28)	Reference	Reference
HF cohort	30,583/1128	4.31 (4.07–4.56)	1.55 (1.44–1.66)	1.35 (1.26–1.46)
Intracerebral hemorrhage				
0-30 days				
CC cohort	169,930/10	0.01 (0.00–0.01)	Reference	Reference
HF cohort	33,986/3	0.01 (0.00–0.03)	1.50 (0.41–5.45)	5.85 (0.30–115.75)
31-365 days				
CC cohort	169,346/146	0.09 (0.07–0.10)	Reference	Reference
HF cohort	33585/40	0.12 (0.09–0.16)	1.42 (1.00–2.01)	1.23 (0.83–1.81)
1-5 years				
CC cohort	162,527/534	0.39 (0.36–0.43)	Reference	Reference
HF cohort	30,583/97	0.38 (0.31–0.46)	1.10 (0.88–1.38)	1.03 (0.80–1.33)
Subarachnoid hemorrhage				
0-30 days				
CC cohort	169,930/0	(.–.)	Reference	Reference
HF cohort	33,986/0	(.–.)	(.–.)	(.–.)
31-365 days				
CC cohort	169,346/30	0.02 (0.01–0.03)	Reference	Reference
HF cohort	33,585/7	0.02 (0.01–0.04)	1.20 (0.53–2.76)	0.88 (0.26–2.96)
1-5 years				
CC cohort	162,527/89	0.07 (0.05–0.08)	Reference	Reference
HF cohort	30,583/26	0.10 (0.07–0.15)	1.72 (1.09–2.72)	1.67 (0.96–2.92)

* Adjusted for matching factors (age, sex, calendar decade of heart failure diagnosis)
† Adjusted for matching factors, myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, intermittent claudication, venous thromboembolism, hypercholesterolemia, hypertriglyceridemia, hypertension, obesity, diabetes, chronic kidney disease, cancer, chronic pulmonary disease, alcoholism-related disorders, and dementia.
Abbreviations: CC: comparison cohort, CI: confidence interval, HF: heart failure.
(.–.) Insufficient numbers for estimates.

Supplemental Table IX. Risk of stroke in heart failure patients and the general population comparison cohort, restricted to patients with primary heart failure diagnoses.

	Number at risk/no. events	Risk, % (95% CI)	Stroke rate ratio controlled for matching factors* (95% CI)	Fully-adjusted stroke rate ratio† (95% CI)
Ischemic stroke				
0-30 days				
CC cohort	581,070/360	0.06 (0.06–0.07)	Reference	Reference
HF cohort	116,214/345	0.30 (0.27–0.33)	5.47 (4.69–6.37)	4.92 (4.16–5.81)
31-365 days				
CC cohort	577,530/3991	0.69 (0.67–0.71)	Reference	Reference
HF cohort	96,525/1339	1.39 (1.32–1.46)	2.40 (2.25–2.57)	2.07 (1.93–2.22)
1-5 years				
CC cohort	539,159/16316	3.16 (3.11–3.21)	Reference	Reference
HF cohort	71,350/2956	4.35 (4.20–4.51)	1.82 (1.74–1.91)	1.61 (1.53–1.68)
Intracerebral hemorrhage				
0-30 days				
CC cohort	581,070/62	0.01 (0.01–0.01)	Reference	Reference
HF cohort	116,214/23	0.02 (0.01–0.03)	2.05 (1.26–3.33)	1.93 (1.09–3.41)
31-365 days				
CC cohort	577,530/564	0.10 (0.09–0.11)	Reference	Reference
HF cohort	96,525/142	0.15 (0.13–0.17)	1.81 (1.50–2.20)	1.72 (1.40–2.12)
1-5 years				
CC cohort	539,159/2141	0.42 (0.40–0.44)	Reference	Reference
HF cohort	71,350/327	0.49 (0.44–0.55)	1.52 (1.34–1.73)	1.34 (1.17–1.54)
Subarachnoid hemorrhage				
0-30 days				
CC cohort	581,070/5	0.00 (0.00–0.00)	Reference	Reference
HF cohort	116,214/5	0.00 (0.00–0.01)	5.00 (1.45–17.27)	2.09 (0.46–9.45)
31-365 days				
CC cohort	577,530/84	0.01 (0.01–0.02)	Reference	Reference
HF cohort	96,525/31	0.03 (0.02–0.05)	2.32 (1.51–3.56)	2.03 (1.26–3.29)
1-5 years				
CC cohort	539,159/336	0.07 (0.06–0.07)	Reference	Reference
HF cohort	71,350/44	0.07 (0.05–0.09)	1.17 (0.84–1.64)	1.11 (0.78–1.59)

* Adjusted for matching factors (age, sex, calendar decade of heart failure diagnosis)
† Adjusted for matching factors, myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, intermittent claudication, venous thromboembolism, hypercholesterolemia, hypertriglyceridemia, hypertension, obesity, diabetes, chronic kidney disease, cancer, chronic pulmonary disease, alcoholism-related disorders, and dementia.
Abbreviations: CC: comparison cohort, CI: confidence interval, HF: heart failure.

Supplemental Table X. Risk of stroke in heart failure patients and the general population comparison cohort, stratified by intensive care unit stay and length of hospital stay.

	Number at risk/no. events	Risk, % (95% CI)	Stroke rate ratio controlled for matching factors* (95% CI)	Fully-adjusted stroke rate ratio† (95% CI)
No intensive care unit stay				
Ischemic stroke				
0-30 days	42628 / 132	0.31 (0.26–0.37)	3.68 (2.94–4.60)	2.73 (2.08–3.57)
31-365 days	40501 / 676	1.67 (1.55–1.80)	2.05 (1.88–2.24)	1.63 (1.46–1.80)
1-5 years	32629 / 1184	4.56 (4.30–4.82)	1.50 (1.41–1.60)	1.22 (1.13–1.31)
Intracerebral hemorrhage				
0-30 days	42628 / 6	0.01 (0.01–0.03)	1.54 (0.62–3.82)	0.87 (0.31–2.48)
31-365 days	40501 / 78	0.19 (0.16–0.24)	1.89 (1.46–2.44)	1.49 (1.10–2.02)
1-5 years	32629 / 129	0.51 (0.42–0.60)	1.27 (1.05–1.53)	1.11 (0.89–1.37)
Subarachnoid hemorrhage				
0-30 days	42628 / 3	0.01 (0.00–0.02)	3.88 (0.87–17.35)	5.43 (0.87–33.70)
31-365 days	40501 / 15	0.04 (0.02–0.06)	1.67 (0.94–2.96)	1.23 (0.62–2.43)
1-5 years	32629 / 30	0.12 (0.08–0.17)	1.41 (0.95–2.09)	1.24 (0.78–1.96)
Intensive care unit stay				
Ischemic stroke				
0-30 days	3182 / 14	0.44 (0.25–0.72)	8.03 (3.47–18.54)	7.56 (2.70–21.13)
31-365 days	2973 / 35	1.18 (0.84–1.62)	2.40 (1.62–3.56)	2.02 (1.22–3.34)
1-5 years	2424 / 64	3.55 (2.75–4.49)	1.46 (1.12–1.92)	1.00 (0.72–1.39)
Intracerebral hemorrhage				
0-30 days	3182 / 0	(.–.)	(.–.)	(.–.)
31-365 days	2973 / 6	0.20 (0.09–0.43)	3.53 (1.28–9.71)	2.85 (0.81–10.05)
1-5 years	2424 / 6	0.38 (0.16–0.80)	1.04 (0.44–2.45)	0.69 (0.26–1.87)
Subarachnoid hemorrhage				
0-30 days	3182 / 1	0.03 (0.00–0.18)	(.–.)	(.–.)
31-365 days	2973 / 1	0.03 (0.00–0.19)	3.00 (0.27–33.04)	3.78 (0.18–77.75)
1-5 years	2424 / 1	0.06 (0.01–0.32)	1.01 (0.12–8.20)	1.55 (0.12–19.41)
Length of hospital stay ≤ 7 days				
Ischemic stroke				
0-30 days	110900 / 222	0.20 (0.18–0.23)	3.25 (2.74–3.84)	2.21 (1.81–2.70)
31-365 days	106875 / 1486	1.39 (1.32–1.46)	2.10 (1.98–2.23)	1.54 (1.43–1.65)
1-30 years	86543 / 3641	4.51 (4.36–4.65)	1.67 (1.61–1.73)	1.31 (1.26–1.37)
Intracerebral hemorrhage				
0-30 days	110900 / 19	0.02 (0.01–0.03)	2.14 (1.25–3.66)	2.07 (1.11–3.87)
31-365 days	106875 / 166	0.16 (0.13–0.18)	1.63 (1.37–1.94)	1.25 (1.02–1.53)
1-30 years	86543 / 382	0.49 (0.44–0.54)	1.32 (1.19–1.48)	1.16 (1.02–1.32)
Subarachnoid hemorrhage				

0-30 days	110900 / 8	0.01 (0.00–0.01)	5.80 (2.10–15.99)	4.72 (1.38–16.16)
31-365 days	106875 / 24	0.02 (0.02–0.03)	1.61 (1.02–2.53)	1.02 (0.60–1.75)
1-30 years	86543 / 57	0.07 (0.06–0.09)	1.28 (0.96–1.69)	0.90 (0.64–1.25)
Length of hospital stay > 7 days				
Ischemic stroke				
0-30 days	128027 / 307	0.24 (0.21–0.27)	5.00 (4.28–5.85)	3.69 (3.08–4.43)
31-365 days	117848 / 1470	1.25 (1.19–1.31)	2.28 (2.14–2.42)	1.65 (1.54–1.77)
1-30 years	86260 / 3126	3.73 (3.61–3.86)	1.73 (1.67–1.80)	1.30 (1.24–1.36)
Intracerebral hemorrhage				
0-30 days	128027 / 31	0.02 (0.02–0.03)	2.03 (1.34–3.07)	1.94 (1.21–3.12)
31-365 days	117848 / 201	0.17 (0.15–0.20)	1.78 (1.52–2.08)	1.51 (1.25–1.81)
1-30 years	86260 / 435	0.53 (0.48–0.58)	1.52 (1.37–1.68)	1.33 (1.18–1.49)
Subarachnoid hemorrhage				
0-30 days	128027 / 5	0.00 (0.00–0.01)	2.38 (0.83–6.84)	2.76 (0.81–9.43)
31-365 days	117848 / 29	0.02 (0.02–0.04)	1.89 (1.25–2.87)	1.75 (1.08–2.84)
1-30 years	86260 / 50	0.06 (0.05–0.08)	1.38 (1.03–1.86)	1.05 (0.74–1.49)

* Adjusted for matching factors (age, sex, calendar decade of heart failure diagnosis)

† Adjusted for matching factors, myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, intermittent claudication, venous thromboembolism, hypercholesterolemia, hypertriglyceridemia, hypertension, obesity, diabetes, chronic kidney disease, cancer, chronic pulmonary disease, alcoholism-related disorders, and dementia.

Abbreviations: CC: comparison cohort, CI: confidence interval, HF: heart failure.

(.–.) insufficient for estimates

AARHUS UNIVERSITY

Declaration of co-authorship

Full name of the PhD student: Kasper Adelborg

This declaration concerns the following article/manuscript:

Title:	Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study
Authors:	Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preparation ☐

If published, state full reference: 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)

If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

The PhD student has contributed to the elements of this article/manuscript as follows:

A. No or little contribution
B. Has contributed (10-30 %)
C. Has contributed considerably (40-60 %)
D. Has done most of the work (70-90 %)
E. Has essentially done all the work

Element	Extent (A-E)
1. Formulation/identification of the scientific problem	C
2. Planning of the experiments and methodology design and development	C
3. Involvement in the experimental work/clinical studies/data collection	B
4. Interpretation of the results	C
5. Writing of the first draft of the manuscript	B
6. Finalization of the manuscript and submission	C

Signatures of the co-authors

Date	Name	Signature
5/4-17	Jens Sundbøll	
6/4-17	Troels Munch	
3/4-17	Trine Frøslev	

AARHUS
UNIVERSITY

05.04.17	Henrik Toft Sørensen	
5/4-17	Hans Erik Bøtker	
5/4-17	Morten Schmidt	

In case of further co-authors please attach appendix

Date: 17/4

Signature of the PhD student

AARHUS UNIVERSITY

Declaration of co-authorship

Full name of the PhD student: Kasper Adelborg

This declaration concerns the following article/manuscript:

Title:	Positive predictive value of cardiac examination, procedure, and surgery codes in the Danish National Patient Registry: a population-based validation study
Authors:	Adelborg K, Sundbøll J, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preparation ☐

If published, state full reference: 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)

If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

The PhD student has contributed to the elements of this article/manuscript as follows:

A. No or little contribution
B. Has contributed (10-30 %)
C. Has contributed considerably (40-60 %)
D. Has done most of the work (70-90 %)
E. Has essentially done all the work

Element	Extent (A-E)
1. Formulation/identification of the scientific problem	D
2. Planning of the experiments and methodology design and development	D
3. Involvement in the experimental work/clinical studies/data collection	E
4. Interpretation of the results	D
5. Writing of the first draft of the manuscript	E
6. Finalization of the manuscript and submission	D

Signatures of the co-authors

Date	Name	Signature
6/4-17	Jens Sundbøll	Jens SJ
6/4-17	Troels Munch	Troels Munch
3/4-17	Trine Frøslev	Frøslev

AARHUS
UNIVERSITY

05.04.17	Henrik Toft Sørensen	
5/4-17	Hans Erik Bøtker	
5/4-17	Morten Schmidt	

In case of further co-authors please attach appendix

Date: 17/4-17

Signature of the PhD student

AARHUS
UNIVERSITY

Declaration of co-authorship

Full name of the PhD student: Kasper Adelborg

This declaration concerns the following article/manuscript:

Title:	Mortality Risk Among Heart Failure Patients With Depression: A Nationwide Population-Based Cohort Study
Authors:	Adelborg K, Schmidt M, Sundbøll J, Pedersen L, Videbech P, Bøtker HE, Egstrup K, Sørensen HT

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preparation ☐

If published, state full reference: 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)

If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

The PhD student has contributed to the elements of this article/manuscript as follows:

A. No or little contribution
B. Has contributed (10-30 %)
C. Has contributed considerably (40-60 %)
D. Has done most of the work (70-90 %)
E. Has essentially done all the work

Element	Extent (A-E)
1. Formulation/identification of the scientific problem	D
2. Planning of the experiments and methodology design and development	E
3. Involvement in the experimental work/clinical studies/data collection	E
4. Interpretation of the results	D
5. Writing of the first draft of the manuscript	E
6. Finalization of the manuscript and submission	D

Signatures of the co-authors

Date	Name	Signature
5/4-17	Morten Schmidt	
5/4-17	Jens Sundbøll	
3/4-17	Lars Pedersen	

AARHUS
UNIVERSITY

05.04.17	Poul Videbech	
5/4-17	Hans Erik Bøtker	
06.04.17	Kenneth Egstrup	
05.04.17	Henrik Toft Sørensen	

In case of further co-authors please attach appendix

Date:

6/4 - 2017

Signature of the PhD student

AARHUS
UNIVERSITY

Declaration of co-authorship

Full name of the PhD student: Kasper Adelborg

This declaration concerns the following article/manuscript:

Title:	Heart failure and risk of dementia: a Danish nationwide population-based cohort study
Authors:	Adelborg K, Horváth-Puhó E, Ording A, Pedersen L, Sørensen HT, Henderson VW

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preparation ☐

If published, state full reference: 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

If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☐ Yes ☐ If yes, give details:

The PhD student has contributed to the elements of this article/manuscript as follows:

A. No or little contribution
B. Has contributed (10-30 %)
C. Has contributed considerably (40-60 %)
D. Has done most of the work (70-90 %)
E. Has essentially done all the work

Element	Extent (A-E)
1. Formulation/identification of the scientific problem	D
2. Planning of the experiments and methodology design and development	E
3. Involvement in the experimental work/clinical studies/data collection	D
4. Interpretation of the results	D
5. Writing of the first draft of the manuscript	E
6. Finalization of the manuscript and submission	D

Signatures of the co-authors

Date	Name	Signature
7/4 - 17	Erzsébet Horváth-Puhó	Horváth-Puhó
3/4-17	Anne Ording	
3/4-17	Lars Pedersen	Lars Pedersen

AARHUS
UNIVERSITY

05.04.17	Henrik Toft Sørensen	
06-04-17	Victor W. Henderson	

In case of further co-authors please attach appendix

Date: 7/4-17

Signature of the PhD student

AARHUS
UNIVERSITY

Declaration of co-authorship

Full name of the PhD student: Kasper Adelborg

This declaration concerns the following article/manuscript:

Title:	Risk of Stroke in Patients with Heart Failure: A Population-based 30-Year Cohort Study
Authors:	Adelborg K, Szépligeti S, Sundbøll J, Horváth-Puhó E, Henderson VW, Ording A, Pedersen L, Sørensen HT

The article/manuscript is: Published ☐ Accepted ☒ Submitted ☐ In preparation ☐

If published, state full reference:

If accepted or submitted, state journal: 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. In press

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

The PhD student has contributed to the elements of this article/manuscript as follows:

A. No or little contribution
B. Has contributed (10-30 %)
C. Has contributed considerably (40-60 %)
D. Has done most of the work (70-90 %)
E. Has essentially done all the work

Element	Extent (A-E)
1. Formulation/identification of the scientific problem	D
2. Planning of the experiments and methodology design and development	E
3. Involvement in the experimental work/clinical studies/data collection	D
4. Interpretation of the results	D
5. Writing of the first draft of the manuscript	E
6. Finalization of the manuscript and submission	D

Signatures of the co-authors

Date	Name	Signature
7 April 2017	Szimonetta Szépligeti	
5/4 17	Jens Sundbøll	
7/4-17	Erzsébet Horváth-Puhó	

AARHUS
UNIVERSITY

06-04-17	Victor W. Henderson	
3/4-17	Anne Ording	
3/4-17	Lars Pedersen	
05.04.17	Henrik Toft Sørensen	

In case of further co-authors please attach appendix

Date: 18/4-17

Signature of the PhD student