Department of Clinical Epidemiology

FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY

Incident heart failure in Denmark: Studies on a nationwide quality improvement initiative

PhD Thesis

Anne Nakano

Faculty of Health Sciences
Aarhus University

2016

Incident heart failure in Denmark: Studies on a nationwide quality improvement initiative

PhD Thesis

Anne Nakano

Faculty of Health Sciences
Aarhus University

Department of Clinical Epidemiology, Aarhus University Hospital, Denmark

Supervisors

Søren Paaske Johnsen, MD, Ph.D, Associate professor
Department of Clinical Epidemiology
Aarhus University Hospital, Denmark

Kenneth Egstrup, MD, DMSc, Professor.
Department of Cardiology
Odense University Hospital, Svendborg, Denmark

Marie Louise Overgaard Svendsen, cand.scient.san., Ph.D.
Department of Data & Documentation, DEFACTUM, Central Denmark Region
Olof Palmes Allé 13, 8200 Aarhus N, Denmark

Evaluation committee

Morten Schou, MD, PhD
Department of Cardiology, Herlev-Gentofte Hospital
Herlev, Denmark

Peter Vedsted MD, PhD
Department of Public Health and Institution for Clinical Medicine
Aarhus University, Aarhus, Denmark

Patrick Doherty MD, PhD
Professor of Cardiovascular Health
University of York, united Kingdom

PREFACE

This Ph.D. thesis is based on studies carried out during my employment at the Department of Clinical Epidemiology, University of Aarhus, the DNIP secretariat in The Danish National Indicator Project, Aarhus, and from 2007 onwards The Danish Clinical Registers, Audit Unit West. It has been a pleasure to work with the Danish Heart Failure Registry and give myself time to wonder.

The work was made possible by a number of people. First of all, I wish to express my sincere gratitude to my primary supervisor, Søren Paaske Johnsen for his enthusiasm and always being an excellent motivator and mentor throughout my time as a Ph.D. student, and for giving me the opportunity to develop my epidemiological and research skills and providing thoughtful and constructive feedback. I also wish to thank my co-supervisors Kenneth Egstrup and Marie Louise Overgaard Svendsen for their engagement, discussions, and support, as well as their valuable comments on my papers and thesis.

I am grateful to the statisticians at the Department of Clinical Epidemiology for their help and good advice.

I would also like to thank the secretaries, clinicians, and staff at the Danish hospital departments I visited during the record review process, as they always helped me find what I needed.
I am also grateful to my colleagues and friends at the Department of Clinical Epidemiology, Competence Center for Clinical Quality and Healthinformatics West (KCKS-V) and the Regional Clinical Quality Development Programme (RKKP) secretariats for their interest in my thesis.

Finally, I want to express never-ending love to my family, my husband Jørn, our children Mariann and Jesper, and their partners Christian and Heidi, for their love, patience, and unconditional support. Very special love goes to my grandchildren Alexander, Astrid, Clara-Emilie, and Nohr - thank you for giving me laughter and pleasure during this work by being small rays of sunshine, asking funny questions and doing funny things.

This work was made possible through financial support from the Danish Heart Foundation, the Central Denmark Research Foundation, and Fabrikant Karl G. Andersens Fond.

LIST OF ABBREVIATIONS

ACEI	Angiotensin Converting Enzyme Inhibitor
ADHF	Acute Decompensated Heart Failure
AHA	American Heart association
AMI	Acute Myocardial Infarction
ARB	Angiotensin Receptor Blocker
CHF	Chronic Heart Failure
CI	Confidence Interval
CVD	Cardiovascular Disease
COPD	Chronic Obstructive Pulmonary Disease
CRS	Civil Registration System
DHFR	Danish Heart Failure Registry
DMP	Disease Management Program
EF	Ejection Fraction
ESC	European Society of Cardiology
GAI-3	Guideline Adherence Indicator to First Three Classes of Heart Failure Medication
HF	Heart Failure
HFmrEF	Heart Failure with mid-range Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Hazard Ratio
ICD	International Classification of Disease
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
LPR	Landspatientregisteret
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MAHLER	Medical Management of Chronic Heart Failure in Europe and its Related Costs
NHS	National Health Service
NPV	Negative Predictive Value

NR	Not Reported
NRP	National Registry of Patients
NYHA	New York Heart Association
OPTIMIZE	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure
PPV	Positive Predictive Value
RCT	Randomized Controlled Trial
RR	Relative Risk
RRCT	Registry-based Randomized Clinical Trial
SD	Standard Deviation
UK	United Kingdom
USA	United States of America

This Ph.D. thesis is based on the following studies:

I. Nakano A, Johnsen SP, Frederiksen BL, Svendsen ML, Agger C, Schjødt I, Egstrup K. Trends in quality of care among patients with incident heart failure in Denmark 2003-2010: a nationwide cohort study. BMC Health Services Research 2013; 13:391

II. Nakano A, Egstrup K, Svendsen ML, Schjødt I, Jakobsen L, Mehnert F, Johnsen SP. Age- and sex-related differences in use of guideline-recommended care and mortality among patients with incident heart failure in Denmark. Age Ageing 2016; 45:635-42

III. Nakano A, Egstrup K, Svendsen ML, Schjødt I, Johnsen SP. Association between process performance measures and 1-year mortality among patients with incident heart failure: A nationwide study
In Preparation.

Contents

1. INTRODUCTION

Heart failure (HF) is a leading cause of morbidity and mortality and a cause of high health care-related costs, posing a great burden on both patients and society (1-3). Thus, there is a global need for continuous monitoring and improvements in the quality of HF care (4-10).

1.1. Introduction to heart failure

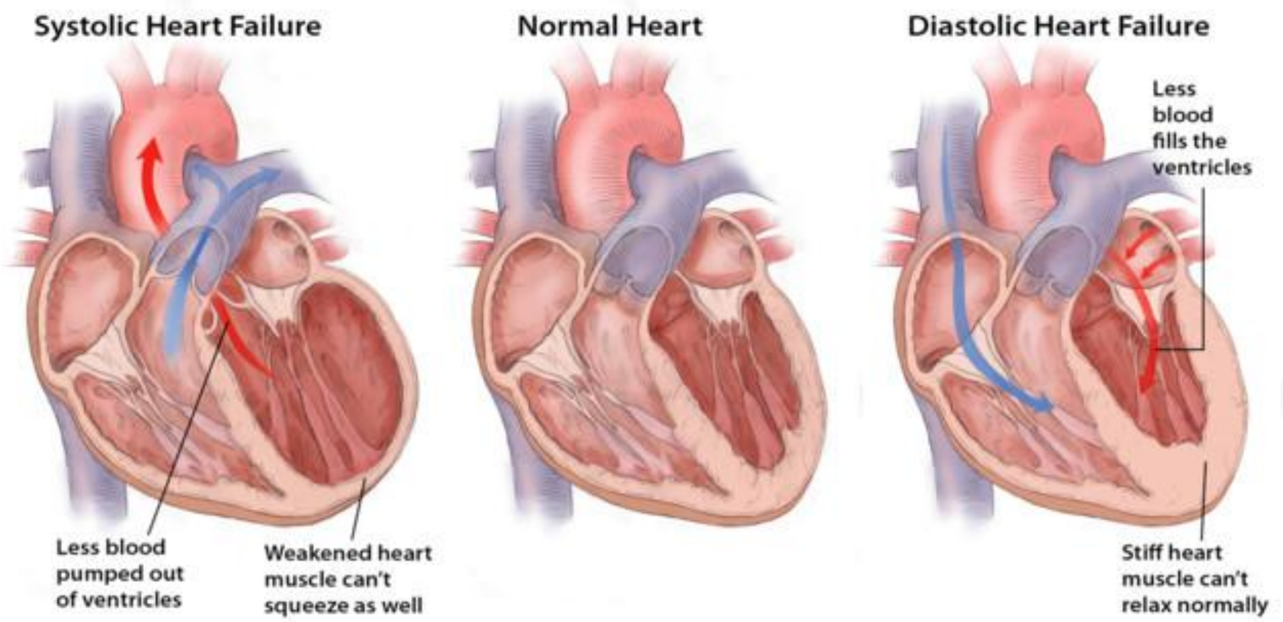
The typical symptoms of HF are breathlessness, ankle swelling, and fatigue (11), which are sometimes accompanied by elevated jugular venous pressure, pulmonary crackles, and peripheral edema caused by structural and/or functional cardiac abnormality resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress. The present definition of HF restricts itself to stages at which clinical symptoms are obvious. Demonstration of the underlying cardiac course is central to the diagnosis of HF and crucial for therapeutic reasons, as an accurate determination of pathology (e.g., abnormalities of the valves, pericardium, or endocardium; acute myocardial infarction [AMI]; or the presence of more than one abnormality) specifies which treatment is required (12).

HF can present suddenly as a consequence of an acute cardiac event, such as myocardial infarction, or more commonly in an acute-on-chronic way when a period of worsening symptoms and signs is followed by emergency presentation with decompensation. Most of the cardinal symptoms are non-specific, especially in elderly patients, and could be due to other problems, including chronic lung disease, renal dysfunction, anemia, venous insufficiency, hypothyroidism, or concomitant treatments, such as calcium-channel blockers or glitazones. Even if HF is correctly diagnosed on the basis of symptoms and signs, differentiating between preserved and reduced left ventricular (LV) function is still difficult (3). Key investigations for the diagnosis of HF are echocardiography to demonstrate structural heart disease; electrocardiography (ECG) to show rhythm, rate, and conduction; chest radiography to exclude primary pulmonary disease and identify edema; and blood chemistry (3).

The terminology used to describe HF is based on measurement of the left ventricular ejection fraction (LVEF). HF includes a wide range of patients, from patients with normal LVEF (≥50%, which is also the cutoff for patients with HF with preserved ejection fraction [HFpEF]) to those with HF with reduced ejection fraction (HFrEF; typically <40%) (2,13,14). HFrEF results mainly from myocardial infarction (systolic dysfunction), hypertension (diastolic and systolic dysfunction), or in many cases both. Other common causes include degenerative valve disease, "idiopathic" dilated cardiomyopathy, some cases of which could have a genetic basis, and alcoholic cardiomyopathy (3). Traditionally, this type of HF presents with an impaired ability of the heart to pump sufficient amounts of blood into the circulation during systole (15).

Patients with HFpEF do not generally have a dilated left ventricle, but instead often have increased LV wall thickness and/or increased left atrial size as a sign of increased filling pressure (Figure 1). Most patients have additional evidence of impaired LV filling or suction capacity, also classified as diastolic dysfunction, which is generally accepted as the likely cause of HF in these patients (i.e., "diastolic heart failure") (12,14).

Figure 1. Hearts with systolic and diastolic heart failure compared to a normal heart (16).



1.2. Prevalence and consequences of heart failure

HF is a major public health problem, with a prevalence >5.8 million in the United States and >23 million worldwide (17). In persons >50 years of age, the prevalence and incidence increase progressively with age to more than 10% among persons ≥70 years of age (12,15). Among people >65 years of age presenting to primary care with breathlessness on exertion, one in six will have unrecognized HF. The lifetime risk of HF at 55 years of age is 33% for men and 28% for women (12).

The syndrome of HF has been compared to an iceberg. The visible section represents established HF cases in the community. The majority of the visible part is managed in the primary care setting, whereas the top is managed by the cardiologists. The larger invisible part "below the water" represents cases of undetected HF and those with asymptomatic left dysfunction considered prone to developing HF (2).

Differentiating patients with HF based on LVEF (normal or reduced ejection fraction) is important due to different underlying etiologies, demographics, co-morbidities, and therapeutic effects (12,18). Accurate estimations of the prevalence in the older population based on echocardiographic assessment are lacking, though the aging of the population, improved survival rates for acute coronary disease, better treatment of HF, and increased prevalence of patients with chronic comorbidities are changing the epidemic of HF (2). In the United States, patients with HFpEF have been reported to account for approximately half of the total patient population. The criteria for HFpEF might vary between International Geographic Regions (12,19).

HF has a substantial impact for the patient, both physically and mentally, as it is a chronic disease that has to be treated both medically and, to a degree, with non-pharmacological treatments, including physical training and patient education. Pharmacological treatment is often lifelong and complex, with multiple medications taken twice or more daily. Therefore, coping and getting the best possible quality of daily life for the patients can be a challenge (20,21). Numerous prognostic markers of death and/or HF hospitalization have been identified in patients with HF, but their clinical applicability is limited and accurate risk stratification in HF remains challenging (12).

1.3. Clinical outcomes and prognostic factors

In a Danish cohort study investigating 30-year trends in HF hospitalization and mortality rates, as well as the prognostic impact of co-morbidity, the standardized first-time hospitalization rate for patients with HF decreased between 1983 and 2012, from 210 to 164 per 100,000 person years (22). The overall decrease reflected an average decrease of 1.1% per year until 2000, followed by a subsequent decline of 3.5% per year (22). The hospitalization rate for women decreased by 25% (from 192 to 144) and for men by 14% (from 217 to 186) per 100,000 persons between 1983 and 2012 (22).

One-year mortality declined from 45% during 1983-1987 to 33% during 2008-2012. During the same calendar periods, 1- to 5-year mortality declined from 59% to 43%, independent of patients' co-morbidity levels. Comparing the period 2008-2012 to the period 1983-1987, the 5-year age, sex, and co-morbidity-adjusted mortality rate ratio was 0.57 (95% confidence interval [CI] 0.56-0.58) (22).

A national registry in Sweden compared the rate of first-ever hospitalization and associated short- and long-term survival for HF, AMI, and the most common forms of cancer on an age and sex-specific basis between 1988 and 2004 in 949,733 Swedish patients. Despite improvements in 30-day and 5-year survival, HF was associated with an unadjusted case-fatality rate of 59% within 5 years and 196,400 deaths compared to a rate of 58% and 131,000 deaths in patients with cancer. During a 10-year follow-up, HF was associated with 66,318 vs. 55,364 premature life-years lost for all common cancers in men. In women, the equivalent figures were 59,535 vs. 64,533 premature life-years lost, which confirmed that HF constitutes a major health burden (23).

Several factors may influence the outcome of HF (2,3,24-29):

The type of severity of HF	HFrEF, HFpEF, HFmrEF
Patient characteristics	Age, sex, genetic factors, comorbidities, lifestyle (alcohol intake, smoke habits), ethnicity
Diagnosis	Access to healthcare, family practitioner, evaluation at admission to hospital, access to a cardiologist at admission, pulse pressure
Clinician performance	Correct medication, echocardiography, processes of care, diagnosis by an experienced cardiologist, cardiology ward, competence, compliance with guidelines, timing of treatment, university vs. local hospital
Patient compliance with treatment	Medical therapy, physical activity, prevention, motivation, plan for rehabilitation

1.4. Quality of care: Background and litterature

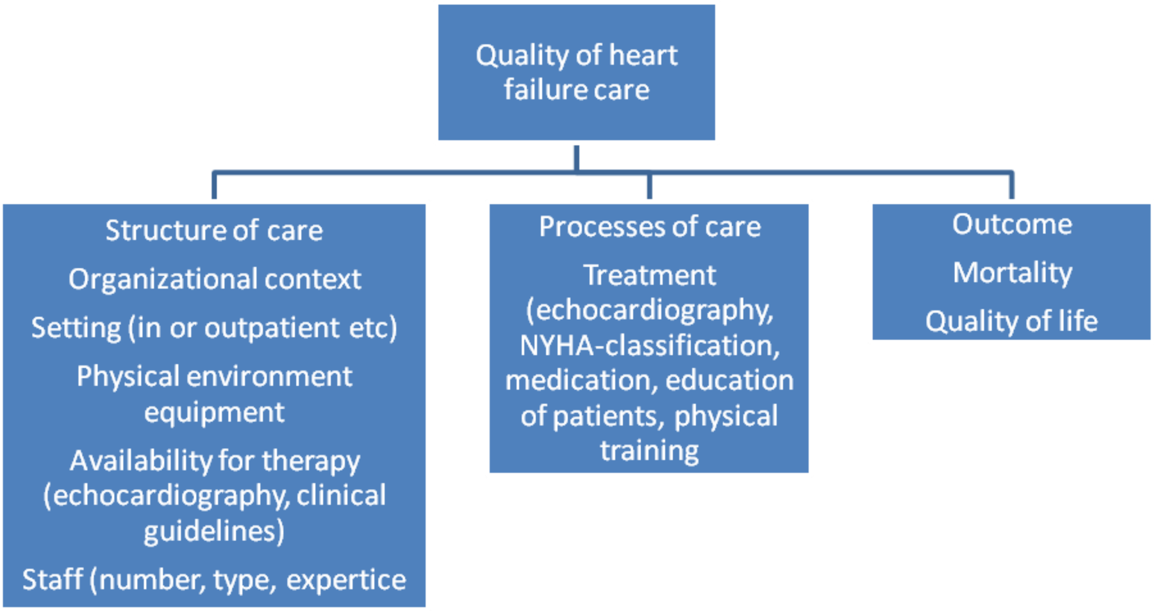
It is a key objective in current health policy to ensure the best value for the money by improving the quality of health services and health outcomes at similar or lower cost (30,31). This need has been reinforced by the economic crisis, increasing costs of an aging population, and new medical advances (30).

Health care quality has traditionally been characterized according to three dimensions: structure, process, and outcome. Structure includes administrative and related processes that support and direct the provision of care. It is concerned with such factors as the adequacy of facilities and equipment, the qualifications of medical staff and their organization, and the administrative structure and operations of programs and institutions providing care. Process reflects whether what is now known to be "good" medical care has been applied. Judgments are based on considerations such as the appropriateness, completeness, and redundancy of information obtained through clinical history, physical examination, and diagnostic tests; justification of diagnosis and therapy; technical competence in the performance of diagnostic and therapeutic procedures, including surgery; evidence of preventive management in health and illness; coordination and continuity of care; and acceptability of care to the recipient. Outcome refers to the effects of care on health status, including mortality, functional gains, and hospital readmissions; changes in patient behavior; and satisfaction with care. Some of the outcomes are generally unmistakable and easy to measure (e.g., death), whereas others are not as clearly defined and can be difficult to measure. Outcomes may indicate good or bad care in the aggregate but do not provide insight into the nature or location of the deficiencies or strengths to which the outcome may be attributed. Outcomes remain the ultimate validators of the effectiveness and quality of medical care.

In theory, these three dimensions interact so that the optimal structure of care allows for improved processes of care, which in turn positively affect the outcome. Included in these dimensions are the interpersonal process, which influences the implementation of care by and for the patient (32-34).

Figure 2 presents a modified version of the Donabedian model of structure, process, and outcome as a conceptual framework for improving HF care (32). The studies in this thesis focus specifically on the guideline-recommended performance measures given to patients admitted to hospital or at first contact with a cardiac care clinic and subsequent mortality, which may all be considered aspects of health care quality.

Figure 2. Modified Donabedian model (32,33).



A number of countries use established databases to monitor the quality of HF care at a national level, including USA (35), Sweden (4), the United Kingdom (36), Canada (5), Australia (6), Poland (7), Japan (8). In addition, multinational efforts have been made across European countries (9,37). In Denmark, national clinical guidelines for the treatment of HF were released in 2002 and updated in 2007 and 2015. These guidelines recommended prompt diagnosis by echocardiography, New York Heart Association (NYHA) classification, and medication assessment, as well as patient education and physical training. This is in line with international consensus guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) (12,38). The Danish Heart Failure Registry (DHFR) monitors and documents, on a national level, whether several of these key recommendations for the early treatment and care of patients with HF are followed using performance measures. A distinction is made between structure, process, and outcome performance measures and time limits are defined for each process performance measure to capture the timeliness of care (39,40).

1.4.1. Search strategy

The strategy for searching the scientific literature was established to identify evidence regarding the following relationships, which are the focus of the thesis:

1. Effect of quality improvement initiatives on HF care,
2. The association between age and gender and quality of HF care and clinical outcome,
3. The association between quality of HF care and clinical outcome.

PubMed, Cochrane Library, Scopus, Embase, and Web of Science were searched for studies published up to April 2016. The searches were built by Medical Subheading (MeSH) to narrow the literature and limited to include only studies in humans that were published in English or Danish. Only studies that applied patient-level data were selected. Additional studies were found by searching the reference lists of the identified publications.

The following terms were used in combinations: "Incident Heart Failure" [Mesh], "Heart Failure" [Majr], "Process assessment [Mesh], "predictive quality" [Mesh], "completeness" [Mesh], "Outcome" [Mesh], "Mortality" [Mesh], "Gender differences" [Majr], "Sex differences" [Majr], "prognosis" [Mesh], "Social class" [Mesh], "Quality Indicators" [Mesh], "Guideline adherence" [Mesh], "Practice Guidelines" [Mesh], "Medical compliance" [Mesh], "Sex, female, male, men, women" [Mesh], "Age" [Majr], "Validity" [Mesh], "Registries" [Mesh], "Databases" [Mesh], "clinical databases" [Mesh], "Human" [Mesh] "Patient compliance consequence" [Mesh]. Furthermore, searches were performed on the websites of the World Health Organization (www.who.int), Danish National Board of health (www.sst.dk, www.rkkp.dk, and www.kcks-vest.dk), and the Danish Heart Association (www.hjerteforeningen.dk).

Data from relevant publications were extracted using a standardized form. Data extracted from each study included: author, year published, and country; patient population, institution, survey, and/or database; study design; main findings in relation to improved processes of care over time; and conclusion.

1.4.2. Effect on quality improvement initiatives on heart failure care

The literature search identified six relevant studies assessing the effect of quality improvement initiatives for HF care (35,41-45).

A short description of the identified publications are provided in Appendix Table 1.

Five of the studies were from the USA and one from Germany. The population included in the studies ranged from 1853 in the German study to 237.225 in the largest of the US studies (43). Four of the six studies showed a correlation between the launch of a quality improvement program and a subsequent improvement in quality of care as reflected by process performance measures for HF (35,41,43,44). The literature revealed diverging opinions about compliance with guideline recommendations over time, which is perhaps not that surprising as the guidelines need to be regularly developed, implemented, used, and evaluated in a continuous process.

The German study, EVIdence based TreAtment in Heart Failure (EVITA-HF), focused on a well-defined patient population with LVEF ≤40% covered by clear guideline recommendations with consecutive patient inclusion and a 1-year follow-up period. The study included 1853 consecutive patients hospitalized in 16 centers, and followed guideline-management of HF with reduced EF in tertiary care facilities. The study found that the use of recommended drug therapy increased significantly from admission to discharge (angiotensin converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB] 73.0% vs. 89.6% and beta-blocker 71.0% vs. 90.4%). In addition, sustained improvement of NYHA status was observed, as 63% of patients were in NYHA III/IV at admission but only 30% were in NYHA III/IV after 1 year, ($p<0.001$ vs. index admission). The study added new information regarding the effectiveness of in-hospital management and guideline adherence in patients with chronic systolic HF (43).

The AHA developed the Get With The Guideline program for HF (GWTG-HF) to implement and target hospital-based quality improvement for HF, following hospital performance for 215 hospitals. The study investigated whether guideline-recommended processes of care were followed better in GWTG hospitals compared to hospitals not enrolled in GWTG. The follow-up period lasted from 2006 to 2007, and found that hospitals enrolled in the GWTG-

HF had significantly more documentation of LVEF (93.4% vs. 88.8%), use of ACEIs or ARBs (88.3% vs. 86.6%), and discharge instructions (74.9% vs. 70.5%; $p<0.005$ for all). A lower risk-adjusted 30-day all-cause readmission rate after a HF hospitalization was also found for hospitals attending the GWTG-HF program compared to hospitals not attending the program (35).

The Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF) included a random sample of 34,810 HF patients from 167 outpatient cardiology practices in the US with reduced LVEF (≤35%) at baseline and after 12 and 24 months. The 24-month assessment compared to baseline was as follows: beta-blocker (92.2% vs. 86.0%, +6.2%), aldosterone antagonist (60.3% vs. 34.5%, +25.1%), HF education (72.1% vs. 59.5%, +12.6%; each $p<0.001$). The study suggested a favorable impact of applying guideline-driven care improvement tools (44).Quality improvement initiatives have been linked with improved clinical outcomes (44)

Limitations of the existing studies

The studies published thus far have varying shortcomings, including selective instead of consecutive patient inclusion, heterogeneous populations including both incident and worsening HF, inclusion of both systolic and diastolic HF, short follow-up time (e.g., 30-day mortality), and required informed consent from the patients (43). Another challenge was that participants were self-selected for outpatient cardiology practices, as were the hospitals participating in the GWTG-HF program, as it was not mandatory reporting for all hospitals (44,46-48). Furthermore, the validity of the HF diagnosis was not assessed in all of the studies, with definitions varying from chronic HF for at least 3 months and documented ejection fraction (EF) ≤40% to those with a clinical diagnosis of HF documented by a cardiologist on at least two separate visits (43,44).

Summary

The implementation of quality improvement initiatives has been associated with improvements in process performance measures and patient outcomes, but the data remain sparse and additional population-based studies are warranted.

1.4.3. Association between age and sex and quality of heart failure care and clinical outcome

The literature search for age- and sex-related differences identified six studies concerning mostly age-related differences, eight studies concerning mostly sex-related differences, and two studies examining both age- and sex-related differences. Most of the studies are from the USA, but Germany, Italy, Sweden, Israel, France, Spain, Switzerland, Poland, Finland Norway, the UK, the Netherlands, and Australia are also represented. Short descriptions of the publications are provided in Appendix Table 2.

Danish and international guidelines for HF care recommend the same level of care for everyone, independently of age and sex (12,49-51). Regardless, age- and sex-related differences in HF care have been reported for different populations and become a hot topic of debate.

Age-related differences

Randomized controlled trial (RCT) data on therapy exclusively in elderly patients with HF are scarce, as elderly patients are underrepresented in RCTs compared to real world patient populations (52-54). This may explain, at least in part, the observed age-related differences in HF care despite guideline recommendations. Komajda et al. studied a large cohort of 3577 patients, including 741 (21%) ≥80 years of age, in the Euro Heart Failure Survey (EHFS)-II and compared treatment and mortality to younger patients (n=2836, 79%). both under-use and under-dosage of medications recommended for HF were found among the elderly (55). Other studies have also reported poor adherence to guidelines and less frequent prescription of recommended HF medications for old HF patients, who remained at greater risk of adverse outcomes (48). In addition, older patients appear to be less likely to receive HF education than younger patients (26).

Sex-related differences

Enrollment of women in randomized clinical trials has increased over time, yet their inclusion in RCTs remains low relative to their representation in real-life patient populations, and not all drug applications to regulatory authorities have included sex-specific analyses (56). Women have, in some but not all studies, been reported to receive less guideline-recommended care, much similar to the pattern for older patients. Lenzen et al. found that, in a population of 8914 patients, women underwent fewer investigations of LVEF (59% vs. 74%, age-adjusted OR 0.67; 95% CI 0.61-0.74) and less therapy with drugs with a documented impact on survival, including (ACEI: adjusted OR 0.72, 95% CI 0.61-0.86; beta-blockers: adjusted OR 0.76, 95% CI 0.65-0.89). However, 12-week mortality was similar for both men and women (57). Nicol et al. found similar results, showing that women were less likely to have had echocardiography (52% vs. 60%, $p<0.001$) and, if previously diagnosed with HF, also less likely to be treated with ACEIs (58.3% vs. 66.8%, $p<0.001$) and beta-blockers (30.1% vs. 35.5%, $p=0.033$). However, the survival rates between men and women were equal (58).

The Norwegian Heart Failure Registry included 3632 patients (70% men). This study reported differences in baseline characteristics between men and women. Compared to men, women were less often smokers, had more severe NYHA classification, and were less likely to have coronary etiology as the underlying cause of their HF. The study had classified EF using a cut-off value of 50% and found that men and women in the two groups (<50% and ≥50%) received equally often beta-blockers and ACEIs. Survival rates were also equal (59).

In contrast, other studies have not found differences in care when comparing women and men (60,61). Though it has been reported that it is more difficult to correctly classify female patients presenting with symptoms of HF (62).

Studies investigating both age-and sex-related differences

Studies concerning both age- and sex-related differences have generally found that evidence-based care is frequently under-implemented in older patients. A geriatric hospital in Israel included 96 consecutive unselected patients >80 years old with either stable chronic HF or acute exacerbation of HF (67% women). Adherence to guideline-recommended HF medications was poor, as ACEIs were given in 42% of patients and beta-blockers in 36% of patients, which could partially explain the higher mortality. The oldest hospitalized HF patients were usually women, who were fully dependent or frail and had a high level of comorbidity; 1-year mortality was 57% (63).

Lindenfeld et al. reviewed a national sample of Medicare patients discharged with a principal diagnosis of HF (2239 patients >65 years of age) and found that EF was measured less often with increasing age (measured in 1325 [59.2%], p<0.0001). A substantial drop was observed in both men and women >85 years of age (64).

Limitations of the existing studies

The published studies have different shortcomings, such as the validity of the HF diagnosis, which could vary from a HF diagnosis documented by a cardiologist on at least two separate visits (26) to patients with suspected or confirmed HF (57). Patient inclusion covered consecutive inclusion of patients from a single HF unit; inclusion from a large number of invited practices for outpatient cardiology (data extracted by trained chart abstractors); large cohorts from US studies in which participants were collected by medical chart review, dependent of the accuracy and completeness of the documentation and abstraction (26,48,61); and patients participating in follow-up data collection who provided written informed consent before enrollment (48). Invitations for participation were also used (62). Patients were heterogeneous with both incident and prevalent populations (55,59), and cutoffs for LVEF were different (26,61,62), which may influence the balance between men and women. Self-selected participation is also a challenge, as the large cohorts in the US programs were not mandatory and could induce a bias if it is a certain type of hospital that participated in the programs (26,48). Follow-up varied greatly, from 60 days to 8 years after discharge (48,62).

Summary

The evidence suggests that older age is associated with a lower chance of receiving guideline-recommended HF therapy. In addition, some studies have indicated that women receive less recommended HF care than men. However, data from large population-based studies on well-defined HF populations are lacking, making it difficult to draw firm conclusions about the extent and clinical implications of any age- and sex-related differences in HF care.

1.4.4. Association between process performance measures and clinical outcome among patients with incident heart failure

Monitoring the quality of HF performance measures has become an important issue in recent years (65), and the literature search identified 19 studies concerning performance measures and clinical outcomes. Short descriptions of the publications are provided in Appendix Table 3.

Studies of the association between process performance measures and clinical outcome have been reported from a wide range of counties. Most of the studies are from the US (65-67), but studies have also included Germany, Italy, the Netherlands, Canada, and South Korea (68-72). Multinational studies have also been published (73).

Earlier studies reported that multicomponent interventions including interdisciplinary teams and following guidelines are associated with a lower rate of hospitalization, readmission, and mortality for patients with HF (65,67). In addition, the use of guideline-recommended drugs is associated with reduced mortality in the elderly population, providing evidence of the benefit of cardiac drugs (65,68,69,72).

A European study enrolled and followed 1410 patients with mild/moderate HF up for 6 months utilizing 150 randomly selected cardiologists/cardiology departments in six European countries. Global indicators of adherence (Guideline Adherence Indicator [GAI]) to the ESC guidelines were associated with decreased rates of HF hospitalization and delayed time to rehospitalization (73). On average, adherence to the ESC guidelines for the diagnosis of chronic HF (CHF) in the six countries was high with slight variations across countries. Overall adherence to diagnosis guidelines was 74% (73).

Fonarow et al. found that, after adjusting for patient and practice characteristics, all guideline-recommended therapies except aldosterone antagonists were independently associated with lower odds of death at 24 months. Use of beta-blockers and cardiac resynchronization therapy (CRT) were associated with the lowest odds of death (betablocker, adjusted OR 0.42, 95% CI 0.34-0.52, $p<0.0001$ and CRT, adjusted OR 0.44, 95% CI 0.29-0.67, $p=0.0001$, respectively). ACEI/ARBs, ICD, HF education, and anticoagulation for atrial fibrillation were also independently associated with lower adjusted odds of death. The study also found an incremental benefit for patients who receive a greater number of treatments at baseline and were, therefore, more likely to be alive at 24 months. The benefit plateaued after 4 to 5 therapies (66).

With a basis in studies showing the impact of non-pharmacological performance measures, such as patient education, recent updates of the guidelines now involve the inclusion of patient education and training (12). In contrast, Wu et al. found that patient education was either not related or related to a slightly increased risk of death (74).

Limitations of the existing studies

The patients in the different studies were often extracted from trials in which patients were included according to different inclusion and exclusion criteria registered in the primary study, e.g. prevalent CHF and NYHA-class II-IV, recruitment from different countries, cardiologists were randomly selected by national medical institutions to assess whether patients should be included in the study for HF following the ESC guidelines, though (MAHLER) (73). Other programs using data from the large cohorts are the External Peer Review Program (EPRP) (74), Survey of Guideline Adherence for Treatment of Systolic Heart Failure in Real World (SUGAR) (72), and the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) (75). Some of the studies included HF patients with LVEF < 45%, and others included all patients presenting with chronic HF of any cause, not specifying any LVEF (72,76). In addition, OPTIMIZE-HF hospitals and GWTG-HF hospitals as well, were self-selected and may not entirely be representative of national care patterns and clinical outcomes, (35,75).

Follow-up data on clinical outcomes have different time spans, comprising 30 days, 60 days, or 90 days after discharge, and even up to 3 years or combinations of follow-up times (72,74,75,77). As in the other literature studies, a shortcoming also concerns the validity of HF diagnosis. It varied from signs and symptoms suggestive of CHF and objective evidence of cardiac dysfunction as recommended in ESC guidelines (73) to patients with a clinical diagnosis of HF documented by at least two separate visits (66), as well as dyspnea and verification of HF by clinical findings that were not specifically described (72). Furthermore, the follow-up time for combined mortality and rehospitalization was 60-90 days (75), and up to 1 year for survival after HF hospitalization (67).

Summary

Following the recommended guidelines have been associated with better clinical outcomes among patients with HF, particularly the use of HF medications, whereas the non-pharmacological processes of care have been less well studied. The exception is patient education, which has been reported to positively influence clinical outcomes including mortality and readmission for HF in a number of studies.

2. HYPOTHESES

The studies included in this thesis were based on the following hypotheses:

1. Compliance with clinical guideline recommendations as reflected by fulfilment of the process performance measures monitored in the DHFR has improved over the years, and mortality has been reduced among incident HF patients in Denmark following the introduction of a nationwide quality improvement program (Study I).

   Paper I: Nakano A, Johnsen SP, Frederiksen BL, Svendsen ML, Agger C, Schjødt I, Egstrup K. Trends in quality of care among patients with incident heart failure in Denmark 2003-2010: a nationwide cohort study. BMC Health Services Research 2013, 13:391

2. Elderly patients and women with incident HF are less likely to receive HF care according to clinical guideline recommendations. Inequalities in care contribute to inequalities in mortality (Study II).

   Paper II: Nakano A, Egstrup K, Svendsen ML, Schjødt I, Jakobsen L, Mehnert F, Johnsen SP. Age and sex-related differences in use of guideline-recommended care and mortality among patients with incident heart failure in Denmark. Age Ageing. 2016 ;45:635-42.

3. Fulfilment of process performance measures reflecting clinical guideline recommendations is associated with lower mortality among patients with incident HF (Study III).

   Paper III: Nakano A, Egstrup K, Svendsen ML, Schjødt I, Johnsen SP. Association between process performance measures and 1-year mortality among patients with incident heart failure: a nationwide study. In preparation

3. MATERIAL AND METHODS

3.1. Datasources

The studies in this thesis relied on data from Danish population-based registries (78), including the DHFR (39), the National Registry of Patients (79), the Civil Registration System (80), the Medical Register of the Danish Medicines Agency, the Integrated Database for Labour Market Research (81), and the Classification of Danish Hospitals and Departments (82).

3.1.1. The Danish Heart Failure Registry

All studies in this thesis used data from the DHFR. The Danish health care system provides tax-financed health care for all inhabitants of Denmark, including free access to hospital care. All medical emergencies, including HF, are exclusively admitted to public hospitals (83).

The DHFR started to monitor incident HF patients in 2003 with the aim of documenting and improving the quality of care at a national level (84). Participation is mandatory for all hospitals treating patients with HF. Evidence-based disease-specific quality of care performance measures have been developed relating to the structure, process, and outcome of care for HF. This includes prospective data collection, data analysis, evaluation, and interpretation, feedback to providers and managers, clinical audit, implementation of quality improvement, and public release of all data. To ensure the quality and completeness of the data, nationwide implementation pilot studies were carried out (84).

3.1.2. The National Registry of Patients

All three studies used data from the National Registry of Patients (79). The registry contains data on all patients discharged from public somatic hospitals in Denmark since 1977 and includes data on admissions and discharges with up to 20 diagnoses for each discharged patient from each hospital contact throughout life. Since 1995, data on outpatients and emergency room patients have also been collected (e.g., dates of admission and discharge for inpatients, dates of visit for emergency room patients). All diagnoses have been classified according to the Danish edition of the International

Classification of Diseases, 10^{th} edition (ICD-10), since 1994, and registration is mandatory. Using the National Registry of Patients makes allows construction of the complete hospitalization history of each patient (80).

3.1.3. The Civil Registration System

All three studies used data from the Civil Registration System. The purpose of the Civil Registration System is to administrate the personal identification number system. Since 1968, all Danish residents have been assigned a unique 10-digit personal identification number called the civil registration number at birth or immigration. The number is used in all public registries and enables unambiguous record linkage between databases. Among other variables, the Civil Registration System contains data on name, date of birth, place of residence, and vital status (updated daily). The validity of the recorded information is considered to be very high because registration is mandatory by law and the information is extensively used for administrative purposes (80,85).

3.1.4. Medical Register of the Danish Medicines Agency

The Medical Register of the Danish Medicines Agency contains information on all filled prescriptions, including the type and amount of drug and the date it was dispensed. From 1995 to the present, this information was collected for all prescription drugs at all Danish pharmacies (86).

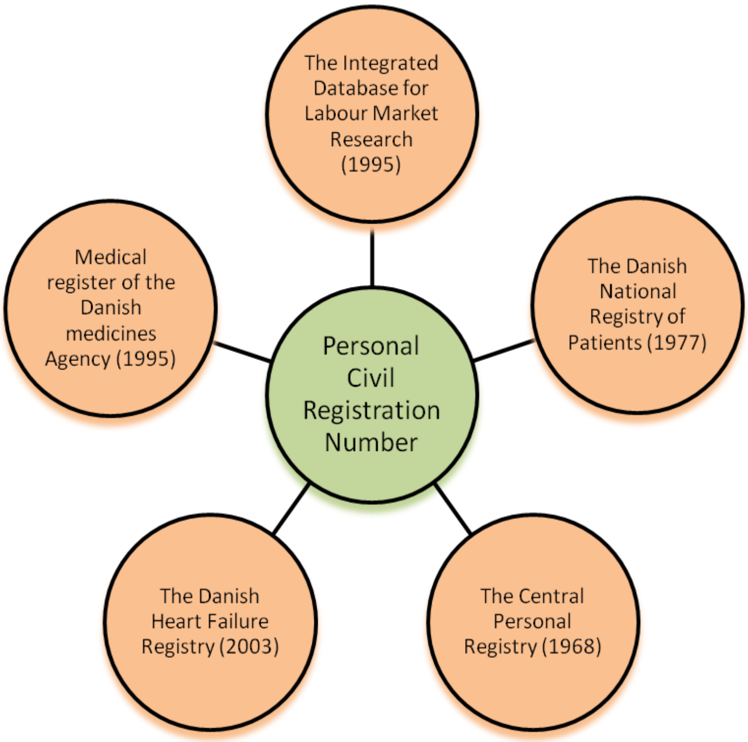
3.1.5. The Integrated Database for Labour Market Research

The Integrated Database for Labour Market Research at Statistics Denmark was established in 1980 and contains information on each Danish citizen regarding socioeconomic status, including data on income, employment status, education level, and marital status. The data are based on other registries in Statistics Denmark, including the tax authority registry (81).

3.1.6. The Classification of Danish Hospitals and Departments

All three studies used data from the Classification of Danish Hospitals and Departments. This registry is used to identify the service provider reporting to the National Registry of Patients. The registry uniquely identifies all Danish hospitals, hospital departments, and hospital units, and includes information on the primary medical specialty of each department/unit (82).

Figure 3. Individual level linkage of nationwide registries using a personal identification number.



3.2. Study design and study population

All three studies included in this thesis were designed as nationwide, population-based cohort studies covering the period 2003 to 2010 (both years inclusive). In all three studies, the study population was identified through the DHFR, which included patients aged ≥ 18 years with a first time hospitalization and a primary diagnosis of HF (including inpatients and outpatients) according to the ESC guidelines for the definition of HF and the Danish guidelines for treatment of HF issued by the Danish Society of Cardiology (12,51), as well as one of the following ICD codes: I11.0, I13.0, I13.2, I42.0, I42.6, I42.7, I42.8, I42.9, I50.0, I50.1, I50.2, I50.3, I50.8, I50.9.

The DHFR uses the following inclusion and exclusion criteria as defined by the expert panel (1 and 2 and/or 3):

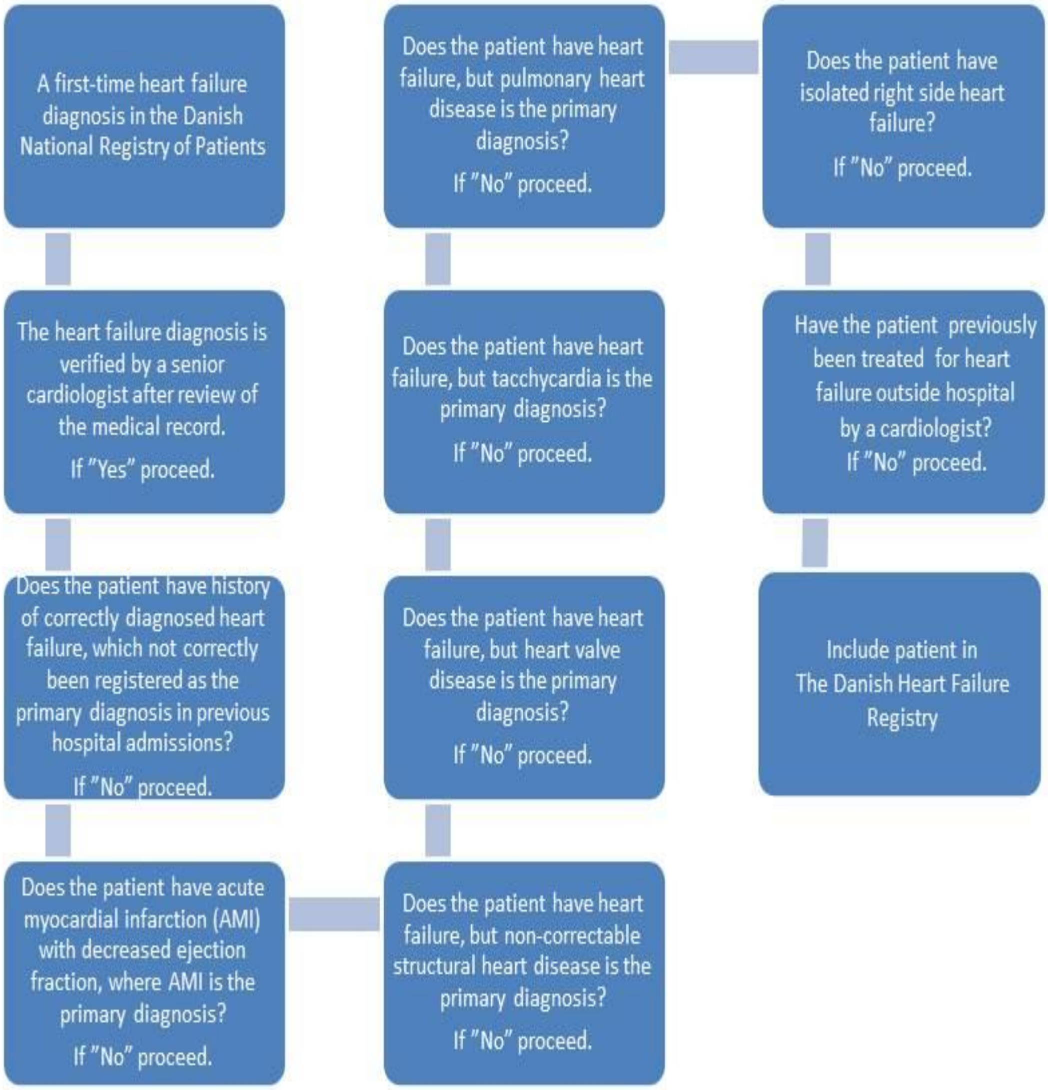
1: Symptoms of HF (breathlessness, ankle swelling, and fatigue) while resting and/or when having physical activity;AND

2: Objective symptoms of dysfunction of the heart, either reduced systolic function and/or diastolic dysfunction or increased filling pressure;AND/OR

3: Responding to treatment for HF.

Patients fulfilling the criteria can enter the flow chart shown in Figure 4 Please note that patients who are admitted with another primary diagnosis (atrial fibrillation, myocardial infarction, or chest infection) and HF as a secondary diagnosis will be captured by the registry if they later have a hospital contact in which HF is registered as the primary diagnosis. The inclusion and exclusion criteria are narrow and the DHFR does not aim to capture all persons with HF in the Danish population, but rather to identify incident patients with verified HF. Among the excluded patients are those with an incorrect HF diagnosis (87). In addition, patients for whom HF is not registered as the primary diagnosis probably include a high proportion of patients with multiple morbidities and a complex clinical history.

Figure 4. Inclusion and exclusion criteria in the DHFR.



A patient can only enter the database once. Only patients with a valid civil registration number were included. Studies I-III included 24,308-24,510 patients with a first time HF diagnosis. The minor difference in the study population reflects patients no longer living in Denmark and patients with an uncertain civil status.

3.3. Validity of the Danish Heart Failure Register

The usefulness of the registries, including the DHFR, is dependent on the validity of the data, including the completeness and quality of the recorded data (88-90). Therefore, the validity of the registered process performance measures in the DHFR was assessed as part of the Ph.D. project.

A computer-generated 5% random sample was obtained covering patients diagnosed between February 2003 and June 2007. A total of 700 patients were identified, representing the 46 HF units in Denmark reporting to the registry (Appendix Table 4). Four medical records could not be found, and one only consisted of nursing observations, leaving a total of 695 medical records for audit.

All medical records were reviewed by a single reviewer (AN, who is a certified and clinically experienced nurse in cardiology) using the data definitions for the DHFR. Data from the medical records were entered and re-entered into a database to ensure accuracy. The assessment made by the reviewer was used as a reference.

As seen in Table 5, there were substantial discrepancies in the registration of the process performance measures on NYHA classification, ACEI/ARBs, beta-blockers, physical training, and patient education. For the non-pharmacological performance, the results were characterized by the lack of relevant information in a high proportion of the medical records. For the pharmacological measures, the primary reason for the discrepancy was a missing date for starting the medication, as the staff member did not record it.

Table 5. Registration of process performance measures in the DHFR and by review of medical records.

Performance measure	Fulfillment of performance measure according to the DHFR (%)	Fulfillment of performance measure according to review of medical records (%)
Indicator 1 (Echocardiography)	489 (71)	478 (69)
Indicator 2 (NYHA classification)	334 (48)	232 (34)
Indicator 3a (ACEI/ARB)	265 (75)	291 (88)
Indicator 3b (Beta-blockers)	218 (63)	230 (69)
Indicator 4 (Physical training)	37 (11)	19 (6)
Indicator 5 (Patient education)	191 (61)	83 (25)

DHFR=Danish Heart Failure Registry, NYHA=New York Heart Association, ACEI=Angiotensin Converting Enzyme Inhibitor, ARB=Angiotensin Receptor Blocker.

Table 6 shows the overall sensitivity, specificity, and predictive values for each of the five process performance measures compared to the information available in the medical records. In general, agreement between the DHFR and medical records varied substantially across the individual performance measures. Sensitivity ranged from 31% to 93.5%, with three performances having a sensitivity of 80% or more (echocardiography: 88.6% [95% CI 0.85-0.91]; ACEI/ARB: 93.5% [95% CI 0.89-0.96]; beta-blockers: 83.6% [95% CI 0.73-0.89]). Specificity ranged from 70% to 96.7%, with four performances having a specificity of 80% or more (NYHA classification: 93.6% [95% CI 0.90-0.96]; beta-blockers: 80.5% [95% CI 0.65-0.91]; physical training: 96.7% [95% CI 0.94-0.99]; patient education: 92.5% [95% CI 0.85-0.97]). The positive predictive values (PPVs) ranged from 53.0% to 98.5%, with five process performance measures having a PPV of 80% or more (echocardiography: 90.6% [95% CI 0.87-0.93]; NYHA classification: 90.1% [95% CI 0.86-0.94]; ACEI/ARB: 98.5% [95% CI: 0.95-1.00]; beta-blockers: 94.9% [95% CI 0.90-0.98]; patient education: 89.9% [95% CI 0.80-0.96]). The negative predictive value (NPV) ranged from 33.3% to 92.1%, with one process performance measure having a NPV of 80% or more (physical training: 92.1% [95% CI 0.88-0.95]).

In summary, we found varying levels of agreement between data on delivered process performance measures of HF recorded in the DHFR and the original medical records. The variation was found in relation to sensitivity, specificity, PPV, and NPV. Documentation of the provided performance measures was incomplete in a high proportion of the examined medical records; thus, the medical records were a problematic gold standard in the validation process.

Table 6. Sensitivity, specificity and predictive values of data on processes of care registered in the DHFR, using medical records as the gold standard

	Verified positive/ total N	Sensitivity % (95% CI)	Verified negative/ total N	Specificity % (95% CI)	Verified N/ total N	PPV% (95% CI)	Total negative N/ total N	NPV% (95% CI)
Processes of care								
Echocardiography	435/491	88,6 (0.85-0.91)	156/201	77.6 (0.71-0.83)	435/480	90.6 (0.87-0.93)	156/212	73.6 (0.67-0.79)
NYHA classification	209/335	62.3 (0.57-0.68)	334/357	93.6 (0.90-0.96)	209/232	90.1 (0.86-0.94)	334/460	72.6 (0.68-0.77)
ACEI/ARB inhibitor	202/216	93.5 (0.89-0.96)	7/10	70.0 (0.34-0.93)	202/205	98.5 (0.95-1.00)	7/21	33.3 (0.15-0.57)
Betablockers	148/177	83.6 (0.73-0.89)	33/41	80.5 (0.65-0.91)	148/156	94.9 (0.90-0.98)	33/62	53.2 (0.40-0.66)
Physical training	9/29	31.0 (0.15-0.51)	234/242	96.7 (0.94-0.99)	9/17	53.0 (0.28-0.77)	234/254	92.1 (0.88-0.95)
Patient Education	62/162	38.3 (0.31-0.46)	86/93	92.5 (0.85-0.97)	62/69	89.9 (0.80-0.96)	86/186	46.2 (0.39-0.54)

NYHA=New York Heart Association, ACEI=Angiotensin Converting Enzyme Inhibitor, ARB=Angiotensin Receptor Blocker, PPV=Positive Predictive Value, NPV=Negative Predictive Value, CI=Confidence Interval.

3.4. Definitions of variables

3.4.1. Process performance measures for heart failure care and mortality

In all three studies, we included process performance measures as exposure or outcome variables. Data on the process performance measures were obtained from the DHFR.

The process performance measures agree with international clinical guidelines for HF care (12,38). A time limit was defined for each process in order to capture the timeliness of care (Table 7). In addition, patients were classified as eligible or ineligible for the individual processes of care depending on whether the staff identified contraindications, such as extremely low blood pressure when starting beta-blockers, delaying medication or not giving it at all, and making other solutions necessary. Only eligible patients were included in the analysis of individual process performance measures.

Table 7. Process performance measures monitored in the Danish Heart Failure Registry

measure	Definition and time limit
Echocardiography	Proportion of patients who undergo echocardiography
NYHA classification	Proportion of patients who undergo NYHA classification, within 3 months before until 4 weeks after admission
Medication (ACEI/ARBs)	Proportion of patients with reduced systolic function (LVEF ≤ 40 %) treated with ACEI/ARBs within 4 weeks of admission
Medication (Beta-blockers)	Proportion of patients with reduced systolic function (LVEF ≤ 40 %) who is treated with betablockers within 8 weeks of admission
Physical training	Proportion of patients with reduced systolic function (LVEF ≤ 40 %) referred to individual physical training within 8 weeks of admission
Patient education	Proportion of patients with reduced systolic function (LVEF ≤ 40 %) who started structured patient education (inclusive nutrition, physical training, understanding medical treatment, risk factors and symptoms of the disease) within 8 weeks of admission

In all three studies, mortality was included as an outcome and defined as death from all-cause within 1 year of hospital admission or the first outpatient contact with incident HF. The mortality was ascertained from the Civil Registration System. We also included a number of covariates in our analyses due to their potential associations with the exposures and outcomes investigated. We included information on some or all of the following covariates

For Study I, the covariates in our analyses were age, sex, LVEF, NYHA classification, previous AMI, stroke, COPD, diabetes, alcohol intake, smoking habits, and treatment for hypertension. The data were obtained from the DHFR for collection at hospital admission and 12 weeks after admission.

The covariates for studies 2 and 3 were the same as in Study I but with a difference in the retrieval of comorbid diseases, which were obtained through the National Registry of Patients.

Employment status was based on annual income collected from tax returns and other public registries. This data were obtained from the Integrated Database for Labour Market Research.

Pharmacological therapy included medication for ASA, clopidogrel, statins, diuretics, insulin, and oral diabetic medication. All prescriptions within the 12-month follow-up were obtained from the Medical Register of the Danish Medicines Agency. Drug use was defined as having filled at least one prescription within 12 months.

3.5. Statistical analysis

In all three studies, data were analyzed using Stata 13.0 (StataCorp LP, College Station, Texas).

3.5.1. Study I

We computed the proportion of patients fulfilling the individual process performance measures among those eligible and the proportion of HF patients who died within 1 year of admission or first contact, both overall for the entire study population and according to calendar year. We used binary regression for comparisons over time and computed the relative risk (RR) with 95% CIs using 2003 as a reference. A composite quality of care measure was also computed for each department. This measure was defined as the total number of received processes of care divided by the total number of processes of care relevant to the patients.

Mortality was analyzed for the entire study population and stratified according to LVEF (≤40% vs. >40%). We used multiple imputation to impute the missing values assuming that data were missing at random (91-93). We compared 1-year mortality between patients from 2010 and 2003 using multivariable Cox proportional hazards regression while controlling for patient characteristics.

3.5.2. Study II

First, we computed the proportion of women and men receiving the individual processes of care, defined as the fulfillment of specific performance measures monitored in the DHFR in the following age and sex groups: men and women ≤65 years, >65-80 years, and >80 years. Only patients fulfilling the inclusion criteria for the individual process performance measures who had available data were included in the analyses.

Binary regression was used to compute RRs for each age group with 95% CIs. Men in the youngest age group (≤65 years) served as the reference in all analyses. In addition, we performed supplementary analyses in which the population was stratified by age and men used as a reference within each age strata.

We used multivariable Cox proportional hazards regression to compare 1-year mortality according to age and sex. We adjusted for patient characteristics and calendar year and then, in an extended multivariable model, adjusted for the proportion of received processes of care and use of pharmacological therapy during follow-up for each patient. The latter was included as time-dependent variables with a prescription length of 90 days. To examine any changes in age- and sex-related differences in mortality, we repeated the analyses with stratification according to year of diagnosis (2003-2006 vs. 2007-2010). Analyses were also stratified according to LVEF (≤40% vs. >40%).

3.5.3. Study III

We used multivariable Cox proportional hazards regression to assess the association between fulfilment of the individual process performance measures and 1-year mortality.

First, we adjusted for patient baseline characteristics and then, in an extended multivariable model, adjusted for drug use at the time of admission and during follow-up, and performed mutual adjustment for other process performance measures. We repeated the analyses using the aggregated measure of overall quality of care (proportion of all performance measures being fulfilled) as the exposure.

3.6. Permissions

Permissions to use and link public registries were obtained from the Danish Data Protection Agency, the Danish clinical registries, and the National Board of Health.

4. RESULTS

4.1. Descriptive statistics

The three studies in this thesis covered the same study period (2003 to 2010) and the same hospitals took care of HF patients. Thus, there were no differences in the sociodemographic and clinical patient profiles between the studies.

4.2. Study I

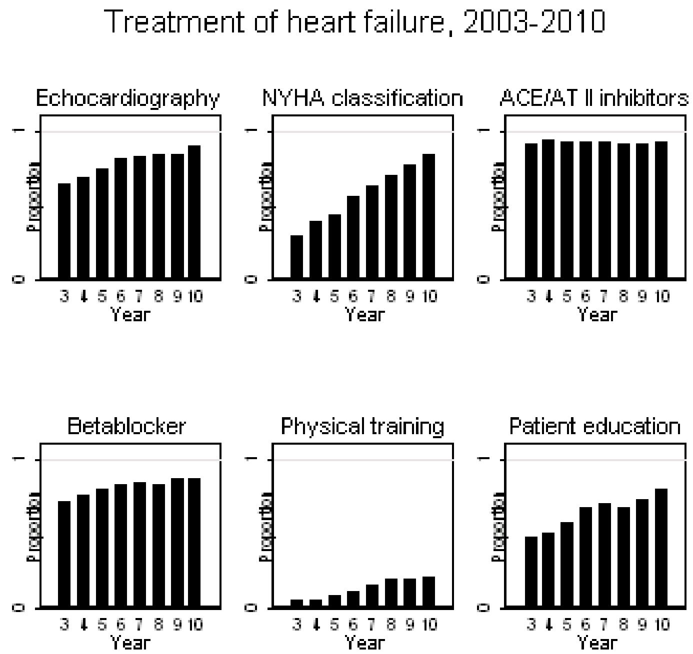
The fulfilment of process performance measures increased from 2003 to 2010 (Table 8 and Figure 5). NYHA classification and physical training was the two measures that improved the most. For the use of ACEI/ARBs, no overall changes were observed (RR 1.01, 95 % CI 0.99-1.04).

Table 8. Process performance measures among patients diagnosed with incident heart failure in Denmark, 2003-2010 (N= 24,504).

Total	2003 - 2010 N (%)	2003 alone N (%)	2010 alone N (%)	Crude RR (95% CI)
Process of care				
Echocardiograpy	19419 (79.5)	1010 (62.7)	3430 (90.5)	1.45 (1.39-1.50)
NYHA classification	15042 (61.6)	475 (29.4)	3237 (85.5)	2.91 (2.69-3.14)
ACEI/ARBs	12565 (93.0)	446 (92.0)	2628 (93.2)	1.01 (0.99-1.04)
Beta-blockers	11272 (84.4)	350 (72.6)	2489 (88.3)	1.23 (1.15-1.29)
Physical training	2278 (15.9)	39 (5.6)	631 (22.8)	4.04 (2.96-5.52)
Patient education	9852 (70.0)	273 (49.3)	2281 (81.4)	1.65 (1.52-1.80)

NYHA=New York Heart Association, ACEI=Angiotensin Converting Enzyme Inhibitor, ARB=Angiotensin Receptor Blocker

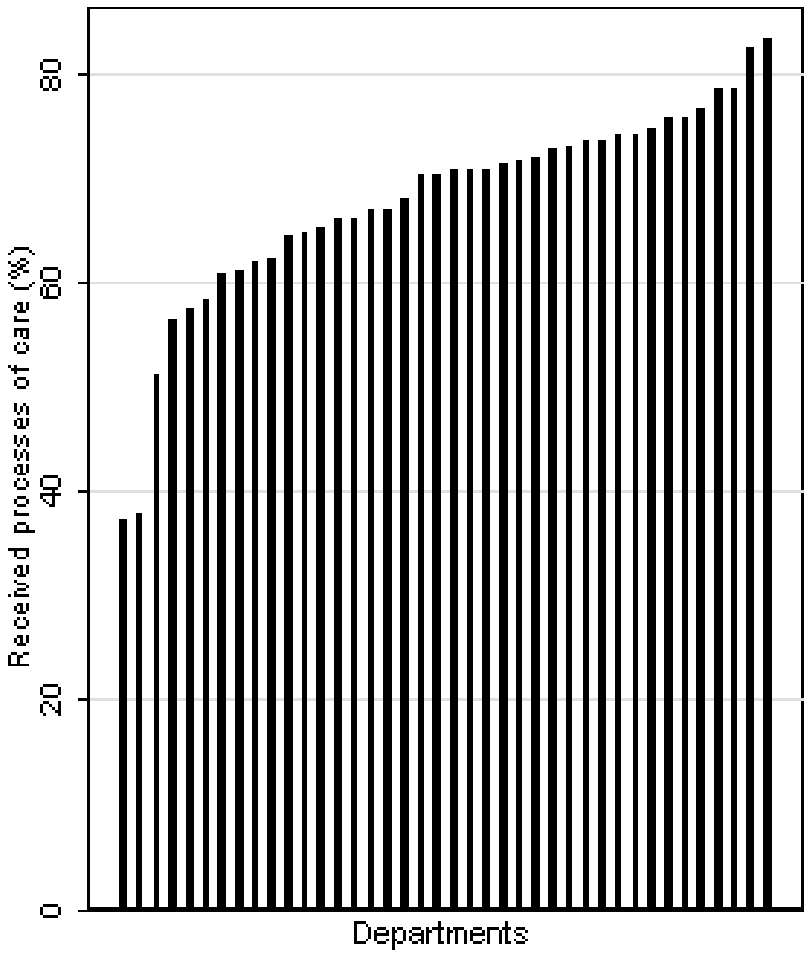
Figure 5. The proportions of patients who fulfilled the process performance measures between 2003 and 2010.



NYHA=New York Heart Association, ACE/AT II inhibitors=Angiotensin Converting Enzyme/Angiotensin II Inhibitors.

Figure 6 presents the overall composite process performance measure, reflecting the proportion of the individual process performance measures delivered in 2010 at the individual departments. Although overall improvements were observed for most performance measures, substantial variation in quality of care remained among Danish hospital departments treating patients with incident HF. The proportion of delivered recommended processes performance measures of care across the departments varied between 50% and 89%.

Figure 6. Overall composite process performance measure in 2010.



Overall 1-year all-cause mortality among patients registered in the DHFR decreased from 20.5% in 2003 to 12.8% in 2010 (Figure 7).

Figure 7. Cumulative mortality curves of 1-year mortality after first contact with incident HF.

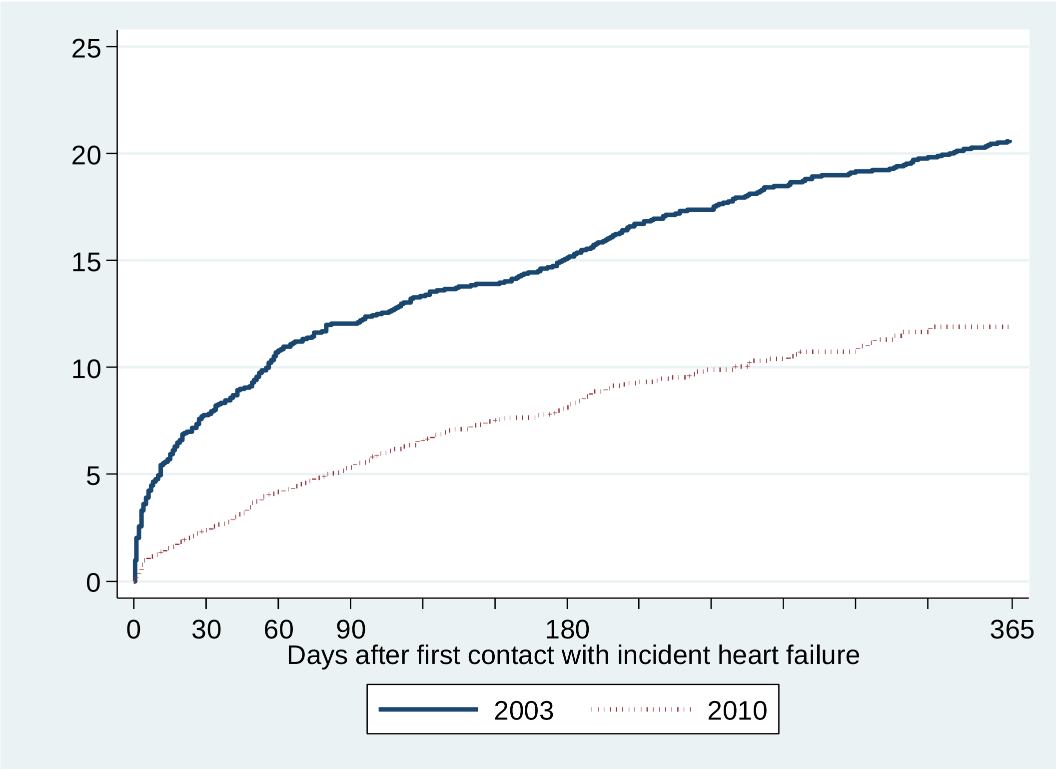


Table 9. One-year mortality among patients diagnosed with incident heart failure in Denmark in 2010 vs. 2003.

	Mortality 2003 N/total (%)	Mortality 2010 N/total (%)	Unadjusted HR (95% CI)	Adjusted HR * (95% CI)	Adjusted HR † (95% CI)
Total population	333/1624 (20.5)	488/3809 (12.8)	0.59 (0.51-0.67)	0.65 (0.56-0.75)	0.79 (0.65-0.96)
LVEF≤40%	277/1379 (20.1)	408/3141 (13.0)	0.61 (0.52-0.71)	0.67 (0.57-0.78)	0.85 (0.69-1.05)
LVEF>40%	56/245 (22.9)	79/668 (11.8)	0.47 (0.31-0.74)	0.58 (0.40-0.84)	0.51 (0.30-0.89)

*Adjusted for age and gender.

†Adjusted for the following patient characteristics: age, gender, LVEF, previous acute myocardial infarction, stroke, chronic obstructive pulmonary disease, treatment for hypertension, diabetes, alcohol intake, and smoking habits.

HR=Hazard Ratio, LVEF=Left Ventricular Ejection Fraction.

The overall adjusted hazard ratio (HR) for 1-year mortality was 0.79 (95% CI 0.65-0.96) after multivariable adjustment for patient characteristics (age, gender, LVEF, previous AMI, stroke, chronic obstructive pulmonary disease, diabetes, alcohol intake, smoking habits, and treatment for hypertension) between patients diagnosed in 2010 and those diagnosed in 2003. Analyses were also stratified for LVEF. The improvements in mortality appeared to be greater in patients with preserved EF than patients with reduced EF. However, the CIs overlapped.

4.3. Study II

In Study II, we found that increasing age was associated with a lower proportion of patients meeting the process performance measures for HF. This pattern was observed in both men and women, particularly for echocardiography, NYHA classification, physical training, and patient education. Sex-related differences were generally smaller, but the proportion of women receiving the individual processes of care tended to be lower than for men of the same age, particularly among patients >80 years of age (Table 10).

Table 10. Relative Risk (RR) for processes of care among patients with incident heart failure stratified by age and sex.

Processes of care	Patients who fulfilled the processes of care, n =yes/total (%)	RR (95 % CI)	Missing cases, n (%)
Echocardiography			
Men ≤ 65 years	4728/5341 (88.5)	1.00	613 (11.5)
Women ≤ 65 years	1591/1829 (87.0)	0.98 (0.96-1.00)	238 (13.0)
Men > 65-80 years	5494/6682(82.2)	0.92 (0.92-0.94)	1188 (17.8)
Women > 65-80 years	2724/3373 (80.8)	0.91 (0.90-0.93)	649 (19.2)
Men > 80 years	2469/3385 (72.9)	0.82 (0.81-0.84)	916 (27.1)
Women > 80 years	2252/3610 (62.4)	0.70 (0.69-0.72)	1358 (37.6)
NYHA classification			
Men ≤ 65 years	3928/5348 (73.5)	1.00	1420 (26.6)
Women ≤ 65 years	1299/1827 (71.1)	0.96 (0.94-1.00)	528 (29.0)
Men > 65-80 years	4427/6685 (66.2)	0.90 (0.88-0.92)	2258 (33.8)
Women > 65-80 years	2025/3373 (60.0)	0.82 (0.79-0.84)	1348 (40.0)
Men > 80 years	1800/3386 (53.2)	0.72 (0.70-0.75)	1586 (46.8)
Women > 80 years	1450/3608 (40.2)	0.55 (0.52-0.57)	2158 (59.8)
ACEI/ARBs			
Men ≤ 65 years	3397/3542 (95.9)	1.00	145 (4.0)
Women ≤ 65 years	1083/1130 (95.8)	1.00 (0.99-1.01)	47 (4.2)

Men > 65-80 years	3170/3933 (94.3)	0.98 (0.97-0.99)	223 (5.7)
Women > 65-80 years	1672/1798 (93.0)	0.96 (0.96-0.98)	126 (7.0)
Men > 80 years	1510/1723 (87.6)	0.91 (0.90-0.93)	213 (12.4)
Women > 80 years	1087/1269 (85.7)	0.89 (0.87-0.91)	182 (14.3)
Betablockers			
Men ≤ 65 years	3107/3522 (88.2)	1.00	415 (11.8)
Women ≤ 65 years	964/1109 (87.0)	0.98 (0.96-1.01)	145 (13.1)
Men > 65-80 years	3372/3912 (86.2)	0.98 (0.96-0.99)	540 (13.8)
Women > 65-80 years	1473/1771 (83.2)	0.94 (0.92-0.97)	298 (16.8)
Men > 80 years	1318/1695 (77.8)	0.88 (0.86-0.91)	377 (22.2)
Women > 80 years	945/1238 (76.3)	0.87 (0.84-0.89)	293 (23.7)
Physical training			
Men ≤ 65 years	718/3750 (19.2)	1.00	3032 (80.9)
Women ≤ 65 years	256/1183 (21.6)	1.13 (1.00-1.28)	927 (78.4)
Men > 65-80 years	658/4203 (15.7)	0.82 (0.74-0.90)	3545 (84.3)
Women > 65-80 years	303/1896 (16.0)	0.83 (0.74-0.94)	1593 (84.0)
Men > 80 years	184/1836 (10.0)	0.52 (0.45-0.61)	1652 (90.0)
Women > 80 years	145/1374 (10.6)	0.55 (0.47-0.65)	1229 (89.4)
Patient education			
Men ≤ 65 years	2792/3693 (75.6)	1.00	901 (24.4)
Women ≤ 65 years	891/1163 (76.6)	1.01 (0.98-1.05)	272 (23.4)

Men > 65-80 years	3013/4121 (73.1)	0.97 (0.94-0.99)	1108 (26.9)
Women > 65-80 years	1335/1876 (71.2)	0.94 (0.91-0.97)	541 (28.8)
Men > 80 years	1039/1780 (58.4)	0.77 (0.74-0.81)	741 (41.6)
Women > 80 years	704/1336 (62.7)	0.70 (0.66-0.74)	632 (47.3)

NYHA=New York Heart Association, ACEI=Angiotensin Converting Enzyme Inhibitor, ARB=Angiotensin Receptor Blocker, LVEF: Left Ventricular Ejection Fraction

As seen in Table 11, the proportion of men and women in the different age groups who died within 1 year ranged from 5.4% to 32.6% and from 6.6% to 33.8%, respectively. When adjusting for patient characteristics, the age-related differences in mortality were reduced, as reflected by the lower HRs (Table 11). Additional adjustment for differences in the use of guideline-recommended processes of care and pharmacological therapy during follow-up further reduced the HRs among the elderly patients (>80 years), but no substantial changes were observed among the younger patients (Table 11). No major sex-related differences in crude mortality were observed in any of the age groups, but elderly women with HF tended to have lower mortality than men of similar age in the adjusted analyses.

Table 11. Crude and adjusted 1 year mortality according to age and sex among patients with incident heart failure.

Age (years)	Sex	Patients who died n=yes/total (%)	Crude HR (95 % CI)	Adjusted HR* (95 % CI)	Adjusted HR** (95 % CI)
≤ 65	Men	291/5361 (5.4)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Women	117/1842 (6.6)	1.18 (0.95-1.46)	1.13 (0.91-1.41)	1.12 (0.90-1.40)
> 65-80	Men	947/6700 (14.1)	2.72 (2.39-3.11)	2.15 (1.87-2.47)	2.09 (1.82-2.40)
	Women	473/3379 (14.0)	2.71 (2.34-3.13)	1.98 (1.69-2.32)	1.92 (1.64-2.25)
> 80	Men	1108/3396 (32.6)	7.10 (6.24-8.07)	4.54 (3.93-5.25)	3.87 (3.35-4.48)
	Women	1223/3623 (33.8)	7.51 (6.61-8.54)	4.08 (3.51-4.75)	3.48 (2.99-4.05)

* Adjusted for patient characteristics

** Adjusted for patient characteristics, process performance measures, and use of pharmacological therapy during follow-up

HR=Hazard Ratio

4.4. Study III

In Study III, we examined the association between the process performance measures and 1-year mortality and found that the absolute 1-year mortality for the total population was 4159 deaths, corresponding to 17.1%. Fulfilling the process performance measures was associated with a lower mortality. The adjusted HR ranged from 0.56 (95% CI 0.51-0.62) for patient education to 1.00 (95% CI 0.91-1.11) for the initiation of beta-blocker therapy (Table 12).

Table 12. Association between fulfillment of performance measures and 1-year mortality

Process performance measure	Patients who died N = yes/total (%)	Crude HR (95 % CI)	Adjusted HR* (95 % CI)	Adjusted HR** (95 % CI)
Indicator 1: Echocardiography	2639/16613 (15.9)	0.40 (0.38-0.43)	0.63 (0.59-0.68)	0.74 (0.69-0.81)
Indicator 2: NYHA classification	1604/13321 (12.0)	0.35 (0.33-0.37)	0.48 (0.44-0.51)	0.61 (0.57-0.66)
Indicator 3a: ACEI/ARBs	1417/11037 (12.8)	0.45 (0.42-0.48)	0.72 (0.66-0.78)	0.79 (0.72-0.88)
Indicator 3b: Beta-blockers	1249/9927 (12.6)	0.47 (0.44-0.50)	0.78 (0.72-0.85)	1.00 (0.91-1.11)
Indicator 4: Physical training	189/2075 (9.1)	0.44 (0.38-0.50)	0.76 (0.65-0.88)	0.93 (0.81-1.10)
Indicator 5: Patient Education	766/9006 (8.5)	0.30 (0.28-0.33)	0.51 (0.47-0.56)	0.56 (0.51-0.62)

HR=Hazard Ratio, NYHA=New York Heart Association, ACEI=Angiotensin Converting Enzyme Inhibitor, ARB=Angiotensin Receptor Blocker.

*Adjusted for baseline characteristics

**Adjusted for baseline characteristics and use of ASA, clopidogrel, statins, diuretics, insulin, and oral diabetic medication during follow-up and mutual adjustment for other process performance measures

Table 13 shows that the association between meeting more processes of performance measures followed a dose-response effect. The HR was 0.28 (95% CI 0.24-0.32) for patients who fulfilled 75%-100% when adjusted for all covariates, compared to 0.51 (95% CI 0.47-0.55) for patients who fulfilled 0%-25% and had more than half the risk of death.

Table 13. Association between proportion of fulfilled process performance measures and 1-year mortality.

Proportion of criteria fulfilled	Patients who died N = yes/total (%)	Crude HR (95% CI)	Adjusted HR* (95% CI)
0 % -25%	1422/2303 (61.7)	Reference: 1	Reference:1
26 % - 50%	1342/5111 (26.3)	0.41 (0.38 – 0.44)	0.51 (0.47 – 0.55)
51 % - 75%	781/5333 (14.6)	0.20 (0.18 – 0.22)	0.32 (0.28 – 0.36)
76 % - 100%	603/7386 (8.2)	0.18 (0.16 – 0.20)	0.28 (0.24 – 0.32)

HR=Hazard Ratio

*Adjusted for baseline characteristics, and use of ASA, chlopidogrel, statins, diuretics, insulin and oral antidiabetics during follow-up

When restricting analyses to patients with LVEF ≤ 40%, we found that fulfillment of the performance measures was strongly associated with 1-year mortality. We did not include separate analyses for patients with LVEF > 40%, as the sample was too small to provide satisfying statistical precision.

5. DISCUSSION

5.1. Methodological considerations

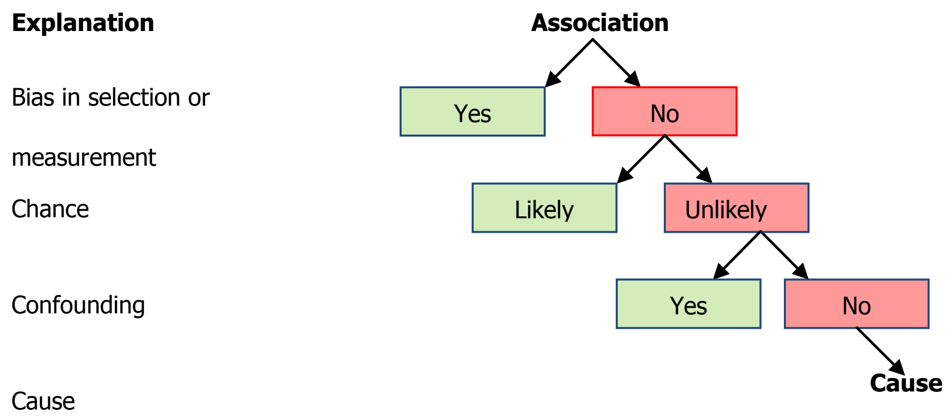
The effects of service interventions within HF care may occur via several mechanisms to improve patient outcome, such as through clinical pathways and specific clinical interventions (94). Furthermore, an outcome (e.g., death) is usually caused by many factors, and environment, behavior, and subcellular biology may act together in a causal pathway (95). The causal interpretation is further challenged as associations between service interventions and outcome may be reversible, contradicting the traditional epidemiological view of a necessary one-way temporal relationship from cause to effect (96). For example, the number of outpatients may increase, not because they are less diseased, but in order to make beds available in the hospitals.

This illustrates the complexity of causation and underlines the need to pay special attention to whether the results in this thesis can be interpreted as causes or associations.

5.2. Internal validity: Bias, confounding and chance

When considering a potential causal relationship, whether the observed association may be an artifact arising from bias, confounding, or chance must be determined. As illustrated in Figure 8, selection bias, information bias, confounding, and chance must be excluded before concluding that a causal association is likely (95).

Figure 8. Association and cause (95).



5.2.1. Selection bias

Selection biases are distortions that result from the selection of study participants and/or from factors that influence study participation (97). In the case of selection bias, the relationship between exposure and outcome differs between those who participate in the study and all those who were theoretically eligible for the study (97).

All studies in this thesis identified the study population through the DHFR independent of the exposures and outcomes in the individual studies. Participation in the DHFR is mandatory for all Danish hospital departments treating patients with HF, and extensive efforts are made to ensure the completeness of patient registration in the project, including detailed written instructions for patient registration and regular comparisons of the completeness of patient registrations to local hospital discharge registries, as well as structured audit processes carried out regularly on a national, regional, and local basis to critically assess the quality of data and results (39,87). Furthermore all included patients had their diagnosis confirmed by a senior cardiologist. Therefore, it seems unlikely that selection bias due to selection of study participants had a major influence on the results presented in the thesis. However, we do not know about the patients who do not make contact with the Danish hospitals or are treated in specialized cardiology practices or by their general practitioner, as they are not a part in the DHFR.

In conclusion, we think that the meticulous assessment and audit of correct patient selection and comparisons of results to the discharge registries reduce selection bias in our studies.

5.2.2. Information bias

Information bias is caused by measurement errors in the needed information. Measurement error that depends on the actual values of other variables is classified as differential misclassification, and measurement error that does not depend on the actual values of other variables is classified as non-differential misclassification (97).

The data used in the studies in this thesis inevitably suffer from misclassification because the information was collected in routine clinical settings. However, the data were collected prospectively and independent of the thesis; therefore, the misclassification was most likely non-differential. The studies were restricted to patients admitted to hospitals treating patients with HF and, as such, expected to follow the principles of HF care due to mandatory participation in the DHFR, which promotes consistent compliance with important clinical guidelines and assessment of essential prognostic factors. Inherent variation in the registration practices between HF units was further minimized by the use of uniform registration forms (98) and detailed written data definitions and instructions (39,99). This will inevitably reduce the variation in HF treatments and registration practices.

Eligibility for the specific processes of care was determined by the staff, which may be a cause for concern, as health professionals could prioritize differently, particularly if there are systematic differences in assessing eligibility (e.g., age- and sex-related differences). We examined the validity of the process performance data recorded in the DHFR but found the medical records to be a problematic gold standard, which made it difficult to draw firm conclusions about the accuracy of the recorded data. However, the overall impression was that any misclassification was most likely of a non-differential nature.

In all three studies, one of the outcomes was death. Information bias from errors in this outcome is unlikely, as deaths were recorded completely and independently of indicators, prognostic factors, and hospital department by the Danish Civil Registration System.

In conclusion, the main potential sources of information bias are the risk of bias due to non-differential misclassification. However, the influence of information bias is generally thought to be low.

5.2.3. Confounding

Confounding may be considered a confusion of effects (97,100). To be a confounder, a variable must be associated with the exposure, be an extraneous risk factor for the outcome, and cannot be an intermediate step in the causal path between the exposure and the outcome (97). The main limitation of the studies in this thesis is the non-randomized design. Consequently, the results may be influenced by residual confounding due to the use of crude variables for some of the included covariates, such as comorbidity, HF severity, or unaccounted socioeconomic factors (101,102).

However, evaluating the importance of care for HF patients based on their clinical presentation, we determined that patients found eligible for care will inevitably minimize the risk of confounding by indication. Several precautions were taken to minimize the impact of possible confounding. We adjusted for a wide range of known prognostic factors, including age, gender, comorbidities, socioeconomic factors, and blood pressure

(103). The findings in Studies I and II were generally robust to confounder adjustment, which may indicate that confounding has no crucial influence on the results, though it should be noted that the average patient profile in the DHFR has changed over time and may have affected the findings in Study I in particular. It should be noted that the DHFR was challenged, during the first years after its launch, with a substantial proportion of patients with missing data for some of the variables.

Extensive confounder adjustment was also applied in Study III, but caution appears to be warranted when interpreting the findings. The majority of the examined associations between the individual process performance measures and mortality appeared to be biologically and clinically plausible and in agreement with previous findings. The exception was early initiation of beta-blocker therapy. Here, the unadjusted and partially adjusted analyses indicated a protective effect of beta-blocker therapy, which is in line with findings from phase 3 clinical trials and observational studies (104). However, in the fully adjusted analysis, no association was observed, which may potentially be attributed to a close correlation with fulfilment of other process performance measures, leading to over-adjustment when mutually adjusting for the other process performance measures.

In conclusion, considering the non-randomized design of the studies, the results may be influenced by confounding. Presumably, there is little indication that confounding could change the overall conclusions of the studies in this thesis, as our results were also found by some of the other studies on the same topic. However, the results, particularly the strength of the associations reported in Studies I and III, should probably be interpreted with some caution.

5.2.4. Chance

Random error resulting from chance is inherent in all observations, and a summary measure of the statistical precision of the point estimate is needed (105). In this thesis, the statistical precision of the point estimates was reflected by 95% CIs; i.e., if the study was repeated many times, the confidence limit would contain the true value in 95% of the repetitions (105). In all of our main analyses in Studies I-III, the large study populations resulted in high statistical precision. However, the statistical precision of the associations was lower in some of the subanalyses. Therefore, some caution is required when interpreting the findings from these subanalyses, as they were more sensitive to chance.

In conclusion, our studies in this thesis are large population-based studies, which have a lower risk of rejecting a true difference/association due to lack of statistical precision. The main risk of chance findings is probably related to the multiple comparisons being made in the data analyses.

5.2.5. Summary: Internal validity

The main strengths of the studies in this thesis are the population-based designs, detailed and prospective data collection, almost complete follow-up of all outcomes, and the large study populations. These features minimized the risk of selection and information bias. However, the results may be affected by unaccounted confounding or residual confounding because of the observational study designs. The findings in this thesis should be considered associations and not evidence of causal relationships.

5.3. External validity

The population-based designs of the studies, the high completeness of patient registration in the DHFR (87), and the global initiatives to standardize HF performance (12,50,106) suggest that the findings may apply to other settings. However, differences exist between countries in the management of patients with HF (107,108). Therefore, before generalizing the findings in this thesis to other care settings, it is necessary to consider whether the factors that distinguish the target population and health care systems from the study populations and settings in this thesis could somehow modify the observed associations.

5.4. Comparison of Studies I-III to existing studies

5.4.1. Trends in quality of care among patients with incident heart failure in Denmark 2003-2010: A nationwide cohort study (Study I)

Our findings are in agreement with the few studies published thus far on trends in quality of HF care following implementation of quality improvement initiatives. Yet, it is difficult to compare our results with those from other countries because the inclusion criteria and number of patients included are quite different. In addition, registration in the DHFR is mandatory, in contrast to the case in other studies, including whereas some of the major US studies (e.g., OPTIMIZE-HF and GWTG HF) include hospitals that are self-selected and may not be entirely representative of national care patterns and clinical outcomes (75).Therefore, it should be noted that our studied population concerns the patients in the DHFR and not the total Danish HF population.

Our development and implementation of process performance measures for HF was nationwide and was followed by an apparent improvement in the use of the guideline recommendations for HF care in Denmark. These findings are very much in line with the findings from IMPROVE-HF (44).

We observed substantial variations between the hospital departments in the fulfillment of process performance measures although the overall national performance improved over time, following yearly national audits in which the results of HF care were discussed and recommendations given. Similarly, the GWTG-HF demonstrated that hospitals enrolled in the program had better process performance measures for the specific performance of ACEI/ARBs and discharge instructions, partly supporting the findings in our study, as we found a trend for increased discharge instruction (patient education) but not ACEI/ARBs (35).

Our findings for ACEIs were supported by the OPTIMIZE-HF, in which the prescription at discharge did not improve during the 2-year study. They also found trends for reduced in-hospital mortality and post-discharge death (109).

The decrease in 1-year mortality from 2003 to 2010 in our study was also found by Kfoury et al., who demonstrated that adherence to Joint Commission on Accreditation of

Healthcare Organizations (JCAHO) core measures was associated with improved 1-year survival after discharge for patients hospitalized with HF (n=2958) (67).

In conclusion, Study I adds further evidence to the hypothesis that systematic quality improvement initiatives may actually improve quality of care, which may translate into better clinical outcomes, including lower mortality. However, much remains to be clarified regarding the optimal design of (cost) effective quality improvement strategies.

5.4.2. Age-and sex-related differences in use of guideline-recommended care and mortality among patients with incident heart failure in Denmark (Study II)

In Study II, we found older age to be associated with lower use of guideline-recommended processes of HF care, both pharmacological and non-pharmacological. The pharmacological findings were supported by Komajda et al., who found that treatment with ACEI or ARBs and beta-blockers is less commonly prescribed in older (octogenarians) patients compared to younger patients. The combination of ACEI/ARB and beta-blockers was less frequently used in older patients (42% vs. 55% in younger patients, $p<0.001$), and high doses of ACEI/ARBs and beta-blockers were less frequently prescribed (ACEI/ARB 30% vs. 34.5%, $p<0.05$ and high dose betablockers 12% vs. 18%, $p<0.001$, respectively) (48,55). Fonarow et al. also examined non-pharmacological treatment, finding that fewer older patients underwent measurements of LVEF. Overall, 7345 patients (15%) had no left ventricular function assessment reported, most of whom were women (57%) (48), which supports our study that found a significant difference for patients >80 years of age. Furthermore, Fonarow et al. found that discharge education did not differ by age group (<75 vs. ≥75 years: 57.5 vs. 49.7, $p<0.001$) (48). This contradicts the findings from our study, as we found a significant decrease for patient education in the old age group (>80 years).

We found no sex-related differences in pharmacological treatment, which is supported by the review by Brandsaeter et al. (59). In contrast, other studies have found female sex to be associated with lower use of guideline-recommended drugs (58,110,111). For the non-pharmacological treatment, we found sex-related differences in the use of echocardiography, which is in accordance with findings from Fonarow et al. (48).

Survival was similar for men and women. Our results are supported by Brandsaeter et al., who found no sex-related differences in mortality among HF patients with coronary etiology (59). Jimenéz-Narvarro et al. also found comparable survival rates among men and women (111). In contrast, Vaartjes et al. found both 1 and 5-year mortality to be higher in men than women for patients >65 years of age (112).

In conclusion, Study II confirms and extends previously reported age-related differences in quality of HF care and mortality. The evidence is more inconsistent when it comes to sex-related differences, and we did not find indications of any substantial differences in HF care in Denmark when comparing men and women of similar age.

5.4.3. Association between process performance measures and 1-year mortality among patients with incident heart failure in Denmark (Study III)

Our findings in Study III are supported by a number of previous studies that also reported an association between performance measures of HF care and lower mortality (67,113-116). However, the evidence is not entirely consistent, as other studies found no or little association between the fulfillment of performance measures and outcomes for HF patients (75,117,118).

Patient education is a commonly used process performance measure. Our results concerning patient education are in accordance with a number of other studies reporting an association of patient education with a lower risk of readmission and death (67,117,119). Fonarow et al. pointed out that patient education for HF is associated with benefit, especially as a cumulative effect (66). Patient education also influences the quality of life after diagnosis and appears to be associated with reductions in both mortality and readmissions (120,121). However, other studies found no strong association, but presented stronger evidence for the benefit of using patient education at discharge than earlier studies (75,122).

For the pharmacological part of our study, our findings were supported by other studies that found a protective effect of ACEI/ARBs on mortality (72,76). Beta-blockers did have a protective effect in our study, but when using a full model to adjust for a wide range of prognostic factors, as we did for ACEI/ARBs, the protective effect disappeared. This contradicts most of the studies on HF, in which beta-blockers had a protective effect on mortality (72,72,76). Fonarow et al. found beta-blockers to be one of the process performances with the strongest 24-month survival benefit (66). We found indications of a dose-response pattern in our analyses, which also was supported by Fonarow et al. (66).

In conclusion, Study III revealed that, when meeting guideline-recommended process performance measures for HF care, substantially lower 1-year mortality is achieved among incident HF patients.

6. CONCLUSIONS

STUDY I

Use of guideline-recommended processes of care increased from 2003 until 2010, and 1-year mortality decreased following the initiation of a systematic quality of care improvement initiative among incident HF patients in Denmark.

STUDY II

Older patients with HF are less likely to receive guideline-recommended processes of care, irrespective of sex. The lower level of care may contribute to the excess mortality observed among older patients.

STUDY III

Meeting process performance measures reflecting clinical guideline recommendations for HF care is associated with substantially lower 1-year mortality among incident HF patients.

7. PERSPECTIVES

Even though Study I adds further evidence to the hypothesis that systematic quality improvement initiatives may actually improve quality of care, and translate into lower mortality, much remains to be clarified regarding the effectiveness of quality improvement strategies. The Danish health care system provides unique possibilities for identifying overall links between health care performance and clinical outcome and is an optimal setting for conducting large population-based studies of HF. The availability of updated and detailed nationwide information may guide clinicians and health care decision makers and provide a basis for further research.

This thesis underlines the need for continued efforts to ensure high quality care for HF patients through adherence to guidelines, and also acknowledges the importance of data registration in the DHFR and the validity of the registered data in the database. The registry provides invaluable clinical information, but the total number of patients with missing data is large, though patients have relatively few missing data on the individual variables, if not taking NYHA classification into account. Further improvement in registration would optimize the foundation for clinical improvements and research applicability and make it possible to use data from the DHFR in everyday clinical practice, which would be important for planning, predicting prognosis, monitoring, and improvement of quality and research (12,123).

Fulfilling the process measures in Study I seemed to have an impact on mortality. However, implementing process measures can be difficult because they require constant awareness and updating as the science of medicine advances. In addition, to be valid, process measures should have links to outcomes, or at least be determined by consensus methods to be judged by clinical experts as important to patient outcomes (124).

Twenty-five percent of Danish citizens will be >65 years of age in 2042, (125). The age-specific incidence of HF has to be reduced considerably to counteract the demographic changes in the population.

We are challenged by the difficulty in diagnosing HF, as it can be categorized as HFrEF, HFpEF, and HF with mid-range EF (HFmrEF) and is followed by comorbidities, such as obesity, hypertension, diabetes, and COPD (126-128). The number of older people with HF is increasing. Our data comprise the Danish population entered into the database and, as early risk stratification and early and accurate diagnosis of HF could identify high risk patients (126), we have to be careful with the data from the beginning (e.g., the correct diagnosed HF patient, typing the correct data into the database, and analyzes the correct way). There is no clear evidence that novel therapeutic interventions can modify the natural history of HFpEF (129).

More knowledge about the care pathways and patient outcomes following hospital discharge are needed (130).

Little is known about how patients manage quality of life and compliance with treatments despite information and HF learning courses after admission to the hospital. Education is an important component and may improve adherence and clinical outcomes, as well as achieving patient responsibility for their own health (131-133). RCTs are the generally trusted method for obtaining answers to questions in routine clinical practice. Randomization could be used within clinical registries of high quality; registry-based RCTs (RRCTs) could become the next major milestone in the quest for improving practice. Importantly, RRCTs would not replace RCTs, but complement them, allowing bigger data for smaller budgets (134).

We have to continuously develop and update clinical guidelines and have to get better at including the individual patient perspective in the treatments and databases to get the patient's point of view.

8. SUMMARY

Heart failure (HF) is a major public health challenge given the high incidence, high mortality, and high burden of morbidity among survivors. Evidence-based care may have a beneficial effect on the outcome of HF, but little is known about the quality of care among real-life patients, including the effect of quality improvement initiatives, unwarranted variation in the quality of care, and the clinical implications of inadequate care. The main objective of this thesis was to examine the fulfilment of process performance measures of HF care in Denmark, including age- and sex-related differences and the association with mortality.

The thesis is based on three population-based cohorts using data from Danish population-based medical registries (the Danish Heart Failure Registry, the National Registry of Patients, the Civil Registration System, the Medicines Agency Denmark, and the Integrated Database for Labour Market Research) to obtain patient-level data on hospital discharges, vital status, filled prescriptions, and socioeconomic status. The study population included patients with incident HF who were admitted to either a hospital or HF outpatient clinic and registered in the database during 2003-2010. The process performance measures reflected whether clinical guideline recommendations for the management of HF patients were followed.

Study I included 24,504 patients. The proportion of patients undergoing the individual process performance measures increased substantially between 2003 and 2010 (i.e., use of echocardiography (relative risk (RR) 1.45, 95% confidence interval (CI) 1.39-1.50), NYHA classification (RR 2.91, 95% CI 2.69-3.14), beta-blockers (RR 1.23, 95% CI 1.15-1.29), physical training (RR 4.04, 95% CI 2.96-5.52), and patient education (RR 1.65, 95% CI 1.52-1.80). ACEI/ARBs were the only exception, as no overall changes were observed (RR 1.01, 95% CI 0.99-1.04). Overall 1-year all-cause mortality among patients decreased from 20.5% to 12.8% during the study period. The adjusted hazard ratio (HR) for 1-year mortality was 0.79 (95% CI 0.65-0.96) when comparing patients admitted in 2010 and 2003.

Study II included 24,308 patients. Among both men and women, increasing age was associated with a lower chance of receiving care that fulfilled the guideline-recommended process performance measures. Using men ≤ 65 years of age as a reference, the RR for fulfilling the process performance measures varied for men >80 years of age from 0.52 (95% CI 0.45-0.61) to 0.91 (95% CI 0.90-0.93). For women >80 years of age, the RR varied from 0.55 (95% CI 0.52-0.57) to 0.89 (95% CI 0.87-0.91). The sex-related differences were smaller, though the proportion of women receiving the individual processes of care tended to be lower than for men of the same age.

Study III also included 24,308 patients. A total of 4159 patients (17.1%) died within 1 year of diagnosis. Fulfilling the process performance measures was associated with a lower mortality; HRs ranged from 0.56 (95% CI 0.51-0.62) for patient education to 1.00 (CI 0.91-1.11) for initiation of beta-blocker therapy. The association between meeting more process performance measures and 1-year mortality exhibited a dose-response pattern. Using patients with 0%-25% of measures fulfilled as a reference, patients who received care and fulfilled 76%-100% of the measures had an adjusted HR of 0.28 (95% CI 0.24-0.32), whereas patients who received care meeting 26%-50% of the measures had an adjusted HR of 0.51 (95% CI 0.47-0.55). Stratifying the analyses according to patients with LVEF ≤ 40% and LVEF > 40%, we found that fulfillment of the performance measures was strongly associated with 1-year mortality for patients with LVEF ≤ 40%, whereas the findings for patients with LVEF > 40% were less clear, with no apparent association with 1-year mortality and wide CIs. Thus, we found that meeting more of the process performance measures reflecting the guidelines for HF was associated with lower 1-year mortality among real-life patients in Denmark.

In conclusion, fulfillment of evidence-based HF process performance measures has increased with time following the introduction of a nationwide mandatory quality improvement initiative based on systematic monitoring and auditing of guideline-recommended performance measures. Elderly patients with incident HF are less likely to receive care according to guideline recommendations. In contrast, no substantial sex-related differences in care have been found. Meeting the process performance measures, which reflects care in concordance with clinical guideline recommendations, is associated with lower 1-year mortality among patients with incident HF.

9. DANISH SUMMARY

Hjertesvigt er en omfattende sundhedsmæssig udfordring, med høj incidens , høj mortalitet og megen comorbiditet blandt de overlevende. Evidensbaseret behandling og pleje kan have en gunstig effekt på outcome af hjertesvigt, men der er ikke så stor viden om kvaliteten af behandling og pleje I forhold til patienterne som ses på de kardiologiske afdelinger, herunder effekten af kvalitetsudviklingsinitiativer, uventet variation I kvaliteten og kliniske implikationer af utilstrækkelig behandling og pleje. Hovedformålet med denne ph.d. afhandling var at undersøge hvorvidt opfyldelse af proces performance indikatorer for danske hjertesvigtpatienter, inklusiv alders og kønsrelaterede forskelle, har en sammenhæng med dødelighed.

Ph.d. afhandlingen er baseret på tre populationsbaserede kohorter som anvender data fra Danske populationsbaserede medicinske register (Dansk Hjertesvigtdatabase, Landspatientregistret, det Centrale Personregister, lægemiddelstatistikregistret og Integreret Database for Arbejdsmarkedsforskning), for at bruge data i forhold til hospitals indlæggelse og udskrivelse, vital status, udfyldte recepter og socioøkonomiske status.

Studiepopulationen inkluderede patienter med incident hjertesvigt enten indlagt på hospital eller, ambulant på en hjertesvigtklinik, og registreret i databasen i perioden fra 2003 til 2010, inklusiv begge år. Proces performance indikatorerne reflekterer hvorledes de anbefalede kliniske guidelines for hjertesvigt følges.

Studie 1 inkluderede 24.504 patienter. Andelen af patienter som fik opfyldt de individuelle process performance indikatorer steg betragteligt mellem 2003 og 2010, f.eks. brug af ekkokardiografi (Relativ Risiko (RR) 1.45, 95% Confidens Interval (CI) 1.39-1.50), NYHA classifikatin (RR 2.91, 95% CI 2.69-3.14), betablocker (RR 1.23, 95% CI 1.15-1.29), fysisk træning (RR 4.04, 95% CI 2.96-5.52), og patient undervisning (RR 1.65, 95% CI 1.52-1.80), ACE/ATII inhibitorer var den eneste undtagelse da der ikke her blev observeret nogen forskel (RR 1.01, 95% CI 0.99-1.04). Overordnet faldt 1-års dødeligheden fra 20.5% til 12.8% gennem studie perioden. Den justerede Hazard Ratio (HR) for 1-års dødelighed var 0.79 (95% CI, 0.65-0.96) når man sammenlignede patienter indlagt i 2010 med de som blev indlagt i 2003.

Studie 2 inkluderede 24.308 patienter. Højere alder var associeret med en lavere chance for at modtage behandling og pleje som opfylder de anbefalede kliniske guidelines, og dette var gældende for både kvinder og mænd. Når mænd ≤ 65 år bruges som reference, er den RR for at opfylde process performance indikatorerne varierende for mænd >80 år fra 0.52 (95% CI 0.45-0.61) til 0.91 (95% CI 0.90-0.93). For kvinder >80 år, varierede RR fra 0.55 (95% CI 0.52-0.57) til 0.89 (95% CI 0.87-0.91). De kønsrelaterede forskelle var mindre endskønt andelen af kvinder som får opfyldt de individuelle performance processer tenderer til at være lavere end for mænd på samme alder.

Studie 3 har ligeledes inkluderet 24.308 patienter. I alt 4159 patienter døde indenfor 1 år fra de fik stillet diagnosen, svarende til 17.1%. Opfyldelse af process performance indikatorerne var associeret med en lavere dødelighed HRs spændte fra 0.56 (95% CI 0.51-0.62) for patient undervisning til 1.00 (95% CI 0.91-1.11) for betablokker behandling. Associationen I forhold til at få opfyldt flere af performance processerne og 1 års dødelighed viste et invers dosis respons mønster. Hvis patienter som får opfyldt 0-25% af processerne som reference, har patienter som får opfyldt mellem 75-100% af processerne en justeret HR på 0.28 (95% CI 0.24-0.32) mens patienter som får opfyldt fra 25-50% af processerne har en justeret HR på 0.51 (95% CI 0.47-0.55). Stratificering af analyserne I forhold til LVEF ≤40% og LVEF>40%, fandt vi at opfyldelsen af performance indikatorerne var stærkt associerede med 1 års dødelighed for patienter med LVEF ≤40%, hvorimod patienter med LVEF>40% ikke havde en klar association med 1 års dødelighed, og med brede konfidensintervaller. Vi fandt at opfyldelse af de anbefalede performance indikatorer, valgt ud fra guidelines for hjertesvigt er associeret med lavere 1 års dødelighed blandt patienter på de danske kardiologiske afdelinger.

Sammenfattende viser studierne at opfyldelsen af evidensbaserede proces performance indikatorer har været stigende over tid når der iværksættes et nationalt kvalitetsudviklings initiativ med systematisk monitorering og auditering af performance indikatorerne. Ældre patienter med incident hjertesvigt får ikke samme optimale pleje i henhold til guideline-rekommandationerne som yngre patienter. Der var ingen betydende forskel i køn i forhold til modtagelsen af relevant pleje. Opfyldelse af proces performance indikatorer, som reflekterer plejen i overensstemmelse med guideline-rekommandationerne er associeret med lavere 1 års risiko for død blandt patienter med incident hjertesvigt.

10. REFERENCES

(1) Schocken DD, Benjamin EJ, Fonarow GC, Krumholz HM, Levy D, Mensah GA, et al. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. Circulation 2008 May 13;117(19):2544-2565.

(2) van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail 2016 Mar;18(3):242-252.

(3) McMurray JJ, Pfeffer MA. Heart failure. Lancet 2005 May 28-Jun 3;365(9474):1877-1889.

(4) Holmstrom A, Sigurjonsdottir R, Edner M, Jonsson A, Dahlstrom U, Fu ML. Increased comorbidities in heart failure patients >/= 85 years but declined from >90 years: data from the Swedish Heart Failure Registry. Int J Cardiol 2013 Sep 10;167(6):2747-2752.

(5) Pongmoragot J, Lee DS, Park TH, Fang J, Austin PC, Saposnik G, et al. Stroke and Heart Failure: Clinical Features, Access to Care, and Outcomes. J Stroke Cerebrovasc Dis 2016 May;25(5):1048-1056.

(6) Iyngkaran P, Tinsley J, Smith D, Haste M, Nadarajan K, Ilton M, et al. Northern Territory Heart Failure Initiative-Clinical Audit (NTHFI-CA)-a prospective database on the quality of care and outcomes for acute decompensated heart failure admission in the Northern Territory: study design and rationale. BMJ Open 2014 Jan 29;4(1):e004137-2013-004137.

(7) Gasior M, Pyka L, Gorol J, Hawranek M, Tajstra M, Slonka G, et al. COnteMporary Modalities In Treatment of Heart Failure: report from the COMMIT-HF Registry. Kardiol Pol 2015 Nov 24.

(8) Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S, Goto D, Takeshita A, JCARE-CARD Investigators. Clinical characteristics and outcome of hospitalized patients with heart failure in Japan. Circ J 2006 Dec;70(12):1617-1623.

(9) Maggioni AP, Van Gool K, Biondi N, Urso R, Klazinga N, Ferrari R, et al. Appropriateness of Prescriptions of Recommended Treatments in Organisation for Economic Co-operation and Development Health Systems: Findings Based on the Long-Term Registry of the European Society of Cardiology on Heart Failure. Value Health 2015 Dec;18(8):1098-1104.

(10) Cleland J, Dargie H, Hardman S, McDonagh T, Mitchell P. National Heart Failure Audit. April 2012 - March 2013. National Institute for Cardiovascular Outcomes Research

(NICOR), Institute of Cardiovascular Science, University College London 2013 21 November 2013:1-86.

(11) Heebøll-Nielsen N, Holme P. Klinisk Vejledning for almen praksis. Kronisk systolisk hjerteinsufficiens . dsam 2013;1. udgave:1-41.

(12) Authors/Task Force Members, Document Reviewers. 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 J Heart Fail 2016 May 20.

(13) Lam CS, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40-50%). Eur J Heart Fail 2014 Oct;16(10):1049-1055.

(14) Orso F, Fabbri G, Maggioni AP. Epidemiology of Heart Failure. Handb Exp Pharmacol 2016 Oct 8.

(15) Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart 2007 Sep;93(9):1137-1146.

(16) Snyder R, Sean M, Kevin T. Diagnosis and treatment of the Patient With Heart Failure. Mar 29 2015; Available at: http://www.emsworld.com/article/12053437/diagnosis-and-treatment-of-the-patient-with-heart-failure. Accessed Accessed May 29, Accessed 2016.

(17) Roger VL. Epidemiology of heart failure. Circ Res 2013 Aug 30;113(6):646-659.

(18) Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB, et al. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. JACC Heart Fail 2014 Apr;2(2):97-112.

(19) Kristensen SL, Kober L, Jhund PS, Solomon SD, Kjekshus J, McKelvie RS, et al. International geographic variation in event rates in trials of heart failure with preserved and reduced ejection fraction. Circulation 2015 Jan 6;131(1):43-53.

(20) Stromberg A, Brostrom A, Dahlstrom U, Fridlund B. Factors influencing patient compliance with therapeutic regimens in chronic heart failure: A critical incident technique analysis. Heart Lung 1999 Sep-Oct;28(5):334-341.

(21) Abshire M, Xu J, Dennison Himmelfarb C, Davidson P, Sulmasy D, Kub J, et al. Symptoms and fear in heart failure patients approaching end of life: a mixed methods study. J Clin Nurs 2015 Nov;24(21-22):3215-3223.

(22) Schmidt M, Ulrichsen SP, Pedersen L, Botker HE, Sorensen 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):490-499.

(23) Stewart S, Ekman I, Ekman T, Oden A, Rosengren A. Population impact of heart failure and the most common forms of cancer: a study of 1 162 309 hospital cases in Sweden (1988 to 2004). Circ Cardiovasc Qual Outcomes 2010 Nov;3(6):573-580.

(24) Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol 2011 Jan;8(1):30-41.

(25) O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Pina IL, Granger CB, et al. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Circulation 2007 Jun 19;115(24):3111-3120.

(26) Yancy CW, Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, et al. Influence of patient age and sex on delivery of guideline-recommended heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. Am Heart J 2009 Apr;157(4):754-62.e2.

(27) Rogers A, Addington-Hall JM, McCoy AS, Edmonds PM, Abery AJ, Coats AJ, et al. A qualitative study of chronic heart failure patients' understanding of their symptoms and drug therapy. Eur J Heart Fail 2002 Jun;4(3):283-287.

(28) Koberich S, Lohrmann C, Mittag O, Dassen T. Effects of a hospital-based education programme on self-care behaviour, care dependency and quality of life in patients with heart failure--a randomised controlled trial. J Clin Nurs 2015 Jun;24(11-12):1643-1655.

(29) Jackson CE, Castagno D, Maggioni AP, Kober L, Squire IB, Swedberg K, et al. Differing prognostic value of pulse pressure in patients with heart failure with reduced or preserved ejection fraction: results from the MAGGIC individual patient meta-analysis. Eur Heart J 2015 May 7;36(18):1106-1114.

(30) Porter ME. A strategy for health care reform--toward a value-based system. N Engl J Med 2009 Jul 9;361(2):109-112.

(31) Danske R. Regionernes Resultater 2016 [Results from the Regions 2016]. 2016:1.

(32) Donabedian A. The quality of care. How can it be assessed? JAMA 1988 Sep 23-30;260(12):1743-1748.

(33) Hoenig H, Lee J, Stineman M. Conceptual overview of frameworks for measuring quality in rehabilitation. Top Stroke Rehabil 2010 Jul-Aug;17(4):239-251.

(34) Donabedian A. Evaluating the quality of medical care. Milbank Mem Fund Q 1966 Jul;44(3):Suppl:166-206.

(35) Heidenreich PA, Hernandez AF, Yancy CW, Liang L, Peterson ED, Fonarow GC. Get with the guidelines program participation, process of care, and outcome for medicare

patients hospitalized with heart failure. Circ Cardiovasc Qual Outcomes 2012 Jan 1;5(1):37-43.

(36) Senoo K, An Y, Ogawa H, Lane DA, Wolff A, Shantsila E, et al. Stroke and death in elderly patients with atrial fibrillation in Japan compared with the United Kingdom. Heart 2016 Jun 16.

(37) Cleland JG, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F, et al. The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. Eur J Heart Fail 2000 Jun;2(2):123-132.

(38) Peterson ED, DeLong ER, Masoudi FA, O'Brien SM, Peterson PN, Rumsfeld JS, et al. ACCF/AHA 2010 Position Statement on Composite Measures for Healthcare Performance Assessment: a report of American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures (Writing Committee to Develop a Position Statement on Composite Measures). J Am Coll Cardiol 2010 Apr 20;55(16):1755-1766.

(39) 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 Apr;16 Suppl 1:i45-50.

(40) Dansk Selskab for Kvalitet i Sundhedsvæsenet, DSKS. Sundhedsvæsenets kvalitetsbegreber og definitioner & Metodehåndbog i Kvalitetsudvikling [The Danish Health Care Sector Quality Concepts and Definition & handbook of methods in Quality Development]. 2016 January 2016:1.

(41) Patel DB, Shah RM, Bhatt DL, Liang L, Schulte PJ, DeVore AD, et al. Guideline-Appropriate Care and In-Hospital Outcomes in Patients With Heart Failure in Teaching and Nonteaching Hospitals: Findings From Get With The Guidelines-Heart Failure. Circ Cardiovasc Qual Outcomes 2016 Nov;9(6):757-766.

(42) DeVore AD, Cox M, Heidenreich PA, Fonarow GC, Yancy CW, Eapen ZJ, et al. Cluster-Randomized Trial of Personalized Site Performance Feedback in Get With The Guidelines-Heart Failure. Circ Cardiovasc Qual Outcomes 2015 Jul;8(4):421-427.

(43) von Scheidt W, Zugck C, Pauschinger M, Hambrecht R, Bruder O, Hartmann A, et al. Characteristics, management modalities and outcome in chronic systolic heart failure patients treated in tertiary care centers: results from the EVIdence based TreAtment in Heart Failure (EVITA-HF) registry. Clin Res Cardiol 2014 Dec;103(12):1006-1014.

(44) Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary

results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). Circulation 2010 Aug 10;122(6):585-596.

(45) Lewis WR, Ellrodt AG, Peterson E, Hernandez AF, LaBresh KA, Cannon CP, et al. Trends in the use of evidence-based treatments for coronary artery disease among women and the elderly: findings from the get with the guidelines quality-improvement program. Circ Cardiovasc Qual Outcomes 2009 Nov;2(6):633-641.

(46) Smaha LA, American Heart Association. The American Heart Association Get With The Guidelines program. Am Heart J 2004 Nov;148(5 Suppl):S46-8.

(47) Hong Y, LaBresh KA. Overview of the American Heart Association "Get with the Guidelines" programs: coronary heart disease, stroke, and heart failure. Crit Pathw Cardiol 2006 Dec;5(4):179-186.

(48) Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Age- and gender-related differences in quality of care and outcomes of patients hospitalized with heart failure (from OPTIMIZE-HF). Am J Cardiol 2009 Jul 1;104(1):107-115.

(49) Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE,Jr, Colvin MM, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2016 May 20.

(50) Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE,Jr, Drazner MH, 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 Oct 15;62(16):e147-239.

(51) Egstrup K, Eiskjær H, Gustafson F, Hassager C, Hildebrandt P, Korup E, et al. Hjerteinsufficiens DCS vejledning 2007. Nr. 3. Dansk Cardiologisk Selskab, Hauser Plads 10, 1127 København K. [Heart Failure DCS guideline 2007. No. 3. The Danish Heart Association, Hauser Plads 10, 1127 København K]. 2007.

(52) Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. Arch Intern Med 2002 Aug 12-26;162(15):1682-1688.

(53) Imazio M, Cotroneo A, Gaschino G, Chinaglia A, Gareri P, Lacava R, et al. Management of heart failure in elderly people. Int J Clin Pract 2008 Feb;62(2):270-280.

(54) Abete P, Testa G, Della-Morte D, Gargiulo G, Galizia G, de Santis D, et al. Treatment for chronic heart failure in the elderly: current practice and problems. Heart Fail Rev 2013 Jul;18(4):529-551.

(55) Komajda M, Hanon O, Hochadel M, Lopez-Sendon JL, Follath F, Ponikowski P, et al. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. Eur Heart J 2009 Feb;30(4):478-486.

(56) Melloni C, Berger JS, Wang TY, Gunes F, Stebbins A, Pieper KS, et al. Representation of women in randomized clinical trials of cardiovascular disease prevention. Circ Cardiovasc Qual Outcomes 2010 Mar;3(2):135-142.

(57) Lenzen MJ, Rosengren A, Scholte op Reimer WJ, Follath F, Boersma E, Simoons ML, et al. Management of patients with heart failure in clinical practice: differences between men and women. Heart 2008 Mar;94(3):e10.

(58) Nicol ED, Fittall B, Roughton M, Cleland JG, Dargie H, Cowie MR. NHS heart failure survey: a survey of acute heart failure admissions in England, Wales and Northern Ireland. Heart 2008 Feb;94(2):172-177.

(59) Brandsaeter B, Atar D, Agewall S, Norwegian Heart failure Registry. Gender differences among Norwegian patients with heart failure. Int J Cardiol 2011 Feb 3;146(3):354-358.

(60) Frankenstein L, Remppis A, Fluegel A, Doesch A, Katus HA, Senges J, et al. The association between long-term longitudinal trends in guideline adherence and mortality in relation to age and sex. Eur J Heart Fail 2010 Jun;12(6):574-580.

(61) Ng AC, Wong HS, Yong AS, Sindone AP. Impact of gender on outcomes in chronic systolic heart failure. Int J Cardiol 2007 Apr 25;117(2):214-221.

(62) Alehagen U, Ericsson A, Dahlstrom U. Are there any significant differences between females and males in the management of heart failure? Gender aspects of an elderly population with symptoms associated with heart failure. J Card Fail 2009 Aug;15(6):501-507.

(63) Vigder C, Ben Israel Y, Meisel SR, Kaykov E, Gottlieb S, Shotan A. Management and 1 year outcome of oldest-old hospitalized heart failure patients: a subacute geriatric hospital survey. Isr Med Assoc J 2010 Aug;12(8):483-488.

(64) Lindenfeld J, Fiske KS, Stevens BR, Debuhr J, Havranek EP, Abrams FR. Age, but not sex, influences the measurement of ejection fraction in elderly patients hospitalized for heart failure. J Card Fail 2003 Apr;9(2):100-106.

(65) Richardson DM, Bain KT, Diamond JJ, Novielli KD, Lee SP, Goldfarb NI. Effectiveness of guideline-recommended cardiac drugs for reducing mortality in the elderly medicare heart failure population: a retrospective, survey-weighted, cohort analysis. Drugs Aging 2010 Oct 1;27(10):845-854.

(66) Fonarow GC, Albert NM, Curtis AB, Gheorghiade M, Liu Y, Mehra MR, et al. Incremental Reduction in Risk of Death Associated With Use of Guideline-Recommended Therapies in Patients With Heart Failure: A Nested Case-Control Analysis of IMPROVE HF. J Am Heart Assoc 2012;1:16-26.

(67) Kfoury AG, French TK, Horne BD, Rasmusson KD, Lappe DL, Rimmasch HL, et al. Incremental survival benefit with adherence to standardized heart failure core measures: a performance evaluation study of 2958 patients. J Card Fail 2008 Mar;14(2):95-102.

(68) Zugck C, Franke J, Gelbrich G, Frankenstein L, Scheffold T, Pankuweit S, et al. Implementation of pharmacotherapy guidelines in heart failure: experience from the German Competence Network Heart Failure. Clin Res Cardiol 2012 Apr;101(4):263-272.

(69) Scrutinio D, Passantino A, Ricci VA, Catanzaro R. Association between conformity with performance measures and 1-year postdischarge survival in patients with acute decompensated heart failure. Am J Med Qual 2013 Mar-Apr;28(2):160-168.

(70) Phillips CO, Singa RM, Rubin HR, Jaarsma T. Complexity of program and clinical outcomes of heart failure disease management incorporating specialist nurse-led heart failure clinics. A meta-regression analysis. Eur J Heart Fail 2005 Mar 16;7(3):333-341.

(71) Roccaforte R, Demers C, Baldassarre F, Teo KK, Yusuf S. Effectiveness of comprehensive disease management programmes in improving clinical outcomes in heart failure patients. A meta-analysis. Eur J Heart Fail 2005 Dec;7(7):1133-1144.

(72) Yoo BS, Oh J, Hong BK, Shin DH, Bae JH, Yang DH, et al. SUrvey of Guideline Adherence for Treatment of Systolic Heart Failure in Real World (SUGAR): a multi-center, retrospective, observational study. PLoS One 2014 Jan 27;9(1):e86596.

(73) Komajda M, Lapuerta P, Hermans N, Gonzalez-Juanatey JR, van Veldhuisen DJ, Erdmann E, et al. Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey. Eur Heart J 2005 Aug;26(16):1653-1659.

(74) Wu WC, Jiang L, Friedmann PD, Trivedi A. Association between process quality measures for heart failure and mortality among US veterans. Am Heart J 2014 Nov;168(5):713-720.

(75) Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. JAMA 2007 Jan 3;297(1):61-70.

(76) Stork S, Hense HW, Zentgraf C, Uebelacker I, Jahns R, Ertl G, et al. Pharmacotherapy according to treatment guidelines is associated with lower mortality in a community-based sample of patients with chronic heart failure: a prospective cohort study. Eur J Heart Fail 2008 Dec;10(12):1236-1245.

(77) Fonarow GC, Yancy CW, Hernandez AF, Peterson ED, Spertus JA, Heidenreich PA. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. Am Heart J 2011 Jun;161(6):1024-30.e3.

(78) Olsen J, Basso O, Sorensen HT. What is a population-based registry? Scand J Public Health 1999 Mar;27(1):78.

(79) Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999 Jun;46(3):263-268.

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

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

(82) Sundheds D. Sygehus-afdelingsklassifikation SHAK. 1. january 2016; Available at: http://docplayer.dk/15977127-Sygehus-afdelingsklassifikation-shak.html. Accessed 12/21, 2016.

(83) Olejaz M, Juul Nielsen A, Rudkjobing A, Okkels Birk H, Krasnik A, Hernandez-Quevedo C. Denmark health system review. Health Syst Transit 2012;14(2):i-xxii, 1-192.

(84) Mainz J, Hansen AM, Palshof T, Bartels PD. National quality measurement using clinical indicators: the Danish National Indicator Project. J Surg Oncol 2009 Jun 15;99(8):500-504.

(85) Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull 2006 Nov;53(4):441-449.

(86) Danish M. Danish Medicines Agency. Available at: http://laegemiddelstyrelsen.dk/en/. Accessed 19 of december 2016, 2016.

(87) Egstrup K, Schjødt I, cerqueira C. Dansk Hjertesvigtdatabase (DHD). National Årsrapport [The Danish Heartfailre Registry (DHFR). Yearly Report] on behalf of the Steering Group for the DHFR. 2016; Available at: https://www.sundhed.dk/content/cms/71/4671_dhd_kommenteret_%C3%A5rsrapport_27012016_final.pdf. Accessed september 18, 2016.

(88) Mahonen M, Jula A, Harald K, Antikainen R, Tuomilehto J, Zeller T, et al. The validity of heart failure diagnoses obtained from administrative registers. Eur J Prev Cardiol 2013 Apr;20(2):254-259.

(89) McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of heart failure diagnoses in administrative databases: a systematic review and meta-analysis. PLoS One 2014 Aug 15;9(8):e104519.

(90) Saczynski JS, Andrade SE, Harrold LR, Tjia J, Cutrona SL, Dodd KS, et al. A systematic review of validated methods for identifying heart failure using administrative data. Pharmacoepidemiol Drug Saf 2012 Jan;21 Suppl 1:129-140.

(91) Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009 Jun 29;338:b2393.

(92) White IR, Royston P. Imputing missing covariate values for the Cox model. Stat Med 2009 Jul 10;28(15):1982-1998.

(93) Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006 Oct;59(10):1087-1091.

(94) Lilford RJ, Chilton PJ, Hemming K, Girling AJ, Taylor CA, Barach P. Evaluating policy and service interventions: framework to guide selection and interpretation of study end points. BMJ 2010 Aug 27;341:c4413.

(95) Fletcher R, Fletcher S. Cause. In: Linkins E, editor. Clinical Epidemiology. The Essentials. 4th edition ed.: Baltimore: Lippincott Williams & Wilkins; 2005. p. 187.

(96) HILL AB. The Environment and Disease: Association Or Causation? Proc R Soc Med 1965 May;58:295-300.

(97) Rothman K, Greenland S, Lash T. Validity in Epidemiologic Studies. In: Bierig L, editor. Modern Epidemiology. 3rd edition ed.: Philadelphia: Lippincott Williams & Wilkins; 2008. p. 128.

(98) Egstrup K, Schjødt I, Cerqueira C, Nakano A. Registreringsskema Hjertesvigt [Registration form Heart Failure]. 2016; Available at: http://www.kcks-vest.dk/siteassets/de-kliniske-databaser/hjertesvigt/11052016_hjerteinsuff_regskemafinal-_2_.pdf. Accessed september 18, 2016.

(99) Egstrup K, Schjødt I, Cerqueira C, Nakano A. Datadefinitioner for Dansk Hjertesvigtdatabase (DHD) [Datadefinitions for the Danish Heart Failure Register (DHFR)]. 2016 ver 3.3; Available at: http://www.kcks-vest.dk/siteassets/de-kliniske-databaser/hjertesvigt/23052016_hjerteinsuff_datadef_final-_2_.pdf. Accessed september 18, 2016.

(100) Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med 2007 Oct 16;147(8):W163-94.

(101) Sulo G, Nygard O, Vollset SE, Igland J, Ebbing M, Sulo E, et al. Higher education is associated with reduced risk of heart failure among patients with acute myocardial

infarction: A nationwide analysis using data from the CVDNOR project. Eur J Prev Cardiol 2016 Jul 19.

(102) Mard S, Nielsen FE. Single living predicts a higher mortality in both women and men with chronic heart failure. Dan Med J 2016 Sep;63(9):A5268.

(103) Lenzi J, Avaldi VM, Hernandez-Boussard T, Descovich C, Castaldini I, Urbinati S, et al. Risk-adjustment models for heart failure patients' 30-day mortality and readmission rates: the incremental value of clinical data abstracted from medical charts beyond hospital discharge record. BMC Health Serv Res 2016 Sep 6;16:473-016-1731-9.

(104) Kotecha D, Manzano L, Krum H, Rosano G, Holmes J, Altman DG, et al. Effect of age and sex on efficacy and tolerability of beta blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis. BMJ 2016 Apr 20;353:i1855.

(105) Fletcher R, Fletcher S. Chance. In: Linkins E, editor. Clinical Epidemiology. The Essentials. 4.th edition ed.: Baltimore: Lippincott Williams & Wilkins; 2005. p. 169.

(106) Sundhedsstyrelsen 2. Pakkeforløb for hjerteklapsygdom og hjertesvigt [National Board of Health procedure for cardiac valve and heart failure]. 2013 May 2013;Version 2.1:2.

(107) Reyes EB, Ha JW, Firdaus I, Ghazi AM, Phrommintikul A, Sim D, et al. Heart failure across Asia: Same healthcare burden but differences in organization of care. Int J Cardiol 2016 Aug 1;223:163-167.

(108) Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail 2016 Jun;18(6):613-625.

(109) Fonarow GC, Abraham WT, Albert NM, Gattis Stough W, Gheorghiade M, Greenberg BH, et al. Influence of a performance-improvement initiative on quality of care for patients hospitalized with heart failure: results of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF). Arch Intern Med 2007 Jul 23;167(14):1493-1502.

(110) Frankenstein L, Clark AL, Ribeiro JP. Influence of sex on treatment and outcome in chronic heart failure. Cardiovasc Ther 2012 Jun;30(3):182-192.

(111) Jimenez-Navarro MF, Ramirez-Marrero MA, Anguita-Sanchez M, Castillo JC, BADAPIC Investigators. Influence of gender on long-term prognosis of patients with chronic heart failure seen in heart failure clinics. Clin Cardiol 2010 Mar;33(3):E13-8.

(112) Vaartjes I, Hoes AW, Reitsma JB, de Bruin A, Grobbee DE, Mosterd A, et al. Age- and gender-specific risk of death after first hospitalization for heart failure. BMC Public Health 2010 Oct 22;10:637.

(113) Jernberg T, Johanson P, Held C, Svennblad B, Lindback J, Wallentin L, et al. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. JAMA 2011 Apr 27;305(16):1677-1684.

(114) Heidenreich PA, Lewis WR, LaBresh KA, Schwamm LH, Fonarow GC. Hospital performance recognition with the Get With The Guidelines Program and mortality for acute myocardial infarction and heart failure. Am Heart J 2009 Oct;158(4):546-553.

(115) Panella M, Marchisio S, Demarchi ML, Manzoli L, Di Stanislao F. Reduced in-hospital mortality for heart failure with clinical pathways: the results of a cluster randomised controlled trial. Qual Saf Health Care 2009 Oct;18(5):369-373.

(116) Fitzgerald AA, Powers JD, Ho PM, Maddox TM, Peterson PN, Allen LA, et al. Impact of medication nonadherence on hospitalizations and mortality in heart failure. J Card Fail 2011 Aug;17(8):664-669.

(117) Maeda JL. Evidence-based heart failure performance measures and clinical outcomes: a systematic review. J Card Fail 2010 May;16(5):411-418.

(118) Patterson ME, Hernandez AF, Hammill BG, Fonarow GC, Peterson ED, Schulman KA, et al. Process of care performance measures and long-term outcomes in patients hospitalized with heart failure. Med Care 2010 Mar;48(3):210-216.

(119) Koelling TM, Johnson ML, Cody RJ, Aaronson KD. Discharge education improves clinical outcomes in patients with chronic heart failure. Circulation 2005 Jan 18;111(2):179-185.

(120) Cameron J, Worrall-Carter L, Driscoll A, Stewart S. Measuring self-care in chronic heart failure: a review of the psychometric properties of clinical instruments. J Cardiovasc Nurs 2009 Nov-Dec;24(6):E10-22.

(121) VanSuch M, Naessens JM, Stroebel RJ, Huddleston JM, Williams AR. Effect of discharge instructions on readmission of hospitalised patients with heart failure: do all of the Joint Commission on Accreditation of Healthcare Organizations heart failure core measures reflect better care? Qual Saf Health Care 2006 Dec;15(6):414-417.

(122) Gwadry-Sridhar FH, Flintoft V, Lee DS, Lee H, Guyatt GH. A systematic review and meta-analysis of studies comparing readmission rates and mortality rates in patients with heart failure. Arch Intern Med 2004 Nov 22;164(21):2315-2320.

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

(124) Rubin HR, Pronovost P, Diette GB. The advantages and disadvantages of process-based measures of health care quality. Int J Qual Health Care 2001 Dec;13(6):469-474.

(125) Statistik D. Vi bliver flere ældre. 2017; Available at: http://www.dst.dk/da/presse/Pressemeddelelser/2010/2010-05-18-Flere-aeldre. Accessed january 17, 2017.

(126) den Ruijter H, Pasterkamp G, Rutten FH, Lam CS, Chi C, Tan KH, et al. Heart failure with preserved ejection fraction in women: the Dutch Queen of Hearts program. Neth Heart J 2015 Feb;23(2):89-93.

(127) Zannad F, Stough WG, Pitt B, Cleland JG, Adams KF, Geller NL, et al. Heart failure as an endpoint in heart failure and non-heart failure cardiovascular clinical trials: the need for a consensus definition. Eur Heart J 2008 Feb;29(3):413-421.

(128) Denolin H, Kuhn H, Krayenbuehl HP, Loogen F, Reale A. The definition of heart failure. Eur Heart J 1983 Jul;4(7):445-448.

(129) Estep JD. Chronic heart failure: what does the horizon look like? Curr Opin Cardiol 2015 Jul;30(4):344-353.

(130) Garin N, Carballo S, Gerstel E, Lerch R, Meyer P, Zare M, et al. Inclusion into a heart failure critical pathway reduces the risk of death or readmission after hospital discharge. Eur J Intern Med 2012 Dec;23(8):760-764.

(131) Granger BB, Swedberg K, Ekman I, Granger CB, Olofsson B, McMurray JJ, et al. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. Lancet 2005 Dec 10;366(9502):2005-2011.

(132) Stromberg A. Educating nurses and patients to manage heart failure. Eur J Cardiovasc Nurs 2002 Feb;1(1):33-40.

(133) Unverzagt S, Meyer G, Mittmann S, Samos FA, Unverzagt M, Prondzinsky R. Improving Treatment Adherence in Heart Failure. Dtsch Arztebl Int 2016 Jun 24;113(25):423-430.

(134) Randomization within quality registries: a cost-effective complement to classical randomized trials. Eur Heart J 2014 Jan;35(1):1-2.

APPENDIX

Table 1. Summary of studies on the effect of quality improvement initiatives for heart failure

Author, year published, country	Population institution, survey or database	Study design	Main findings in relation to improvement of processes of care over time	Conclusion
Patel et al. 2016 USA (41)	197.187 HF patients admitted to Teaching Hospitals and 106.924 patients admitted to Non Teaching Hospitals between 2005 and 2014.	Cohort	Over time in the GWTG-HF program, adherence increased with performance measures, such as defect-free care (defined as 100% compliance with all required performance measures), discharge instructions, documentation of LVEF, betablockers and ACEI/ARBs for patients with LV dysfunction.	Data from the GWTG-HF program suggest improved and comparable adherence with HF performance measures and use of guideline-recommended therapies.
DeVore et al. 2015 USA (42)	147 hospitals participating in GWTG HF quality improvement program from October 2009 to March 2011. (73 hospitals (n=33.886 patients) received the intervention, 74 hospitals (n=37.943 patients) did not).	Cluster-randomized trial. The intervention provided sites with specific data on their HF achievement and quality measures in addition to the usual GWTG HF tools. Primary outcome for the trial was improvement in site composite quality of care score.	One year after the intervention, both the intervention and control arms had similar mean changes in their composite quality score (absolute change, +0.31 [SE, 1.51] v.s. +3.18 [SE, 1.68] p=0.21).	None of the individual achievement measures or quality measures improved more at intervention v.s. control hospitals. The site-based intervention was not able to improve quality.

von Scheidt et al. 2014 Germany (43)	Between February 2009 and June 2011, 1.853 consecutive hospitalized patients were included in 16 centers in Germany, the EVITA-HF registry.	Cohort	At discharge, guideline recommended drug and device therapy was significantly improved.	1-year follow-up indicates a moderate mortality rate, high drug adherence, and sustained improvement of NYHA status.
Heidenreich et al., 2012, USA (35)	Comparing 215 hospitals enrolled in GWTG-HF (5%) from 2006-2007 with 4460 other hospitals using data on HF care measures.	Cohort	Four processes of HF care were assessed. GETG-HF hospitals had significantly higher documentation of LVEF (93.4% vs. 88.8%), use of ACEI or ARB antagonist (88.3% vs. 86.6%), and discharge instructions (74.9% vs. 70.5%, $p<0.005$).	Hospitals enrolled in GWTG-HF program had better process of care than other hospitals, but there are few clinically important differences in outcome.
Fonarow, 2011, USA (135)	NR	Review	Significant individual variability was found among hospitals and outpatient practices providing care for HF in their conformity to quality-of-care indicators, in addition to a substantial gap in overall performance.	Participation in performance improvement registries for HF has been shown to increase the initiation of evidence-based HF therapies, improve quality of care, decrease the risk of future hospitalizations, and prolong life in patients with HF.
Fonarow et al., 2010, USA (44)	Random sample of 34,810 HF patients from 167 US outpatient cardiology practices, IMPROVE-HF.	Cohort	7 quality measures were assessed.	Practices participating in IMPROVE-HF demonstrated a significant increase in the use of 5 of 7 guideline-recommended therapies in eligible patients without contraindications.

Lewis et al., 2009, USA (45)	Treatment of 237,225 patients hospitalized with CAD evaluated with the GWTG-CAD program from 2002 to 2007.	Cohort	Over time, composite adherence for the chosen measures increased from 86.5% to 97.4% (+10.9%) in men and 84.8% to 96.2% (+11.4%) in women. A slight difference in composite adherence by sex remained over time ($p<0.0001$), but this was confined to patients <75 years of age. Composite adherence in younger patients (<75 years) increased from 87.1% to 97.7% (+10.6%) and from 83.0% to 95.1% (+12.1%) in the elderly (≥75 years).	Among hospitals participating in GWTG-CAD, guideline adherence has improved substantially over time for both men and women, and both younger and older CAD patients, with only slight age and sex differences in some measures persisting.
Roccaforte et al., 2005, Canada, Italy (71)	33 randomized controlled studies to summarize evidence supporting DMPs.	Systematic review	Mortality was significantly reduced by DMPs compared to usual care (OR=0.80, 95% CI 0.69-0.93, $p=0.003$). All-cause and HF-related hospitalization rates were also significantly reduced (OR=0.76, CI 0.69-0.94, $p<0.0001$ and OR=0.58, CI 0.50-0.67, $p<0.00001$).	DMPs reduce mortality and hospitalizations in HF patients. Various types of DMPs appear to be similarly effective.

HF=Heart failure; SE=Standard Error; VHA=Veterans Health Administration; EVITA-HF=Evidence-based Treatment in Heart Failure; NYHA=New York Heart Association; GWTG-HF=Get With the Guidelines Program for Heart Failure; NR=Not Reported; IMPROVE-HF= Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting; CAD=Coronary Artery Disease; DMP=Disease Management Program; OR=Odds Ratio; CI=Confidence Interval; LV=Left Ventricular; LVEF=Left Ventricular Ejection Fraction.

Table 2. Summary of studies on age- and sex-related differences in heart failure care and clinical outcome among patients with heart failure

Author, year published, country	Population, institution, survey, and/or database	Study design	Main findings	Conclusion
Age-related differences				
Rich et al., 2016, USA (136)	Scientific statement	Summarize current guideline recommendations	There is limited evidence to guide clinical decision-making in patients over 75 to 80 years of age, and practically no high-quality evidence in patients > 80 years of age with multiple coexisting conditions, major physical or cognitive disabilities, frailty, or residence in long-term care facilities.	Older patients are at increased risk of complications arising from both pharmacological agents and diagnostic and therapeutic procedures. Thus, there is a fundamental shift in the balance of risk and benefit in older patients that has been inadequately addressed in clinical trials and must be considered on an individual basis.
Abete et al., 2013, Italy (54)	NR	Review	In elderly patients, first choice drugs (ACEIs and beta-blockers) are still underused.	Optimal management of CHF in elderly patients requires multiple approaches, including non-pharmacologic, pharmacologic, and palliative therapies.
Vigde et al., 2010, Israel (63)	96 consecutive unselected HF patients (67% women) hospitalized from January to June 2003.	Cohort	Adherence to guidelines and use of recommended HF medications were poor.	The study confirms that the management of oldest-old HF patients hospitalized in a subacute geriatric hospital is

				suboptimal and their mortality exceptionally high.
Fonarow et al., 2009, USA (48)	48,612 patients with HF from 259 hospitals, OPTIMIZE-HF.	Cohort	All guideline-recommended cardiac medications were prescribed less frequently at discharge to eligible patients ≥75 years old than those <75 years old (all p<0.001). Older age was independently associated with increases in in-hospital and post-discharge mortality risk (76% and 62%, p<0.001).	Older patients with HF are less likely to receive guideline-recommended therapies and remain at greater risk of adverse outcomes.
Komajda et al., 2009, France, Germany, Spain, Switzerland, Poland, Finland, Norway, Italy (55)	741 octogenarians hospitalized for acute/decompensated HF between March 2004 and May 2005 (median age 83.7 years; 44% males) and 2836 younger patients (median age 68.4 years; 66% males, EHFS II.	Cohort	A significant improvement was observed compared to EHFS I in both the overall HF octogenarian population and the subgroup with EF ≤ 45% for prescription rates of ACEI/ARBs, beta-blockers, and aldosterone antagonists at discharge (82 vs. 71%, 56 vs. 29%, 54 vs. 18.5%), as well as for recommended combinations and dosages.	Female gender, new onset HF, hypertension, atrial fibrillation, comorbidities, disabilities, and low quality of life were more common in the elderly. Mortality rates during hospital stay and 12 months after discharge were increased in octogenarians. Underuse and underdosage of medications recommended for HF in the elderly.
Yancy et al., 2009, USA (26)	15,381 from 167 outpatient cardiology practices (71.1% male), IMPROVE-HF.	Cohort	Patients in the oldest age group were less likely to receive recommended interventions than their younger counterparts. The largest absolute difference by patient age group was 19.5% for use of aldosterone antagonists.	Older patients with HF receive less pharmacological and device therapy and less HF education than younger patients.

Sex related differences				
Brandsaeter et al., 2011, Norway (59)	3632 Norwegian HF patients (2545 men and 1087 women, 70%/30%) included from January 2000 to February 2006.	Cohort	In the group with EF ≥ 50%, the only difference between basic characteristics was that men had a lower heart rate. In the group with EF < 50%, women were older, had a higher heart rate, had less frequent atrial fibrillation, were less often smokers, and had a more severe NYHA classification than men.	Differences exist in basic characteristics, medical history, and treatment between men and women in the Norwegian Heart Failure Registry. The survival rates were equal between men and women.
Vaartjes et al., 2010, the Netherlands (112)	Patients admitted for the first time with HF (14,529 men, 14,524 women), identified through linkage of national registries.	Nationwide cohort	Mortality risk after admission for HF increased with age, and the risk of death was higher among men than women. HR (men versus women and adjusted for age and comorbidity) was 1.21 (95% CI 1.14-1.28), 1.26 (95% CI 1.21-1.31), and 1.28 (95% CI 1.24-1.31) for 28-day, 1-year, and 5-year mortality, respectively.	Age and gender differences are present in short- and long-term risk of death after first hospitalization for HF, with men having higher short- and long-term risk of death than women.
Frankenstein et al., 2010, Germany (60)	1481 HF patients from 1994 to 2000 (cohort I) and 1811 patients from 2001 to 2007 (cohort II). Specialized HF clinics of the University Hospital Heidelberg, the Klinicum Ludwigshafen, and the TKH Mannheim, Germany (HELUMA, multi-site cooperation founded in 1995).	Cohort (I and II)	Multivariable analysis showed that NYHA class LVEF, hypertension, dyslipidemia, and COPD are significant predictors of complete medication according to guidelines, whereas age and sex were not.	Trends in mortality seem to mirror the temporal trends in medication according to guidelines, and the survival benefit is independent from age, sex, or lead time bias and does not reflect the impact of comorbidity.
Alehagen et al., 2009, Sweden (62)	HF patients aged 70 to 80 years in a rural municipality (443 men, 433 women).	Cohort	Females had more hypertension and smoked less than their male counterparts. There was also a preponderance of females in the	The female patients did not show signs of having received less modern HF treatment than the male

			group with preserved systolic function and symptoms of HF. In the different classes of systolic impairment, males dominated. During the 8 years of follow-up, more cardiovascular mortality was found among the males than females.	group, but it was more difficult to correctly interpret the symptoms of HF in the female group.
Nicol et al., 2008, UK (58)	176/177 (99%) acute NHS trusts in UK, 9387 records were surveyed.	Retrospective cohort	On average, women were 5 years older than men (80 vs. 75 years p<0.001), less likely to have had echocardiography (52% vs. 60%, p<0.001), and if previously diagnosed with HF less likely to be treated with ACEIs (58.3% vs. 66.8%, p<0.001), beta-blockers (30.1% vs. 35.5%, p<0.033), or aldosterone antagonists (18.9% vs. 22.5%, p<0.001) at admission. In-hospital mortality was 15%. Age-adjusted mortality was higher in men (16% vs. 14%, p=0.042). Women were less likely to be prescribed anti-failure medication on discharge (ACEI/angiotensin II receptor antagonist 66.5% vs. 73.4%, beta-blockers 31.3% vs. 37.5%, aldosterone antagonist 23.4% vs. 30.1%, all p<0.001).	Women seem to be less well managed against recommended guidelines.
Lenzen et al., 2008, Netherlands, Sweden, Switzerland, UK, France (57)	8914 patients (47% women) with confirmed diagnosis of HF, EHS-HF.	Cohort	Women were older (74.7 vs. 68.3 years, p<0.001) and less often presented evidence of CAD (56% vs. 66%, age adjusted OR 0.62, 95% CI 0.57-0.68) than men. Fewer women had investigation of LV function (59% vs. 74% age adjusted OR 0.67, 95% CI 0.61-	Women were less often treated with evidence-based drugs but had similar adjusted 12-week mortality as men.

			0.74). ACEIs and beta-blockers were given less often to women, even in the adjusted analysis (OR 0.72, 95% CI 0.61-0.86 and OR 0.76, 95% CI 0.65-0.89, respectively). 12-week mortality was similar for men and women.	
Ng et al., 2007, Australia (61)	Consecutive HF patients (116 men, 52 women) from a single HF unit.	Cohort	Women had higher mean LVEF and worse NYHA functional class at baseline than men. Fewer women remained on ACEIs. NYHA functional class was the strongest predictor of mortality.	Women had better LVEF but worse NYHA functional class than men. Predictors of mortality differed between genders. NYHA functional class at baseline was the strongest predictor of mortality for men, whereas age at baseline was the strongest predictor for women.
Ghali, 2004, USA (137)	NR	Review on UNC, FIRST, CIBIS II, MERIT-HF, BEST, COPERNICUS	Pooling of total mortality by sex from CIBIS II, MERIT-HF, and COERNICUS showed very similar and significant survival benefits in women (RR 0.69, 95% CI 0.51-0.93) and men (0.66, 95% CI 0.58-0.75).	The significant differences in clinical and laboratory characteristics in systolic HF between men and women may serve to explain the lower mortality rate in women.
Age and sex-related differences				
Lewis et al., 2009, USA (45)	Treatment of 237,225 patients hospitalized with CAD evaluated with the GWTG-CAD program from 2002 to 2007.	Cohort	Over time, composite adherence for the chosen measures increased from 86.5% to 97.4% (+10.9%) in men and 84.8% to 96.2% (+11.4%) in women. A slight difference in composite adherence	Among hospitals participating in GWTG-CAD, guideline adherence has improved substantially over time for both men and women, as

			by sex remained over time ($p<0.0001$), but this was confined to patients <75 years of age. Composite adherence in younger patients (<75 years) increased from 87.1% to 97.7% (+10.6%), and from 83.0% to 95.1% (+12.1%) in the elderly (≥75 years).	well as both younger and older CAD patients, with only slight age and sex differences in some measures persisting.
Lindenfeld et al., 2003, USA (64)	2239 patients with a principal discharge diagnosis of HF (59.2% of all discharges were women, 40.6% were men).	Cohort	EF was measured in 758 of 1331 (56.9%) women and 567 of 908 (62.4%) men ($p<0.001$). In both men and women, the EF was measured more often in younger patients than in older patients. A decline in the number of patients in which EF was measured was evident beginning at 75-79 years of age in both men and women, with a substantial drop at 85 years and above.	EF is measured in only 60% of patients with CHF in community hospitals across the country. All CHF guidelines have recommended that patients have at least 1 determination of EF. Increasing age is associated with a decline in the measurement of EF in both men and women.

NR=Not Reported, CHF=Chronic Heart Failure; ACE=Angiotensin Converting Enzyme; HF=Heart Failure; OPTIMIZE-HF=Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; EHFS=Euro Heart Failure Survey (I and II); IMPROVE-HF=Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting; ACEI =Angiotensin Converting Enzyme Inhibitor; ARB=Angiotensin Receptor Blocker; NYHA=New York Heart Association; LVEF=Left Ventricular Ejection Fraction; COPD=Chronic Obstructive Pulmonary Disease; NHS=National Health Service; EHS-HF=Euro Heart Survey on Heart Failure; LV=Left Ventricular; CI=Confidence Interval; OR=Odds Ratio; FIRST=Flolan International Randomized Survival Trial; CIBIS II=Cardiac Insufficiency Bisoprolol Study II; MERIT-HF=Metropol Extended-Release Randomized Intervention Trial in Heart Failure; COPERNICUS=Results of the Carvedilol Prospective Randomized Cumulative Survival Study; RR=Relative Risk; CAD=Coronary Artery Disease; CHF=Chronic Heart Failure.

Table 3. Summary of studies on the association between process performance measures and mortality in patients with heart failure

Author, year published, country	Population, institution, survey, and/or database	Study design	Main findings in relation to performance measures and mortality	Conclusion
Yoo et al., 2014, Korea (72)	1319 patients were divided into two groups: good guideline adherence (GAI≥50%) and poor guideline adherence (GAI<50%), SUGAR trial.	Cohort	Adherence to drugs at discharge: ACEI or ARB, 89.7%; BB, 69.2%; and AA, 65.9%. Overall, 82.7% of the patients had good guideline adherence. Overall mortality and rehospitalization rates at 1 year were 6.2% and 37.4%. Survival analysis by log-rank test showed a significant difference in event-free survival rate for mortality (94.7% vs. 89.8%, p=0.003) and re-hospitalization (62.3% vs. 56.4%, p=0.041) between the good and poor guideline adherence groups.	Adherence to pharmacological treatment guidelines including prescription of ACEI/ARB and BB at discharge was associated with improved clinical outcomes.
Wen-Chih Wu et al., 2014, USA (74)	107,045 patients with HF treated at 128 VHA hospitals between 2001 and 2007 and followed up at 2008.	Retrospective study	A relationship was assessed between receipt of each HF care process and death at 30 days (in-patients) and 1 year (all patients).	Care processes related to recommended medications were associated with lower 30-day and/or 1-year risk-adjusted mortality in patients with HF, whereas care processes that assess patient counseling or chart documentation were either not related or related to a slight increase in mortality.
Scrutinio et al., 2013, Italy (69)	496 patients with acute decompensated HF.	Cohort	After adjusting for established prognostic factors, the RR for mortality in patients eligible for treatment was: 0.49 (p<0.001) for discharge prescription of RAS-Is, 0.59 (p=0.015) for BBs, 0.44 (p<0.001) for combination therapy (i.e,. BB and RAS-I), 0.87 (p>0.05) for	The data suggest that performance measures for RAS-Is, BBs, and combination therapy are strongly associated with improved 1-year survival.

			aldosterone antagonists, and 0.49 (p>0.05) for planned cardioverter-defibrillator implantation. After adjusting for propensity score, the RR was 0.49 (p<0.001) for RAS-Is, 0.67 (p=0.04) for BBs, and 0.57 (p<0.001) for combination therapy.	
Fonarow et al., 2012, USA (66)	HF patients enrolled in IMPROVE-HF: 1376 cases and 2752 matched controls.	Nested case control study. Cases were patients who died within 24 months and controls were patients who survived to 24 months, propensity matched 1:2 for multiple prognostic variables.	BB and cardiac resynchronization therapy were associated with the greatest 24-month survival benefit (adjusted OR for death 0.42, 95% CI 0.34-0.52; and 44%, 95% CI 0.29-0.67, respectively). ACEI/ARBs, implantable cardioverter-defibrillators, anticoagulation for atrial fibrillation, and HF education were also associated with benefit, whereas aldosterone antagonist use was not. Incremental benefits were observed with each successive therapy, plateauing once any 4 to 5 therapies were provided (adjusted OR 0.31, 95% CI 0.23-0.42 for 5 or more versus 0/1, p<0.0001).	Individual and incremental use of guideline-recommended therapies was associated with survival benefit, with a potential plateau at 4 to 5 therapies. The data provide further rationale for implementing guideline-recommended HF therapies in the absence of contraindications to patients with HF and left ventricular ejection fraction.
Zugck et al., 2012, Germany (68)	Pooled data from 2682 patients participating in 7 studies performed within the context of the CNHF: the randomized INH Study, the Gene Study, the HELPS Study, the Ikarius Study, the ACVB-Out study, the Train-The-Trainer Study, and the CIBIS-ELD Study.	Cohort	1-year mortality risk was closely related to GAI-3 in both groups of NYHA functional class I/II (excellent vs. medium or poor GAI-3: 7.2 vs. 14.5%, log rank=0.004) and class III/IV (13.5 vs. 21.5% log rank=0.005). In Cox regression, excellent GAI-3 remained an independent predictor of survival (HR 0.70, 95% CI 0.51-0.95, p=0.023) after adjusting for predictor variables.	Patients receiving and tolerating optimal pharmacotherapy experience a better prognosis.
Maeda, 2010, USA (117)	Prospective cohort, retrospective cohort, case control, cross sectional, pre/post intervention study,	Systematic review	ACEI/ARB and BB use at discharge had the strongest association with improved patient outcomes, whereas discharge instructions had a weaker but positive	An increase in compliance with HF performance measures has a consistently positive impact on patient

	a randomized controlled trial, and a literature review based on empirical data were selected for inclusion.		effect,	outcomes, though the strength, magnitude, and significance of the effect is variable across individual performance indicators.
Richardson et al., 2010 USA (65)	12,697 beneficiaries: 1062 diagnosed with HF and 577 eligible to receive cardiac drugs.	Cohort	Mortality rate among the 577 eligible beneficiaries with HF was 9.7%. Mortality rate for those receiving an ACEI or ARB alone, a BB alone, or both was 6.1%, 5.9%, and 5.3%, respectively. In the absence of any of the three cardiac drugs, the mortality rate was 20.0% ($p<0.0001$). In multivariable analyses, mortality rates remained significantly lower for beneficiaries receiving an ACEI or ARB alone (OR 0.24, 95% CI 0.11-0.50) a BB alone (OR 0.17, 95% CI 0.70-0.41), or both (OR 0.24, 95% CI 0.10-0.55) compared to patients who did not receive any of the three cardiac drugs.	Use of guideline-recommended cardiac drugs is associated with reduced mortality in the elderly Medicare HF population.
Kfoury et al., 2008, USA (67)	JCAHO HF measures were implemented within a 20-hospital health care system. 2958 patients with a principal discharge diagnosis of HF were included.	Cohort	One-year survival benefits were seen in an item-by-item evaluation of HF measures.	Adherence to JCAHO HF core measures is associated with improved 1-year survival after HF hospitalization.
Störk et al., 2008, Germany (76)	1054 consecutive (unselected) patients with CHF, 61% with reduced LVEF and 39% with normal LVEF.	Cohort	Quality of pharmacotherapy was assessed by calculating a GAI (GAI-3, range 0-100%) based on the prescription of BBs, ACEIs, or angiotensin receptor II type-I blockers and mineralocorticoid receptor antagonists. Median follow-up in survivors was 595 days (100% complete). In patients with reduced	In this community-based cohort with CHF, better implementation of pharmacotherapy was associated with better prognosis in patients with reduced LVEF, irrespective of age and sex.

			LVEF, the median GAI-3 was 67% and inversely associated with age, CHF severity, and important comorbidities. Mortality rates in GAI-3 categories low/medium/high were 79/30/11 per 100 person-years. In multivariable Cox regression, high GAI-3 was independently predictive of lower mortality risk (HR 0.50, 95% CI 0.32-0.74, p<0.001 vs. low GAI-3). This association was also observed in subgroups of high age (HR 0.42, 95% CI 0.27-0.66, p<0.001) and women (HR 0.42, 95% CI 0.23-0.79, p=0.007).	
Fonarow et al., 2007, USA (75)	5791 patients at 91 US hospitals.	Cohort sampled between March 2003 and December 2004	Conformity with the performance measure for ACEIs/ARBs for LVSD was a significant predictor of reduced risk for mortality/rehospitalization (OR 0.51, 95% CI 0.34-0.78; p=0.002).	Better methods for identifying and validating HF performance measures may be needed to accurately assess and improve care of patients with HF.
Komajda et al., 2005, France, Spain, Netherlands, Germany, Italy, UK (73)	1410 patients with CHF (69% males) followed for 6 months for adherence to care by cardiologists, MAHLER.	Cohort	GAI-3 was an independent predictor of time to CV hospitalization in a multivariable model along with NYHA class, history of CHF hospitalization, ischemic etiology, diabetes mellitus, and hypertension.	Physicians' adherence to treatment guidelines is a strong predictor of fewer CV hospitalizations in actual practice.
Philips et al., 2005, USA, the Netherlands (70)	Determine whether a hierarchy of effectiveness exists with respect to the complexity of published protocols of HF DM incorporating specialist nurse-led HF clinics. Six trials were selected	Systematic review	Compared to usual care, the overall RR (95% CI) for re-admission by this strategy was 0.91 (0.72-1.16), mortality 0.80 (0.57-1.06), and the combined endpoint of mortality and hospitalization 0.88 (0.74-1.04). Better outcomes were observed for programs with versus programs without hospital discharge planning and immediate post-discharge	A dose-response relationship is suggested with more complex DM programs. HF DM with specialist nurse-led HF clinics is a promising strategy or effective alternative that may be optimized by programs with

	(n=949).		follow-up: re-admission 0.30 (0.04-2.60) vs. 1.00 (0.86-1.17), mortality 0.96 (0.63-1.47) vs. 0.75 (0.55-1.03), the combined endpoint of mortality and hospitalization 0.61 (0.18-2.02) vs. 0.91 (0.80-1.03), HF re-admission 0.09 (0.10-0.65) vs. 0.65 (0.43-1.00), and hospitalized days utilized per patient -0.26 (-0.49,-0.02) vs. 0.09 (-1.17,-1.34).	a homogenous structure and components that are delivered consistently.

GAI=Guideline Adherence Indicator; SUGAR=Survey of Guideline Adherence for Treatment of Systolic Heart Failure in Real World; ACEI=Angiotensin-Converting Enzyme Inhibitor; ARB=Angiotensin Receptor II Blocker; BB=Beta-blocker; HF=Heart Failure; VHA=Veterans Health Administration; RAS-I=Renin-Angiotensin System Inhibitor; RR=Relative Risk; IMPROVE-HF=The Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting; OR=Odds Ratio; CI=Confidence Interval; CNHF=Competence Network Heart Failure; GAI-3= Adherence to First Three Classes of Heart Failure Medication; HR=Hazard Ratio; JCAHO=Joint Commission on Accreditation of Healthcare Organizations; CHF=Chronic Heart Failure; LVEF=Left Ventricular Ejection Fraction; LVSD=Left Ventricular Systolic Dysfunction; CV=Cardiovascular; CHF=Chronic Heart Failure; NYHA=New York Heart Association; MAHLER=Medical Management of Chronic Heart Failure in Europe and its Related Costs; DM=Disease Management.

Table 4. Overview of collection of 700 patient records (5% of total sample registered 2003-3007) from hospitals in Denmark. Number of patient records is given in the parentheses.

Capital Region (8 hospitals)	Region of Sealand (10 hospitals)	Region of Southern Denmark (10 hospitals)	Region of Central Jutland (10 hospitals)	Region of Northern Jutland (8 hospitals)
Bispebjerg Hospital (20)	Hillerød Hospital (8)	Odense University Hospital (24)	Holstebro Hospital (27)	Thy-Mors Hospital (10)
Hvidovre Hospital (23)	Frederikssund Hospital (16)	Svendborg Hospital (33)	Herning Hospital (35)	Ålborg University Hospital (8)
Amager Hospital (17)	Helsingør Hospital (9)	Sønderborg Hospital (13)	Horsens, Brædstrup, Odder Hospitals (29)	Vendsyssel Hjørring Hospital (24)
Frederiksberg Hospital (22)	Roskilde Hospital (13)	Haderslev Hospital (21)	Ringkøbing Hospital (3)	Vendsyssel Frederikshavn Hospital (10)
Gentofte Hospital (30)	Køge Hospital (19)	Tønder Hospital (2)	Silkeborg Hospital (16)	Himmerland Farsø Hospital (8)
Herlev Hospital (6)	Slagelse Hospital (16)	Esbjerg Hospital (17)	Århus University Hospital NBG (4)	Himmerland Hobro Hospital (5)
Glostrup Hospital (11)	Holbæk Hospital (15)	Grindsted Hospital (6)	Århus University Hospital THG (8)	Brovst Hospital (4)

Bornholms Hospital	Kalundborg Hospital	Fredericia Hospital	Randers Hospital	Dronninglund Hospital
(1)	(7)	(21)	(29)	(5)
	Næstved Hospital	Vejle Hospital	Århus University Hospital Skejby	
	(2)	(23)	(20)	
	Nykøbing Falster Hospital	Kolding Hospital	Viborg, Skive, Kjellerup Hospitals	
	(6)	(14)	(40)	

Ph.D. PAPERS

Paper I: Nakano A, Johnsen SP, Frederiksen BL, Svendsen ML, Agger C, Schjødt I, Egstrup K. Trends in quality of care among patients with incident heart failure in Denmark 2003-2010: a nationwide cohort study. BMC Health Services Research 2013, 13:391

Paper II: Nakano A, Egstrup K, Svendsen ML, Schjødt I, Jakobsen L, Mehnert F, Johnsen SP. Age and sex-related differences in use of guideline-recommended care and mortality among patients with incident heart failure in Denmark. Age Ageing. 2016 ;45:635-42.

Paper III: Nakano A, Egstrup K, Svendsen ML, Schjødt I, Johnsen SP. Association between process performance measures and 1-year mortality among patients with incident heart failure: a nationwide study. In preparation

Nakano et al. BMC Health Services Research 2013, 13:391
http://www.biomedcentral.com/1472-6963/13/391

BMC Health Services Research

RESEARCH ARTICLE Open Access

Trends in quality of care among patients with incident heart failure in Denmark 2003–2010: a nationwide cohort study

Anne Nakano[1,2*], Søren Paaske Johnsen[1†], Birgitte Lidegaard Frederiksen[3,4], Marie Louise Svendsen[1†], Carsten Agger[4], Inge Schjødt[5] and Kenneth Egstrup[6†]

Abstract

Background: The treatment of heart failure (HF) is complex and the prognosis remains serious. A range of strategies is used across health care systems to improve the quality of care for HF patients. We present results from a nationwide multidisciplinary initiative to monitor and improve the quality of care and clinical outcome of HF patients using indicator monitoring combined with systematic auditing.

Methods: We conducted a nationwide, population-based prospective study using data from the Danish Heart Failure Registry. The registry systematically monitors and audits the use of guideline recommended processes of care at Danish hospital departments treating incident HF patients. We identified patients registered between 2003 and 2010 (n = 24504) and examined changes in use of recommended processes of care and 1-year mortality.

Results: The use of the majority of the recommended processes of care increased substantially from 2003 to 2010: echocardiography (from 62.7% to 90.5%; Relative Risk (RR) 1.45 (95% CI, 1.39-1.50)), New York Heart Association classification (from 29.4% to 85.5%; RR 2.91 (95% CI, 2.69-3.14)), betablockers (from 72.6% to 88.3%; RR 1.23 (95% CI, 1.15-1.29)), physical training (from 5.6% to 22.8%; RR 4.04 (95% CI, 2.96-4.52)), and patient education (from 49.3% to 81.4%; RR 1.65 (95% CI, 1.52-1.80)). Use of ACE/ATII inhibitors remained stable (from 92.0% to 93.2%; RR 1.01 (95% CI, 0.99-1.04)). During the same period, 1-year mortality dropped from 20.5% to 12.8% (adjusted Hazard Ratio 0.79 (95% CI, 0.65-0.96).

Conclusions: Use of guideline recommended processes of care has improved among patients with incident HF included in the Danish Heart Failure Registry between 2003 and 2010. During the same period, a decrease in mortality was observed.

Keywords: Quality indicators, Registries, Treatment and care, Heart failure

Background

Heart failure (HF) is an important cause of morbidity and mortality worldwide [1]. The prevalence of HF is increasing globally due to ageing populations in the developed countries, improved survival in patients suffering from coronary events and the success achieved in postponing coronary events using effective preventive measures [2-8]. HF care has developed substantially in recent decades and clinical trials have established several new therapies which have improved clinical outcomes for patients with HF and reduced left ventricular ejection fraction (LVEF) [8]. However, treatment guidelines are adopted slowly and applied inconsistently and may thus not result in the expected improvements in patient care and clinical outcomes [9-12]. Consequently, in many health care systems, major efforts are made to implement recommended guidelines [13]. However, population-based data on the implementation of the recommendations in everyday clinical practice and the possible impact on patient outcomes are still sparse [14].

* Correspondence: anne.nakano@stab.rm.dk
†Equal contributors
[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[2]The Danish Clinical Registers, Audit Unit West, Olof Palmes Allé 15, Aarhus, Denmark
Full list of author information is available at the end of the article

In Denmark, the quality of care for patients with incident HF has been monitored and audited continuously in a national multidisciplinary quality improvement program since 2003. We aimed to examine whether the quality of care and the mortality among incident HF patients hospitalized in Denmark has changed following the introduction of the program.

Methods

The Danish heart failure registry

All Danish residents (approximately 5.5 million) have free access to hospital care provided by the tax-financed Danish National Health Service. The Danish Heart Failure Registry (DHFR) was established as a part of a larger nationwide initiative, The Danish National Indicator Project, in 2003 in order to monitor and improve the quality of care for HF patients [15].

Since 2003, the DHFR has monitored and supported implementation of evidence-based treatment and care for incident hospitalized HF patients. Participation is mandatory for all hospital units and outpatient cardiology clinics treating patients with HF. However, not all hospitals were able to report to the register when it was launched in 2003.

The prognostic factors recorded in the registry as well as the evidence-based quality of care indicators were identified by a multidisciplinary national expert panel based on national [15] and international guidelines from the American College of Cardiology, the American Heart Association [16], and the European Society of Cardiology [17], supplemented by a systematic literature review. The expert panel followed a structured, rigorous and evidence-based guideline-driven process to develop pathways and tools for clinicians in hospitals and outpatient HF clinics in order to ensure data accuracy by standardizing procedures. This included developing detailed instructions for the data collection with strict data definitions ensuring that clinicians register data in the same manner at every hospital, as well as providing regular performance reports to the participating hospitals as also done in the American Heart Association Get With the Guidelines Program for Heart Failure [18]. The feasibility of collecting the required data in routine clinical settings, and the ability of the processes to reflect the multidisciplinary efforts involved in modern HF care, were also considered.

The expert panel identified 6 process indicators and 1 outcome indicator (Table 1), and a number of prognostic factors (Table 2).

Data are registered for HF patients admitted to hospital or at the first outpatient visit as part of the clinical routine by cardiologists and nursing staff.

The use of 2 processes of care (echocardiography and New York Heart Association classification (NYHA classification) and 1-year mortality is monitored in all patients. The remaining processes of care (Angiotensin Converting Enzyme/Angiotensin II antagonist (ACE/ATII) inhibitors, betablockers, physical training, and patient education) are only monitored in patients with systolic HF (LVEF ≤ 40%).

Regular, structured audits are conducted on a national, regional, and local basis, and include validation of the completeness of patient registration against local hospital discharge registries and the National Registry of Patients [19]. Furthermore, every 3 months, the participating departments receive feedback data on their performance regarding the process indicators as well as unadjusted data on mortality. The feedback data are reported on a web-based information system allowing each participating hospital to review its performance data, and benchmark them against the region and the whole country.

Study population

The study population included patients with a first time hospitalization (including in- and out-patients) with HF

Table 1 Processes of care monitored in the Danish heart failure registry

Processes of care	
Echocardiography	Proportion of patients who undergo echocardiography
NYHA classification	Proportion of patients who undergo NYHA classification
Medication (ACE/ATII inhibitors)	Proportion of patients with reduced systolic function (LVEF below 40%) who is treated with ACE/ATII inhibitors
Medication (Betablockers)	Proportion of patients with reduced systolic function (LVEF below 40%) who is treated with betablockers
Physical training	Proportion of patients with reduced systolic function (LVEF below 40%) referred to individual physical training
Patient education	Proportion of patients with reduced systolic function (LVEF below 40%) who started a structured patient education (inclusive nutrition, physical training, understanding medical treatment, risk factors and symptoms of the disease)
1-year mortality	Proportion of patients who die within one year of admission to a hospital or first outpatient contact

NYHA New York Heart Association, *ACEI/ATII* Angiotensin Converting Enzyme/Angiotensin II Antagonist inhibitors, *LVEF* Left Ventricular Ejection Fraction.

Table 2 Baseline characteristics among patients diagnosed with incident heart failure in Denmark between 2003 and 2010 (N = 24504)

	N (%)
Total	24504 (100)
Age mean (SD)	70.8 (13.2)
Gender	
Male	15607 (63.7)
Female	8897 (36.3)
Left Ventricular Ejection Fraction (LVEF)	
LVEF < 25	6609 (27.0)
25 ≤ LVEF ≤ 35	7803 (31.8)
35 < LVEF ≤ 40	3498 (14.3)
40 < LVEF < 50	2287 (9.3)
LVEF ≥ 50	1134 (4.6)
Missing	3173 (13.6)
New York Heart Association (NYHA) classification	
NYHA-class 1	1912 (7.8)
NYHA-class 2	8209 (33.5)
NYHA-class 3	4462 (18.8)
NYHA-class 4	459 (1.9)
Missing	9462 (38.6)
Previous Acute Myocardial Infarction (AMI)	
Yes	8046 (32.8)
No	14859 (60.6)
Missing	1599 (6.5)
Stroke	
Yes	2561 (10.5)
No	19576 (79.9)
Missing	2367 (9.7)
Chronic Obstructive Pulmonary Disease (COPD)	
Yes	3759 (15.3)
No	18480 (75.4)
Missing	2265 (9.2)
In treatment for hypertension	
Yes	8335 (34.0)
No	14378 (58.7)
Missing	1791 (7.3)
Diabetes	
Yes	4530 (18.5)
No	18362 (74.9)
Missing	1612 (6.6)
Alcohol intake	
Maximum 14 drinks for women and 21 for men per week	16683 (68.1)
More than 14 drinks for women and 21 for men per week	1639 (6.7)
Missing	6010 (25.7)
Smoking habits	
Smoker	7101 (29.0)
Non-smoker	17335 (70.8)
Missing	48 (0.2)

SD Standard Deviation, *LVEF* Left Ventricular Ejection Fraction, *NYHA* New York Heart Association, *AMI* Acute Myocardial Infarction, *COPD* Chronic Obstructive Pulmonary Disease.
It was not possible to differentiate between inpatients and outpatients until 2006. Results from 2006 to 2010 are available in the supplementary online material.

as the primary diagnosis. Diagnoses are made by an experienced cardiologist, using the ESC guidelines for definition of HF, and recorded according to the International Classification of Diseases, 10^{th} revision (ICD-10) (Codes: I11.0, I13.0, I13.2, I42.0, I42.6, I42.7, I42.8, I42.9, I50.0, I50.1, I50.2, I50.3, I50.8, I50.9).

Outpatients had typically previously been admitted to a cardiology ward with acute myocardial infarction and had during the admission developed symptoms of HF. After treatment for the acute myocardial infarction, the patients were then referred to an outpatient cardiology clinic for treatment of the HF.

The decision of recording a patient in the registry is always made by a senior cardiologist to ensure the validity of the HF diagnosis [7,20]. Each patient was only included once in the analyses. Patients were 18 years of age or older and Danish residents. They were enrolled irrespective of their left ventricular function. The total number of patients registered in the DHFR was 24510 in the study period, but six patients were under 18 years of age, and therefore excluded, leaving 24504 patients for analysis.

A total of 41 hospitals and 54 departments were represented in this study. The hospitals and departments, which represent all hospitals and departments responsible for treating HF patients in Denmark, were identified by Danish Regions, which are responsible for running the hospitals. For the majority of the departments, the completeness of the registration of patients was 98-100% in 2010 compared with local hospital discharge registries and the Danish National Registry of Patients [16].

Data on patient characteristics and mortality

Data on patient characteristics, including gender, age, comorbidity, left ventricular ejection fraction and NYHA classification as well as alcohol intake and smoking habits, were obtained from the DHFR. Information on vital status (1-year mortality) was obtained from the Danish Civil Registration System [21], which maintains electronic records of changes in the vital status of all residents. Each record carries a unique 10-digit civil registration number, which is used in all Danish population based registries and enables unambiguous linkage among these registries. The study was approved by the Danish Data Protection Agency (J.no. 2008-41-2072), the DHFR, and the Danish Ministry of Health.

Statistics

We computed the proportion of patients receiving the individual processes of care among those eligible as well as the proportion of HF patients who died within 1 year of admission or first contact, both overall for the entire study period and according to calendar year (2003–2010). Comparisons over time were made using binary regression to compute the relative risk (RR) with 95% confidence intervals (CI) using 2003 as reference. A composite quality of care measure was also computed for each department. This measure was defined as the total number of received processes of care divided by the total number of processes of care relevant to the patients admitted to the individual department.

Analyses on mortality were conducted for the entire study population and stratified according to LVEF (40% or less vs. more than 40%). For some patients, data on one or more of the covariates were missing (Table 2). We used multiple imputation to impute the missing values assuming that data was missing at random (stata command: ice) [22-24]. We created 5 datasets based on the following covariates: age, gender, left ventricular ejection fraction, previous acute myocardial infarction, stroke, chronic obstructive pulmonary disease, diabetes, alcohol intake, smoking habits and patients in treatment for hypertension. The proportion of patients, for whom data on these variables were missing, varied between 0.0%-25.7%.

We compared 1-year mortality between patients from 2010 and 2003, respectively using multivariable Cox proportional hazards regression, while controlling for the patient characteristics presented in Table 2 (except for NYHA class, due to a high proportion missing data and inpatient/outpatient status, which was not registered before 2006).

Data were analysed using Stata 10.0 (StataCorp LP, College Station, Texas).

Results

Processes of care

Baseline characteristics of the total patient population are presented in Table 2. In the Additional file 1: Table S1, the characteristics are listed according to year of registration (2003 to 2010). The proportion of patients receiving the individual processes of care increased substantially between 2003 and 2010 (Table 3), i.e., use of echocardiography (RR 1.45, 95% CI, 1.39-1.50), NYHA classification (RR 2.91, 95% CI, 2.69-3.14) , betablockers (RR 1.23, 95% CI 1.15-1.29), physical training (RR 4.04, 95% CI, 2.96-5.52) and patient education (RR 1.65, 95% CI, 1.52-1.80). The only exception was the use of ACE/ATII inhibitors, where no overall changes were observed (RR 1.01, 95% CI, 0.99-1.04).

Figure 1 shows the increase in the proportion of patients who received the recommended processes of care between 2003 and 2010.

Figure 2 presents the overall composite process indicator, reflecting the proportion of all recommended processes of care that was delivered in 2010 at the individual departments. Although overall improvements were observed for most processes of care, substantial variation in quality of care remains among hospital departments treating patients with incident HF in Denmark. The proportion of delivered recommended processes of care varied between 50% and 89% across the departments.

Mortality

Overall 1-year all-cause mortality among patients registered in the DHFR decreased from 20.5% in 2003 to 12.8% in 2010 (Table 4).

The overall adjusted hazard ratio (HR) for 1-year mortality was 0.79 (95% CI, 0.65-0.96) after multivariable

Table 3 Received processes of care among patients diagnosed with incident heart failure in Denmark between 2003 and 2010 (N = 24504)

Total	Year 2003 to 2010 N (%) 24504 (100)	Year 2003 N (%) 1624 (100)	Year 2010 N (%) 3809 (100)	Crude RR (95% CI)
Processes of care				
Echocardiograph performed	19419 (79.5)	1010 (62.7)	3430 (90.5)	1.45 (1.39-1.50)
NYHA classification assessed	15042 (61.6)	475 (29.4)	3237 (85.5)	2.91 (2.69-3.14)
ACE/ATII inhibitors given	12565 (93.0)	446 (92.0)	2628 (93.2)	1.01 (0.99-1.04)
Betablockers given	11272 (84.4)	350 (72.6)	2489 (88.3)	1.23 (1.15-1.29)
Physical training	2278 (15.9)	39 (5.6)	631 (22.8)	4.04 (2.96-5.52)
Patient education	9852 (70.0)	273 (49.3)	2281 (81.4)	1.65 (1.52-1.80)

NYHA New York Heart Association, *ACE/ATII* Angiotensin Converting Enzyme/Angiotensin II Antagonist inhibitors.

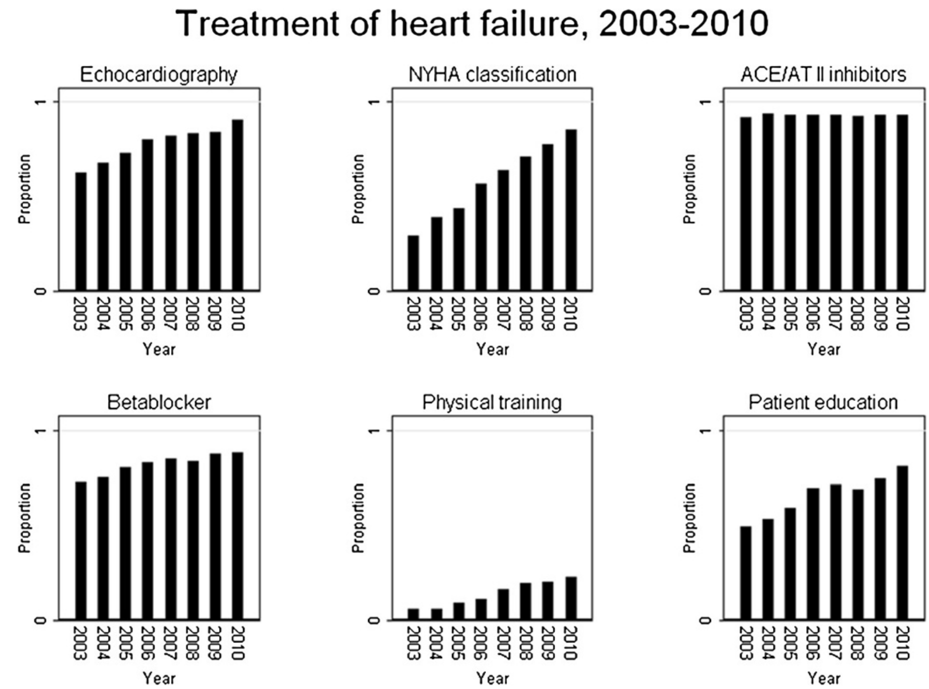


Figure 1 Proportion of patients receiving the recommended processes of care among patients diagnosed with incident heart failure in Denmark 2003–2010. NYHA classification: New York Heart Association classification, ACE/ATII inhibitors: Angiotensin Converting Enzyme/ Angiotensin II antagonist inhibitor.

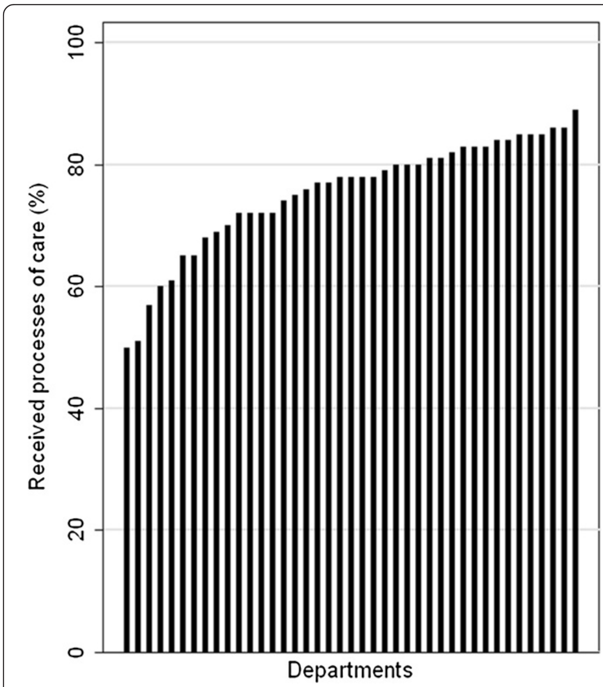


Figure 2 Variation between Danish hospital departments in overall proportion of delivered processes of recommended care to patients with incident heart failure in 2010. The bars represent individual hospital departments.

adjustment for patient characteristics (age, gender, LVEF, previous acute myocardial infarction, stroke, chronic obstructive pulmonary disease, diabetes, alcohol intake, smoking habits and in treatment for hypertension), when comparing patients diagnosed in 2010 with patients diagnosed in 2003. Analyses were also stratified for LVEF (Table 4). The improvements in mortality appeared to be better in patients with preserved ejection fraction compared to patients with reduced ejection fraction. The confidence intervals were, however, overlapping.

Discussion

We found that implementation of indicator monitoring for HF care in Denmark has been associated with substantial improvements in the use of guideline recommended processes of care among patients registered in the national HF registry. Similar results have been observed in at least two other major quality improvement initiatives: The Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF) for outpatient cardiology practices where 7 quality measures were assessed and significant improvement achieved for 5 of the measures. Identical to our study, they did not reach statistical significance in angiotensin-converting enzyme inhibitor/angiotensin receptor blocker [10]. Likewise, The Get With the Guidelines Programme for Heart Failure demonstrated better processes of care as well as

Table 4 One-year mortality among patients diagnosed with incident heart failure in Denmark in 2010 vs. 2003

	Mortality 2003 N/total (%)	Mortality 2010 N/total (%)	Unadjusted HR (95% CI)	Adjusted HR * (95% CI)	Adjusted HR † (95% CI)
Total	333/1624 (20.5)	488/3809 (12.8)	0.59 (0.51-0.67)	0.65 (0.56-0.75)	0.79 (0.65-0.96)
LVEF ≤40%	277/1379 (20.1)	408/3141 (13.0)	0.61 (0.52-0.71)	0.67 (0.57-0.78)	0.85 (0.69-1.05)
LVEF >40%	56/245 (22.9)	79/668 (11.8)	0.47 (0.31-0.74)	0.58 (0.40-0.84)	0.51 (0.30-0.89)

*Hazard Ratio (HR) adjusted for age and gender.
† Hazard Ratio (HR) adjusted for the following patient characteristics: age, gender, LVEF, previous acute myocardial infarction, stroke, chronic obstructive pulmonary disease, diabetes, alcohol intake, smoking habits, and in treatment for hypertension.
LVEF Left Ventricular Ejection Fraction.
Overall and stratified according to selected patient characteristics.

improved performance over time in hospitals following the guidelines compared to hospitals that did not [18], as also shown in our study.

Furthermore, we observed a reduced 1-year mortality rate among Danish HF patients included in the DHFR when comparing patients diagnosed in 2010 with patients diagnosed in 2003.

Direct comparisons with other studies is somewhat hampered by the use of different study designs (population-based vs. selected institutions) and patient populations (prevalent vs. incident patients, inpatients vs. outpatients). However, the baseline profile of our patients appears to be comparable with the profile reported in a number of other studies [10,11,25,26]. Furthermore, our findings are in general in accordance with and extend findings from other existing studies, which have addressed the effects of implementation of clinical guidelines and indicator monitoring. According to two studies by Fonarow et al. based on data from OPTIMIZE-HF (The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) and IMPROVE HF (Primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting cohort), use of guideline recommended therapies, including discharge instructions, assessment of left ventricular function, ACE inhibitors or angiotensin II receptor blockers (ARBs) and betablockers at discharge, was associated with lower mortality [10,27]. There are conflicting results, though, as Heidenreich et al. found a decrease in the 30-day readmission rate, but not in the 30-day mortality rate using data from the American Heart Association's Get With The Guidelines Program. The inconsistency may be related to the studied processes of care and outcomes. The Get With The Guidelines Program focused on documentation of LVEF, use of ACE inhibitors if LVEF was less than 40%, as well as discharge instructions and smoking cessation. A stronger association between the processes of care and short-term mortality could possibly have been found if the use of betablockers or aldosterone antagonists had also been assessed since use of these drugs has been shown to improve survival in randomized trials [18].

Our population included both patients with and without preserved ejection fraction, although it should be noted that the proportion of included patients with preserved ejection fraction was quite small (4.6%). Although we found no statistically significant difference in the improvements in mortality during the study period for patients with versus patients without preserved ejection fraction, we did observe an indication of a stronger improvement among patients with preserved ejection fraction. This is noteworthy as the existing evidence base for treatment of patients with preserved ejection fraction is weak as no treatment has yet been shown to reduce morbidity and mortality in this patient group [17].

Studies on other cardiovascular patient groups, including patients with acute coronary syndrome and stroke, have also provided evidence for the effectiveness of optimizing guideline recommended care among patients encountered in real-world clinical practice [28-31]. Our study appear to add further support to the important role of clinical guidelines and HF programmes as tools for bridging the gap between research and routine clinical practice.

In the DHFR, the continuous monitoring of the quality of care is supplemented by regular audits and public reporting and release of the performance data from the individual departments. Such steps may further ensure commitment and active involvement of the stakeholders, including clinicians, administrators, patients and politicians. However, challenges remain as demonstrated by the substantial variation between the hospital departments in the overall quality of care even after years of monitoring and auditing.

Strengths and limitations

The strengths of our study include the prospective nationwide population-based design and the large number of patients included, as well as the fact that registration is mandatory to all hospitals in Denmark treating patients with HF, keeping in mind that not all hospitals were capable of beginning registration at the same time.

In addition, thorough efforts are made to ensure data validity in the DNIP. Regular multidisciplinary structured audits are conducted, which include validation of the completeness of patient registration against hospital discharge registries and discussion and exchange of experience and knowledge in order to explain the results and implement improvements [15].

The main limitation is the observational nature of our study, which precludes firm conclusions about causality, in particular with regards to the findings on mortality. The completeness of the registration of a patient is important in this context and it should therefore be noted that the number of patients included in DHFR per year clearly increased during the study period (from 1624 patients in 2003 to 3809 patients in 2010). This reflected an increasing completeness of the DHFR as all relevant hospitals and departments began reporting to the registry at some point between 2003 and 2010. The DHFR aims to include all incident patients admitted with HF as the primary diagnosis. Consequently, the DHFR will not reflect the incidence of HF in the general Danish population. The low proportion of patients with preserved ejection fraction (4.6%) also indicates that not all hospitalized HF patients were included since it has been estimated that as many as 20% to 60% of HF patients have a normal or near normal LVEF [8]. However, the high completeness of the DHFR compared with hospital discharge registries, indicates that the registry probably did cover the vast majority of incident HF patients admitted to Danish hospitals with HF as the primary diagnosis during the study period.

Other factors, besides the nationwide initiative, may potentially have contributed to the improved quality of care and lower mortality including a major structural reform of the Danish health care system in 2007 and a generally increased awareness among clinicians of guideline recommendations and in particular increased focus on caring for persons with chronic conditions. The latter has during the study period been specifically stimulated by reports from the National Board of Health presenting different options for improving care for those with chronic conditions as well as the publication of disease management programs for persons with chronic conditions [32,33]. Changes over time in the prognostic profile of the patients with incident HF, e.g., the increase in the proportion of patients being treated as outpatients, is another important issue. Although we controlled for a range of well-established prognostic factors in the analyses on changes in mortality over time, data was not available on all relevant factors (e.g., creatinine levels and use of implantable cardioverter defibrillators, cardiac resynchronization therapy, and aldosterone antagonist medications). In addition, the proportion of patients for whom data were missing was substantial for some of the registered variables, e.g., NYHA class (38.6%). Assuming that our data were missing at random, we used multiple imputation to account for missing data on the covariates included in the multivariable analyses on mortality. This approach is not without pitfalls, in particular due to the difficulties with assessing whether data are truly missing at random. However, the implications of using the technique appeared modest in the analyses, as all analyses indicated a lower mortality among patients diagnosed in 2010 patients compared with patients diagnosed in 2003 patients independently on how the available covariates were included in the multivariable analyses (data not shown).

Finally, the inherent risk of gaming in top-down initiated quality improvement initiatives such as the DHFR should not be forgotten. “Gaming” is here understood as reactive subversion such as “hitting the target and missing the point” or reducing performance where targets do not apply. The phenomenon is described by the economist Charles Goodhart, who following the failure of the UK government’s reliance on money supply targets in the 1980s to control inflation, to stated: “Any observed statistical regularity will tend to collapse once pressure is placed on it for control purposes’ because actors will change their conduct when they know that the data they produce will be used to control them” (Goodhart [34], p. 96). However, the risk of gaming in the DHFR was probably quite low due to the regular national, regional and local multidisciplinary clinical audits, where data collection and performance was discussed in details. Furthermore, the data validity was also ensured by multiple audits of medical journals and consistently updated manuals with explicit instructions to the staff involved in data collection.

Conclusions

In conclusion, use of guideline recommended processes of care has improved substantially between 2003 and 2010 following the initiation of systematic quality of care monitoring among incident HF patients admitted to Danish hospitals and registered in the DHFR. The 1-year mortality appear to have decreased during the same period.

Additional file

Additional file 1: Table S1. Baseline characteristics of 24504 incident heart failure patients in Denmark registered in the Danish National Indicator Project between 2003 and 2010, and each separate year from 2003 to 2010.

Competing interest

The authors declare that they have no competing interest.

Authors’ contributions

AN, SPJ, MLS and KE designed the study. AN was the principal investigator and lead author in the analysis of the data and wrote the draft of the manuscript. All

authors participated in the interpretation of the findings. All authors took part in reviewing and editing the manuscript and approved the final version to be published.

Acknowledgements
We thank the staff of the hospital departments caring for patients with HF for their continuous effort and contribution in the collection of data to the Danish Heart Failure Registry and thus for making this study possible.

Author details
[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark. [2]The Danish Clinical Registers, Audit Unit West, Olof Palmes Allé 15, Aarhus, Denmark. [3]Danish Health and Medicines Authority, Copenhagen, Denmark. [4]Research Centre for Prevention and Health, Glostrup, Denmark. [5]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark. [6]Department of Cardiology, Odense University Hospital, Svendborg Hospital, Svendborg, Denmark.

Received: 28 March 2013 Accepted: 30 September 2013
Published: 5 October 2013

References

1. Fonarow GC: **Improving quality of care and outcomes for heart failure. -Role of registries-.** *Circ J* 2011, **75**(8):1783–1790.
2. Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology, ESC Committee for Practice Guidelines, Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, Van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL: **Document reviewers: ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the european society of cardiology. Developed in collaboration with the heart failure association of the ESC (HFA) and endorsed by the european society of intensive care medicine (ESICM).** *Eur Heart J* 2008, **29**(19):2388–2442.
3. Bonow RO, Bennett S, Casey DE Jr, Ganiats TG, Hlatky MA, Konstam MA, Lambrew CT, Normand SL, Pina IL, Radford MJ, Smith AL, Stevenson LW, Bonow RO, Bennett SJ, Burke G, Eagle KA, Krumholz HM, Lambrew CT, Linderbaum J, Masoudi FA, Normand SL, Ritchie JL, Rumsfeld JS, Spertus JA, American College of Cardiology, American Heart Association Task Force on Performance Measures (Writing Committee to Develop Heart Failure Clinical Performance Measures), Heart Failure Society of America: **ACC/AHA clinical performance measures for adults with chronic heart failure: a report of the american college of cardiology/american heart association task force on performance measures (Writing committee to develop heart failure clinical performance measures) endorsed by the heart failure society of america.** *J Am Coll Cardiol* 2005, **46**(6):1144–1178.
4. McMurray JJ, Stewart S: **Epidemiology, aetiology, and prognosis of heart failure.** *Heart* 2000, **83**(5):596–602.
5. McAlister FA, Teo KK, Taher M, Montague TJ, Humen D, Cheung L, Kiaii M, Yim R, Armstrong PW: **Insights into the contemporary epidemiology and outpatient management of congestive heart failure.** *Am Heart J* 1999, **138**(1Pt1):87–94.
6. Teng TH, Finn J, Hobbs M, Hung J: **Heart failure: incidence, case fatality, and hospitalization rates in Western Australia between 1990 and 2005.** *Circ Heart Fail* 2010, **3**(2):236–243.
7. Bui AL, Horwich TB, Fonarow GC: **Epidemiology and risk profile of heart failure.** *Nat Rev Cardiol* 2011, **8**(1):30–41.
8. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW: **2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation.** *Circulation* 2009, **119**(14):e391–e479.
9. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Pieper K, Sun JL, Yancy C, Young JB, OPTIMIZE-HF Investigators and Hospitals: **Association between performance measures and clinical outcomes for patients hospitalized with heart failure.** *JAMA* 2007, **297**(1):61–70.
10. Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, McBride ML, Inge PJ, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Yancy CW: **Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF).** *Circulation* 2010, **122**(6):585–596.
11. Fonarow GC, Abraham WT, Albert NM, Gattis Stough W, Gheorghiade M, Greenberg BH, O'Connor CM, Pieper K, Sun JL, Yancy CW, Young JB, OPTIMIZE-HF Investigators and Hospitals: **Influence of a performance-improvement initiative on quality of care for patients hospitalized with heart failure: results of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF).** *Arch Intern Med* 2007, **167**(14):1493–1502.
12. Fonarow GC, Yancy CW, Heywood JT, ADHERE Scientific Advisory Committee, Study Group, and Investigators: **Adherence to heart failure quality-of-care indicators in US hospitals: analysis of the ADHERE Registry.** *Arch Intern Med* 2005, **165**(13):1469–1477.
13. Maeda JL: **Evidence-based heart failure performance measures and clinical outcomes: a systematic review.** *J Card Fail* 2010, **16**(5):411–418.
14. Fonarow GC, Yancy CW, Hernandez AF, Peterson ED, Spertus JA, Heidenreich PA: **Potential impact of optimal implementation of evidence-based heart failure therapies on mortality.** *Am Heart J* 2011, **161**(6):1024–1030. e3.
15. 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–i50.
16. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW: **2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation.** *Circulation* 2009, **119**(14):1977–2016.
17. Authors/Task Force M, ESC Committee for Practice Guidelines (CPG), McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, *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.
18. Heidenreich PA, Hernandez AF, Yancy CW, Liang L, Peterson ED, Fonarow GC: **Get with the guidelines program participation, process of care, and outcome for medicare patients hospitalized with heart failure.** *Circ Cardiovasc Qual Outcomes* 2012, **5**(1):37–43.
19. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH: **The Danish National Hospital Register. A valuable source of data for modern health sciences.** *Dan Med Bull* 1999, **46**(3):263–268.
20. Zannad F, Stough WG, Pitt B, Cleland JG, Adams KF, Geller NL, Torp-Pedersen C, Kirwan BA, Follath F: **Heart failure as an endpoint in heart failure and non-heart failure cardiovascular clinical trials: the need for a consensus definition.** *Eur Heart J* 2008, **29**(3):413–421.
21. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB: **The Danish civil registration system. A cohort of eight million persons.** *Dan Med Bull* 2006, **53**(4):441–449.
22. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR: **Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls.** *BMJ* 2009, **338:**b2393.
23. White IR, Royston P: **Imputing missing covariate values for the Cox model.** *Stat Med* 2009, **28**(15):1982–1998.
24. Donders AR, van der Heijden GJ, Stijnen T, Moons KG: **Review: a gentle introduction to imputation of missing values.** *J Clin Epidemiol* 2006, **59**(10):1087–1091.
25. Cowie MR, Wood DA, Coats AJ, Thompson SG, Suresh V, Poole-Wilson PA, Sutton GC: **Survival of patients with a new diagnosis of heart failure: a population based study.** *Heart* 2000, **83**(5):505–510.

26. Jhund PS, Macintyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A, Chalmers JW, Capewell S, McMurray JJ: **Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people.** *Circulation* 2009, **119**(4):515–523.
27. Fonarow GC, Albert NM, Curtis AB, Gheorghiade M, Liu Y, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Yancy CW: **Incremental Reduction in Risk of Death Associated With Use of Guideline-Recommended Therapies in Patients With Heart Failure: A Nested Case–control Analysis of IMPROVE HF.** *J Am Heart Assoc* 2012, **1**:16–26.
28. Jernberg T, Johanson P, Held C, Svennblad B, Lindback J, Wallentin L, SWEDEHEART/RIKS-HIA: **Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction.** *JAMA* 2011, **305**(16):1677–1684.
29. Ingeman A, Pedersen L, Hundborg HH, Petersen P, Zielke S, Mainz J, Bartels P, Johnsen SP: **Quality of care and mortality among patients with stroke: a nationwide follow-up study.** *Med Care* 2008, **46**(1):63–69.
30. Komajda M, Lapuerta P, Hermans N, Gonzalez-Juanatey JR, Van Veldhuisen DJ, Erdmann E, Tavazzi L, Poole-Wilson P, Le Pen C: **Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey.** *Eur Heart J* 2005, **26**(16):1653–1659.
31. Eagle KA, Montoye CK, Riba AL, DeFranco AC, Parrish R, Skorcz S, Baker PL, Faul J, Jani SM, Chen B, Roychoudhury C, Elma MA, Mitchell KR, Mehta RH, American College of Cardiology's Guidelines Applied in Practice (GAP) Projects in Michigan, American College of Cardiology Foundation (Bethesda, Maryland) Guidelines Applied in Practice Steering committee: **Guideline-based standardized care is associated with substantially lower mortality in medicare patients with acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice (GAP) Projects in Michigan.** *J Am Coll Cardiol* 2005, **46**(7):1242–1248.
32. Strandberg-Larsen M, Nielsen M, Vallgårda S, Krasnik A, Vrangbæk K, Mossialos E: **Denmark: Health system review.** *Health systems in transition* 2007, **9**(6):1–164.
33. Christiansen T: **Ten years of structural reforms in Danish healthcare.** *Health Policy* 2012, **106**(2):114–119.
34. Goodhart C, Problems of Monetary management: **Problems of Monetary management: The UK Experience.** In *Monetary Theory and Practice. The UK Experience.* London: The Macmillan Press LTD; 1984:91–121.

doi:10.1186/1472-6963-13-391
Cite this article as: Nakano *et al.*: Trends in quality of care among patients with incident heart failure in Denmark 2003–2010: a nationwide cohort study. *BMC Health Services Research* 2013 **13**:391.

Age and Ageing 2016; **45:** 635–642
doi: 10.1093/ageing/afw119
Published electronically 18 July 2016

Age- and sex-related differences in use of guideline-recommended care and mortality among patients with incident heart failure in Denmark

Anne Nakano[1], Kenneth Egstrup[2], Marie Louise Svendsen[1], Inge Schjødt[3], Lars Jakobsen[3], Frank Mehnert[1], Søren Paaske Johnsen[1]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, Aarhus 8200, Denmark
[2]Department of Cardiology, Odense University Hospital, Svendborg, Denmark
[3]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

Address correspondence to: A. Nakano. Danish Clinical Registers - Audit Unit West, Olof Palmes Allé 15, Aarhus 8200, Denmark. Tel: +45 23435047. Email: anne.nakano@stab.rm.dk

Abstract

Background: data are sparse on age- and sex-related differences in use of guideline-recommended care and subsequent mortality among patients with heart failure (HF).
Methods: we identified 24,308 incident patients with a verified primary diagnosis of HF recorded during 2003–2010 in the Danish Heart Failure Registry. The registry monitors guideline-recommended processes of care: echocardiography, New York Heart Association Classification, treatment with angiotensin converting enzyme inhibitors/angiotensin II receptor blockers, betablockers, physical training and patient education.
Results: older age was associated with lower use of recommended processes of care. Relative risk (RR) for receiving processes of care varied for men >80 years from 0.52 to 0.91 compared with men ≤65 years. Corresponding RRs among women >80 years varied from 0.55 to 0.89 compared with women ≤65 years. Older age was as expected associated with higher 1 year mortality (32.6% among men >80 years versus 5.4% among men ≤65 years and 33.8% among women >80 years versus 6.6% among women ≤65 years). The corresponding hazard ratios (HRs) were 4.54 (95% CI 3.93–5.25) and 4.08 (95% CI 3.51–4.75) for the oldest versus youngest men and women, after adjustment for patient characteristics. Adjustment for differences in care lowered HRs among the oldest age groups (adjusted HR 3.87 for men and 3.48 for women, respectively). The findings were also confirmed when stratifying the patients according to left ventricular ejection fraction ≤40% and >40%.
Conclusion: older patients with HF were less likely to receive guideline-recommended processes of care, irrespective of sex. Lower level of care may contribute to an excess mortality observed among the older patients.

Keywords: *heart failure, gender differences, older people, performance measures*

Introduction

Although heart failure (HF) is a serious condition in all patients [1], marked age- and sex-related differences in clinical outcome, including mortality and functional level, have been reported [2].

Effective treatment and preventive measures have been developed for patients with HF [3], however, the long-term prognosis including survival remains poor although improvements have been made [1, 4].

Older patients and women have generally been under-represented in clinical trials within HF care and the evidence for effective therapies is therefore weaker in these patient groups [5]. This may play a role for implementation of guideline recommended care in routine clinical settings since existing studies suggest that older patients (i.e. 65 years or older) receive fewer evidence-based diagnostic examinations and less care [6].

Sex-related differences in HF care have been reported, but the findings appear less consistent with some studies reporting superior care [4], whereas other studies did not observe differences in HF care among women compared to men [7]. Available data on the implications of the possible differences in care is sparse and consequently, it is unknown whether differences in use of guideline-recommended care play a role for the observed age- and sex-related differences in mortality in real-life settings [7]. We examined age- and sex-related differences in HF care, including use of pharmacological therapy during follow-up, and whether potential differences in care affect mortality. This was assessed in a nationwide population-based follow-up study among patients with incident HF registered in the Danish Heart Failure Registry (DHFR).

Methods

Setting

The study included Danish residents diagnosed with incident HF during 2003–2010 (the Danish population ≈ approximately 5.6 million). All Danish residents have free access to hospital care provided by the tax-financed Danish National Health Service, who also refunds a variable proportion of prescription medication costs.

Study population

The study population included Danish residents registered in the DHFR for the period 2003–2010, who codes, 10th revision (ICD-10): I11.0, I13.0, I13.2, I42.0, were hospitalised or had a first contact to an outpatient cardiology clinic and a primary diagnosis of first-time ever observed HF, according to national and international guidelines from the American College of Cardiology/the American Heart Association, and the European Society of Cardiology [1, 8], and verified by an experienced cardiologist (International Classification of Disease I42.6, I42.7, I42.8, I42.9, I50.0, I50.1, I50.2, I50.3, I50.8, I50.9). Each patient was included only once in the database. Patients were 18 years of age or older and Danish residents and were enrolled irrespective of their left ventricular function. The registry includes patients at the time when they have their first hospital contact with HF as the primary diagnosis (i.e. the most important condition and primary reason for the hospital contact). Patients who have previously been admitted with other conditions as the primary diagnosis (e.g. myocardial infarction, atrial fibrillation or a chest infection) as the primary diagnosis and HF as a secondary diagnosis will therefore also be eligible if they at any time during the course of their disease is admitted or seen as an outpatient with HF as the primary diagnosis. See Figure 1 in the supplementary data available at *Age and Ageing* online for a detailed description of the inclusion and exclusion criteria used in the DHFR.

The DHFR is a nationwide initiative to monitor and improve the quality of care for HF. This is accomplished by monitoring fulfilment of quality performance measures related to process and outcome of health care, see Table 1a in the supplementary data available at *Age and Ageing* online for a description of the monitored processes of care. The performance measures were identified by a multidisciplinary national expert panel. Detailed data definitions and registration forms have been developed and disseminated. All data registered in the DHFR are entered manually after a paper form has been filled out for each patient by the staff responsible for treating the patient. Detailed data definitions are available and the reported data are audited on a yearly basis both nationally and regionally to ensure a uniform data registration practice.

Participation is mandatory for all hospital departments in Denmark treating patients with HF. The completeness of the registry is high for the vast majority of the departments (98–100% of the patients fulfilling the inclusion criteria) when compared with local hospital discharge registries/the Danish National Registry of Patients.

We identified a total of 24,443 patients in DHFR during the study period. Of these 129 had been residents in Denmark for less than one year, 6 were <18 years of age at the time of diagnosis, leaving us with a total of 24,308 patients for analyses.

HF care, including use of pharmacological therapy during follow-up

Two of the assessed processes of care (use of echocardiography and New York Heart Association (NYHA) classification) are monitored in all patients. The remaining processes of care (initiation (including unsuccessful attempts) or continuation of treatment with Angiotensin Converting Enzyme/Angiotensin II antagonist (ACE/ATII) inhibitors and betablockers, physical training and patient education) are only monitored in patients with systolic HF (defined as Left Ventricular Ejection Fraction (LVEF) ≤40%), see Table 1a in the supplementary data available at *Age and Ageing* online".

We also obtained data regarding use of pharmacological therapy during follow-up from the Danish Medicines Agency´s Register of Medicinal Product Statistics, a national prescription registry which contains information on all redeemed prescriptions for reimbursable drugs dispensed from all pharmacies in Denmark since 1995. We identified all prescriptions for beta-blockers, alpha-betablockers, ACE inhibitors, angiotensin II receptor blocker (ARB), statins and glucose lowering drugs from hospital discharge until the end of follow-up. All drugs were available by prescription only. We assumed a prescription length of 90 days, as this is the standard length in Denmark.

Mortality

The Danish Civil Registration System maintained electronic records of changes in vital status of all citizens since 1968 [9].

Each record carries a unique 10-digit civil registration number that is assigned to every Danish citizen and is used in all Danish registries. For this study, we obtained information on 1 year mortality after admission to hospital or first hospital contact.

Patient characteristics

Data on patient characteristics were obtained from the DHFR. The Charlson Comorbidity Index (CCI) covers 19 major disease categories [10], and was constructed based on the hospitalisation history of each individual recorded before the incident hospitalisation for HF. Data on previous hospitalisations were obtained from the National Registry of Patients, which contains data on all discharge diagnoses in Denmark since 1977. Information about marital status, employment status, personal income and educational level were obtained from the Integrated Database for Labour Market Research at Statistics Denmark. This database contains socioeconomic information at the individual level of Danish citizens.

Our study complied with the declaration of Helsinki, and was approved by the Danish Data Protection Agency (J.nr. 2008-41-2072 cvr-nr. 11-88-37-29) and the Danish Clinical Registers.

Declaration of sources of funding

This work was supported by grants from The Danish Heart Association [Grant numbers 08-4-R64-A1918-B252-22469, 09-04-R71-A2370_09-S1-22524F], Research Foundation of Health Science in the Central Denmark Region, and Fabrikant Karl G. Andersens Fond.

Financial sponsors played no role in design, execution, analysis or interpretation of data.

Statistics

We first computed the proportion of women and men receiving the individual processes of care, defined as the fulfilment of the specific performance measures monitored in DHFR in the following age and sex groups: Men and women ≤65 years; >65–80 years and >80 years. Only patients fulfilling the inclusion criteria for the individual processes of care and with available data were included in the analyses. The proportions of patients receiving the individual processes of care were compared, and binary regression was used to compute relative risks (RRs) for each age group with 95% confidence intervals (CIs). Men in the youngest age group (≤65 years) served as the reference in all analyses. In addition, we also did supplementary analyses in which the population was stratified by age and men used as reference within each age strata.

We used multivariable Cox proportional hazards regression to compare 1 year mortality according to age and sex. We first adjusted for patient characteristics and calendar year and then in an extended multivariable model also adjusted for the proportion of received processes of care as well as use of pharmacological therapy during follow-up for each patient. The latter were included as time-dependent variables with a prescription length of 90 days. To examine any changes in age- and sex-related differences in mortality, we also repeated the analyses stratifying according to year of diagnosis (2003–2006 vs. 2007–2010). Furthermore, analyses were also stratified according to LVEF (≤40% and >40%).

Data were analysed using Stata 13.0 (StataCorp LP, College Station, Texas).

Results

Table 1 shows the characteristics of the 24.308 patients according to age and sex. Age and sex specific characteristics according to LVEF (≤40% and >40%) are available, see Tables 2a and 2b in the supplementary data available at *Age and Ageing* online.

Table 2 shows the use of the guideline-recommended processes of care. Increasing age was associated with lower proportion of patients receiving recommended processes of care among both men and women, in particular echocardiography, NYHA-classification, physical training and patient education. Sex-related differences were, in general, smaller, however, the proportion of women receiving the individual processes of care tended to be lower than that of men of the same age, in particular among the older patients with HF (>80 years) see Table 3a in the supplementary data available at *Age and Ageing* online.

Age- and sex-related differences in mortality

Age- and sex-specific mortality rate ratios are presented in Table 3. The proportion of men who died within 1 year in the different age groups ranged from 5.4% to 32.6%. The corresponding proportions for women ranged from 6.6% to 33.8%. The strongest predictors of 1 year mortality in both the crude and multivariable analysis were age and NYHA classification.

When adjusting for patient characteristics, the age-related differences in mortality were reduced as reflected by the lower hazard ratios (HRs) in Table 3. Additional adjustment for differences in the use of guideline-recommended processes of care and pharmacological therapy during follow-up further reduced the HRs among the older patients (>80 years), whereas no substantial changes were observed among the younger patients (Table 3). No major sex-related differences in crude mortality were observed in any of the age groups, however older women with HF tended to have a lower mortality than men of similar age in the adjusted analyses.

When stratifying the analyses according to the year of diagnosis, we found no statistical significant difference between the two periods (2003–2006 vs. 2007–2010), see Tables 4 and 5 in the supplementary data available at *Age and Ageing* online.

The overall pattern regarding age- and sex-related differences also remained when stratifying the analyses

Table 1. Descriptive characteristics of 24,308 patients with incident heart failure in Denmark registered in the Danish Heart Failure Registry stratified by age

	Patients ≤65 years of age		Patients 65–80 years of age		Patients >80 years of age	
	Men, *n* (%) 5362 (34.7)	Women, *n* (%) 1842 (20.8)	Men, *n* (%) 6702 (43.3)	Women, *n* (%) 3380 (38.2)	Men, *n* (%) 3398 (22.0)	Women, *n* (%) 3624 (41.0)
Left ventricular ejection fraction						
LVEF≤40%	4581 (85.4)	1465 (79.5)	5253 (78.4)	2393 (70.8)	2276 (67.0)	1790 (49.4)
Missing	216 (4.0)	98 (5.3)	636 (9.5)	370 (11.0)	697 (20.5)	1135 (31.3)
New York Heart Association Classification						
NYHA I	742 (13.8)	197 (10.7)	539 (8.0)	200 (5.9)	130 (3.8)	89 (2.5)
NYHA II	2245 (41.9)	718 (39.0)	2488 (37.1)	1162 (34.4)	844 (24.8)	694 (19.2)
NYHA III	860 (16.0)	359 (19.5)	1305 (19.5)	607 (18.0)	717 (21.1)	577 (15.9)
NYHA VI	81 (1.5)	25 (1.4)	95 (1.4)	56 (1.7)	109 (3.2)	90 (2.5)
Missing	1434 (26.7)	543 (29.5)	2275 (34.0)	1355 (40.1)	1598 (47.0)	2174 (31.3)
Smoking habits						
Smoking	2387 (44.5)	750 (40.7)	1944 (29.0)	985 (29.1)	561 (816.5)	413 (11.4)
Missing	5 (0.1)	6 (0.3)	16 (0.2)	8 (0.2)	7 (0.2)	5 (0.1)
AMI[a]	1832 (34.2)	476 (25.8)	2945 (44.0)	1137 (33.6)	1374 (40.4)	1066 (29.4)
Stroke[a]	472 (8.8)	133 (7.2)	1138 (17.9)	478 (14.1)	634 (18.7)	629 (17.4)
COPD[a]	614 (11.5)	294 (16.0)	1367 (20.4)	782 (23.1)	636 (18.7)	478 (13.2)
Hypertension[a]	1646 (30.7)	574 (31.2)	2494 (37.2)	1400 (41.4)	1206 (35.5)	1539 (42.5)
Diabetes[a]	1031 (19.2)	338 (18.4)	1640 (24.5)	730 (21.6)	591 (17.4)	588 (16.2)
Use of pharmacological therapy during follow-up: At least 1 prescription/12 months[b]						
Betablockers	2549 (47.5)	821 (44.6)	3229 (48.2)	1658 (49.0)	1387 (40.8)	1550 (42.3)
Beta-Alpha blockers	2725 (50.8)	917 (49.8)	2717 (40.5)	1131 (33.5)	821 (24.2)	583 (16.1)
ACE inhibitors	4609 (86.0)	1474 (80.0)	5193 (77.5)	2403 (71.1)	2099 (61.8)	1886 (52.0)
AT II receptor antagonists	934 (17.4)	457 (24.8)	1263 (18.8)	781 (23.1)	418 (12.3)	475 (13.1)
Statin	3285 (61.3)	968 (52.6)	4271 (63.7)	1919 (56.8)	1231 (36.2)	972 (26.8)
Insulin	390 (7.3)	156 (8.5)	562 (8.4)	264 (7.8)	151 (4.4)	169 (0.5)
Oral glucose lowering drugs	736 (13.7)	204 (11.1)	1079 (16.1)	444 (13.1)	331 (9.7)	296 (8.2)

LVEF, Left Ventricular Ejection Fraction; NYHA, New York Heart Association; AMI, Acute Myocardial Infarction; COPD, Chronic Obstructive Pulmonary Disease.
[a]Data are from the Danish National Registry of Patients,
[b]Note that the data on pharmacological therapy reflects use at any time during the entire 12 months follow-up period and that patients may not necessarily have used the drugs throughout the period.
Calender year 1–7 are not shown in this table.

according to LVEF (i.e. ≤40% and >40%, respectively) (data not shown).

Discussion

In this nationwide follow-up study, we found older age to be associated with lower use of guideline- recommended processes of HF care. Sex-related differences were, in general, smaller and non-systematic. The age-related differences in care may contribute to the higher mortality observed among older patients.

The strengths of our study include the prospective nationwide population-based design with virtually complete long-term follow-up, a large number of patients and consecutive inclusion of in-hospital and out-patients with a first time primary diagnosis of HF. Furthermore, thorough efforts are made to ensure data validity in the DHFR and all patients are included only after the diagnosis has been verified by a senior cardiologist, who has reviewed the medical record. Regular audits are conducted, which include validation of the completeness of patient registration against hospital discharge registries [11]. Although the completeness of the patient registration in DHFR is very high with respect to the target population, it is important to emphasise that the registry does not capture all persons with HF in the Danish population. The inclusion criteria in the DHFR are quite strict in order to ensure a relatively homogenous patient population in which it is possible to make comparisons between hospitals and over time regarding the quality of care. However, the total number of patients registered with a hospital discharge diagnosis of HF is substantially higher than the number of patients included in the DHFR (e.g. in 2014/2015 a total of 6,819 patients were registered with a first-time HF diagnosis at Danish hospitals, including all diagnostic positions, but only 3,742 were included in the DHFR indicating that the total population of patients registered with incident HF during our study period may have been >50.000) [12]. Indeed, identification of patients with HF is challenging and hospital discharge registries have been reported to underestimate the true prevalence of HF [13]. Among the excluded patients in our database were patients with an incorrect HF diagnosis [14] but also patients where HF was not registered as the primary diagnosis, probably including patients with multiple morbidities and a complex clinical history. Caution is therefore required before generalising our findings to the entire

Table 2. RR for processes of care stratified by age and sex among patients with incident heart failure

Processes of care	Patients who fulfilled the processes of care, n = yes/total (%)	RR (95% CI)	Missing cases (%)
Echocardiography			
Men ≤ 65 years	4728/5341 (88.5)	1.00	613 (11.5)
Women ≤ 65 years	1591/1829 (87.0)	0.98 (0.96–1.00)	238 (13.0)
Men > 65–80 years	5494/6682 (82.2)	0.92 (0.92–0.94)	1188 (17.8)
Women > 65–80 years	2724/3373 (80.8)	0.91 (0.90–0.93)	649 (19.2)
Men > 80 years	2469/3385 (72.9)	0.82 (0.81–0.84)	916 (27.1)
Women > 80 years	2252/3610 (62.4)	0.70 (0.69–0.72)	1358 (37.6)
NYHA-classification			
Men ≤ 65 years	3928/5348 (73.5)	1.00	1420 (26.6)
Women ≤ 65 years	1299/1827 (71.1)	0.96 (0.94–1.00)	528 (29.0)
Men > 65–80 years	4427/6685 (66.2)	0.90 (0.88–0.92)	2258 (33.8)
Women > 65–80 years	2025/3373 (60.0)	0.82 (0.79–0.84)	1348 (40.0)
Men > 80 years	1800/3386 (53.2)	0.72 (0.70–0.75)	1586 (46.8)
Women > 80 years	1450/3608 (40.2)	0.55 (0.52–0.57)	2158 (59.8)
ACE/ATII inhibitors			
Men ≤ 65 years	3397/3542 (95.9)	1.00	145 (4.0)
Women ≤ 65 years	1083/1130 (95.8)	1.00 (0.99–1.01)	47 (4.2)
Men > 65–80 years	3170/3933 (94.3)	0.98 (0.97–0.99)	223 (5.7)
Women > 65–80 years	1672/1798 (93.0)	0.96 (0.96–0.98)	126 (7.0)
Men > 80 years	1510/1723 (87.6)	0.91 (0.90–0.93)	213 (12.4)
Women > 80 years	1087/1269 (85.7)	0.89 (0.87–0.91)	182 (14.3)
Betablockers			
Men ≤ 65 years	3107/3522 (88.2)	1.00	415 (11.8)
Women ≤ 65 years	964/1109 (87.0)	0.98 (0.96–1.01)	145 (13.1)
Men > 65–80 years	3372/3912 (86.2)	0.98 (0.96–0.99)	540 (13.8)
Women > 65–80 years	1473/1771 (83.2)	0.94 (0.92–0.97)	298 (16.8)
Men > 80 years	1318/1695 (77.8)	0.88 (0.86–0.91)	377 (22.2)
Women > 80 years	945/1238 (76.3)	0.87 (0.84–0.89)	293 (23.7)
Physical training			
Men ≤ 65 years	718/3750 (19.2)	1.00	3032 (80.9)
Women ≤ 65 years	256/1183 (21.6)	1.13 (1.00–1.28)	927 (78.4)
Men > 65–80 years	658/4203 (15.7)	0.82 (0.74–0.90)	3545 (84.3)
Women > 65–80 years	303/1896 (16.0)	0.83 (0.74–0.94)	1593 (84.0)
Men > 80 years	184/1836 (10.0)	0.52 (0.45–0.61)	1652 (90.0)
Women > 80 years	145/1374 (10.6)	0.55 (0.47–0.65)	1229 (89.4)
Patient education			
Men ≤ 65 years	2792/3693 (75.6)	1.00	901 (24.4)
Women ≤ 65 years	891/1163 (76.6)	1.01 (0.98–1.05)	272 (23.4)
Men > 65–80 years	3013/4121 (73.1)	0.97 (0.94–0.99)	1108 (26.9)
Women > 65–80 years	1335/1876 (71.2)	0.94 (0.91–0.97)	541 (28.8)
Men > 80 years	1039/1780 (58.4)	0.77 (0.74–0.81)	741 (41.6)
Women > 80 years	704/1336 (62.7)	0.70 (0.66–0.74)	632 (47.3)

RR: Relative Risk; NYHA: New York Heart Association; ACE/ATII: Angiotensin converting enzyme/Angiotensin II antagonist inhibitors; LVEF: Left Ventricular Ejection Fraction.

Table 3. Crude and adjusted 1 year mortality according to age and sex among patients with incident heart failure

1 year mortality					
Age (years)	Sex	Patients who died n = yes/total (%)	Crude hazard ratio (HR) (95% CI)	Adjusted hazard ratio (HR)[a] (95% CI)	Adjusted hazard ratio (HR)[b] (95% CI)
≤ 65	Men	291/5361 (5.4)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Women	117/1842 (6.6)	1.18 (0.95–1.46)	1.13 (0.91–1.41)	1.12 (0.90–1.40)
> 65–80	Men	947/6700 (14.1)	2.72 (2.39–3.11)	2.15 (1.87–2.47)	2.09 (1.82–2.40)
	Women	473/3379 (14.0)	2.71 (2.34–3.13)	1.98 (1.69–2.32)	1.92 (1.64–2.25)
> 80	Men	1108/3396 (32.6)	7.10 (6.24–8.07)	4.54 (3.93–5.25)	3.87 (3.35–4.48)
	Women	1223/3623 (33.8)	7.51 (6.61–8.54)	4.08 (3.51–4.75)	3.48 (2.99–4.05)

[a]Adjusted for patient characteristics listed in Table 2.
[b]Adjusted for patient characteristics listed in Table 2, and processes of care and use of pharmacological therapy during follow-up.

HF population, but one could hypothesise that the age-related differences in quality of care that we have identified in the DHFR is a conservative estimate of the potential age-related differences occurring in the entire population as these differences may even be larger among older HF patients with a less clear clinical picture and not seen by specialists.

The baseline prevalence of AMI, hypertension and diabetes found in our study is in accordance with some HF populations [15], but in contrast to others [16, 17]. It is difficult directly to compare the details of the HF register-based studies, due to the lack of an accurate and operational universal definition of HF [1, 15], which gives room for substantial variation in the inclusion criteria in the studies.

Although efforts were made to ensure the data validity in the DHFR, data collection in routine clinical practice is prone to misclassification and incomplete reporting. It should be noted that for some variables we observed a higher proportion of missing data among older patients (e.g. LVEF). The incomplete data reporting was primarily observed in the first years after the launch of the DHFR and has subsequently declined substantially. Although we can, by principle, not exclude the possibility that incomplete data may have influenced our findings, we find it unlikely to explain the overall patterns of care observed. Thus, when we stratified the analyses according to calendar time, we found similar age- and sex-related patterns in the early (2003–2006) and late (2007–2010) part of our study period.

We did not have access to information on the reasons of non-adherence to recommended processes of care in the individual (e.g. poor tolerance or contraindication to specific drugs), and even though we controlled for a wide range of factors possibly affecting clinical outcome, we cannot exclude the possibility that the results remain influenced by residual or unaccounted confounding either due to missing data for some of the patients (e.g. NYHA class) or complete lack of data (e.g. patient preferences) [18].

The lower use of guideline-recommended processes of care among older patients in our study is in accordance and extends findings from previous studies [19]. The reasons for lower use of recommended care among older patients are not clear, but the diagnosis of HF may be particularly challenging, because atypical symptoms and presentations are common, and comorbid conditions may mimic or complicate the clinical picture [20]. It should be noted that lower use of selected key processes (e.g. use of echocardiograph and NYHA-classification) may directly impact the likelihood of using other processes of care (e.g. ACE-inhibitor and beta-blocker therapy) [21]. Our study showed that findings on age- and sex-related differences were similar among both HF patients with and without preserved ejection fraction (HFPEF and HFREF, respectively). This is an important finding since HFPEF is common among older patients, in particular women [22] and the evidence-based underlying treatment of patients with HFPEF is modest-to-weak [23], which may also influence treatment practices although studies have indicated that therapy with ACE inhibitors and beta-blockers is also effective in HFPEF patients [24, 25].

One could therefore suspect that the age-related differences found in our study were explained by age-related differences in the ratio of patients with HFPEF/HFREF, however this appeared not to be the case.

Focusing on the age-related differences in care and mortality, it is important to keep the natural ageing of humans in mind [26], taking into account the existing comorbidities in the old population causing either difficulty in tolerating the medications or being titrated up to the recommended doses. We assessed use of pharmacological therapy using data on filled prescriptions. Lack of filled prescriptions could reflect lack of prescribing from the hospital doctor or the general practitioner, but it may also reflect that the patient did not go to the pharmacy to fill the prescription. Whereas the first may reflect insufficient care, the later phenomenon is more complex and may reflect a range of patient-related challenges (e.g. lack of motivation and knowledge about the rationale of the prescribed treatment or lack of ability or willingness to cover any out of pocket expenses). Furthermore, the older patients may also be less likely to be prescribed evidence-based HF medications due to a shorter expected length of survival as a consequence of a higher level of comorbidity. It should be noted that we did not have information on the exact prescribed daily dosages of the examined drugs and therefore only assessed whether the patients received the drugs or not. Our analyses may therefore not fully reflect the true differences in the quality of the pharmacological therapy. However, if the treatment have a positive effect on the quality of the remaining life, it is relevant to consider it to old as well as younger patients [1].

In accordance with our findings for ACE/ATII receptor inhibitors and betablockers, Pinã *et al.* similarly found that women were likely to get ARBs instead of ACE inhibitors probably because of the higher prevalence of ACE inhibitor cough, but no difference in betablockers [5, 27]. In contrast to our study, others found a significant difference between men and women for guideline-recommended drugs [4].

As for mortality, our findings extend our understanding of the mechanisms behind the age-related differences for mortality. The increased mortality among the older patients appeared to a large extend to be explained by differences in the prognostic profile of the patient as well as differences in the HF care including compliance with pharmacological treatment.

The latter indicates a possibility to further reduce age-related differences in mortality through a targeted effort to optimise HF care for the oldest patients. However, it should be borne in mind that it is essential that the care is arranged in close accordance with the individual patient's preferences.

In accordance with most [19, 28] but not all previous studies [29], we found no major differences in mortality according to sex in our study. The inconsistency between the studies may reflect real differences in care patterns across healthcare systems, but could potentially also reflect different methodological approaches e.g. differences between the study populations including the proportion of patients with HFPEF [30].

Conclusion

Older Danish patients with a verified incident primary hospital diagnosis of HF were less likely to receive evidence-based care than younger patients, irrespective of sex. These age-related differences in use of evidence-based HF care may contribute to a higher mortality among older patients. In contrast, no systematic sex-related differences in mortality were identified. Continuous efforts are required to ensure optimal care among patients with HF regardless of their age

Key points

- Older patients with heart failure (HF) were less likely to receive guideline-recommended processes of care.
- Lower use of evidence-based care may contribute to excess mortality among older patients with HF.
- Use of evidence-based care did not depend on gender
- The age-specific mortality among HF patients did not differ according to gender.

Supplementary data

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

Conflicts of interest

None declared.

References

1. Authors/Task Force Members, McMurray JJ, Adamopoulos S *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: 1787–847.
2. Lenzen MJ, Rosengren A, Scholte op Reimer WJ *et al.* Management of patients with heart failure in clinical practice: Differences between men and women. Heart 2008; 94: e10.
3. Yancy CW, Fonarow GC, Albert NM *et al.* Influence of patient age and sex on delivery of guideline-recommended heart failure care in the outpatient cardiology practice setting: Findings from IMPROVE HF. Am Heart J 2009; 157: 754,62.e2.
4. Jimene-Navarro MF, Ramirez-Marrero MA, Anguita-Sanchez M, Castillo JC, BADAPIC Investigators. Influence of gender on long-term prognosis of patients with chronic heart failure seen in heart failure clinics. Clin Cardiol 2010; 33: E13–8.
5. Alehagen U, Ericsson A, Dahlstrom U. Are there any significant differences between females and males in the management of heart failure? Gender aspects of an elderly population with symptoms associated with heart failure. J Card Fail 2009; 15: 501–7.
6. Matusik P, Dubiel M, Wizner B *et al.* Age-related gap in the management of heart failure patients. the national project of prevention and treatment of cardiovascular diseases - POLKARD. Cardiol J 2012; 19: 146–52.
7. Frankenstein L, Remppis A, Fluegel A *et al.* The association between long-term longitudinal trends in guideline adherence and mortality in relation to age and sex. Eur J Heart Fail 2010; 12: 574–80.
8. Jessup M, Abraham WT, Casey DE *et al.* 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: A report of the american college of cardiology Foundation/American heart association task force on practice guidelines: Developed in collaboration with the international society for heart and lung transplantation. Circulation 2009; 119: 1977–2016.
9. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The danish civil registration system. A cohort of eight million persons. Dan Med Bull 2006; 53: 441–9.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987; 40: 373–83.
11. 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.
12. Yearly report for the danish heart failure registry 2014-2015 [Internet]. Available from: https://www.sundhed.dk/content/cms/71/4671_dhd_kommenteret_årsrapport_27012016_final.pdf.
13. Khand AU, Shaw M, Gemmel I, Cleland JG. Do discharge codes underestimate hospitalisation due to heart failure? validation study of hospital discharge coding for heart failure. Eur J Heart Fail 2005; 7: 792–7.
14. 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.
15. Cleland JG, Swedberg K, Follath F *et al.* The EuroHeart failure survey programme–a survey on the quality of care among patients with heart failure in europe. part 1: Patient characteristics and diagnosis. Eur Heart J 2003; 24: 442–63.
16. Johansson I, Dahlström U, Edner M, Näsman P, Rydén L, Norhammar A. Risk factors, treatment and prognosis in men and wonen with heart failure with and without diabetes. BMJ 2015; 101: 1139–48.
17. Cleland J, Dargie H, Hardman S, McDonagh T, Mitchell P. National heart failure audit. april 2012 – march 2013. National Institute for Cardiovascular Outcomes Research (NICOR), Institute of Cardiovascular Science, University College London 2013 21 November 2013.
18. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol 2011; 8: 30–41.
19. Komajda M, Hanon O, Hochadel M *et al.* Contemporary management of octogenarians hospitalized for heart failure in europe: Euro heart failure survey II. Eur Heart J 2009; 30: 478–86.

20. Imazio M, Cotroneo A, Gaschino G *et al.* Management of heart failure in elderly people. Int J Clin Pract 2008; 62: 270–80.
21. Teng TH, Hung J, Finn J. The effect of evidence-based medication use on long-term survival in patients hospitalised for heart failure in western australia. Med J Aust 2010; 192: 306–10.
22. den Ruijter H, Pasterkamp G, Rutten FH *et al.* Heart failure with preserved ejection fraction in women: The dutch queen of hearts program. Neth Heart J 2015; 23: 89–93.
23. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: Comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013; 62: 263–71.
24. Fu M, Zhou J, Sun A *et al.* Efficacy of ACE inhibitors in chronic heart failure with preserved ejection fraction–a meta analysis of 7 prospective clinical studies. Int J Cardiol 2012; 155: 33–8.
25. van Veldhuisen DJ, Cohen-Solal A, Bohm M *et al.* Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data from SENIORS (study of effects of nebivolol intervention on outcomes and rehospitalization in seniors with heart failure). J Am Coll Cardiol 2009; 53: 2150–8.
26. Thomas S, Rich MW. Epidemiology, pathophysiology, and prognosis of heart failure in the elderly. Heart Fail Clin 2007; 3: 381–7.
27. Pina IL, Kokkinos P, Kao A *et al.* Baseline differences in the HF-ACTION trial by sex. Am Heart J 2009; 158(4 Suppl): S16–23.
28. Brandsaeter B, Atar D, Agewall S, Norwegian Heart failure Registry. Gender differences among norwegian patients with heart failure. Int J Cardiol 2011; 146: 354–8.
29. Vaartjes I, Hoes AW, Reitsma JB *et al.* Age- and gender-specific risk of death after first hospitalization for heart failure. BMC Public Health 2010; 10: 637.
30. O'Meara E, Clayton T, McEntegart MB *et al.* Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: Results of the candesartan in heart failure: Assessment of reduction in mortality and morbidity (CHARM) program. Circulation 2007; 115: 3111–20.

Received 7 May 2015; accepted in revised form 11 May 2016

Age and Ageing 2016; **45:** 642–651
doi: 10.1093/ageing/afw098
Published electronically 13 June 2016

The development, implementation and evaluation of a transitional care programme to improve outcomes of frail older patients after hospitalisation

Noor Heim[1†], Herbert Rolden[2†], Esther M. van Fenema[3], Annelies W. E. Weverling - Rijnsburger[4], Jolien P. Tuijl[5], Peter Jue[6], Anna M. Oleksik[1], Anton J. M. de Craen[1‡], Simon P. Mooijaart[1], Gerard Jan Blauw[1,5], Rudi G. J. Westendorp[1,7], Roos C. van der Mast[3], Irma E. C. van Everdinck[8]

[1]Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, Netherlands
[2]Institute for Health Sciences, Radboudumc, Nijmegen, Netherlands
[3]Department of Psychiatry, Leiden University Medical Center, Leiden, Netherlands
[4]Department of Geriatrics, Diaconessenhuis Leiden, Leiden, Netherlands
[5]Department of Geriatrics, Bronovo Hospital, The Hague, Netherlands
[6]Department of Geriatric Medicine, Rijnland Hospital, Leiderdorp, Netherlands
[7]Department of Public Health and Center of Healthy Ageing, University of Copenhagen, Copenhagen, Denmark
[8]Directorate Medical Affairs, Leiden University Medical Center, Leiden, Netherlands

Address correspondence to: N. Heim. Tel: +31 71 526 6640. Email: n.heim@lumc.nl
[†]These authors contributed equally to this work.
[‡]Dr Anton J.M. de Craen passed away in January 2016.

Association between process performance measures and 1-year mortality among patients with incident heart failure: a nationwide study

Anne Nakano MHSc[1, 2], Kenneth Egstrup DrMSci[3], Marie Louise Svendsen PhD[1, 4], Inge Schjødt MSc[5], Søren Paaske Johnsen PhD[1]

1 Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

2 The Danish Clinical Registers, Audit Unit West, Aarhus, Denmark

3 Department of Cardiology, Odense University Hospital, Svendborg Hospital, Denmark

4 Data & Documentation, DEFACTUM, Denmark

5 Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

Corresponding Author: MHSc Anne Nakano

The Danish Clinical Registers, Audit Unit West, Olof Palmes Allé 17, 8200 Aarhus N, Denmark

Department of Clinical Epidemiology, Olof Palmes Allé 45, 8200 Aarhus N, Denmark

Phone: +45 2343 5047

E-Mail: anne.nakano@stab.rm.dk

This study was supported by grants from The Danish Heart Association [Grant number 08-4-R64-A1918-B252-22469] and [Grant number 09-04-R71-A2370_09-S1-22524F], Research Foundation of Health Science in the Central Denmark Region, and Fabrikant Karl G. Andersens Fond.

Abstract

Objective: To examine the association between fulfilment of performance measures supported by clinical guidelines recommendations and 1-year mortality among patients with incident heart failure in Denmark.

Design: A nationwide population-based follow-up study with data from the Danish Heart Failure Registry.

Setting: All Danish hospital departments caring for patients with heart failure.

Participants: We identified 24.308 in-and-outpatients diagnosed from 2003 to 2010.

Intervention: We used data from the Danish Heart Failure Registry. Quality of care was defined as receiving the guideline recommended processes of care: use of echocardiography, New-York-Heart-Association -classification, treatment with angiotensin-converting-enzyme inhibitors/angiotensin-II-receptor blocker, betablockers, physical training and patient education.

Main outcome measure: 1-year mortality. Multivariable Cox Proportional Hazard Regression was used to compute Hazard Ratios (HRs) for 1-year mortality adjusted for potential confounding factors.

Results: 17.1% of patients died within 1 year. Adjusted HRs ranged from 0.56 (95 % Confidence Interval ((CI) 0.51-0.62)) for patient education to 1.00 (95 % CI 0.91-1.11) for betablocker therapy. The association between meeting more performance measures and 1-year mortality appeared to follow a dose-response pattern: Using 0 % -25 % of measures fulfilled as reference, patients who fulfilled between 76 and 100 % of the performance measures had an adjusted HR of 0.28 (95 % CI 0.24-0.32), while the adjusted HR was 0.51 (95 % CI 0.47-0.55) for patients who fulfilled between 26% - 50 % of the performance measures.

Conclusion: Meeting process performance measures, which reflects care in concordance with clinical guidelines recommendations, was associated with substantially lower 1-year mortality risk among patients with incident heart failure.

Keywords: Performance measures of care, quality, Heart Failure, Guidelines, mortality

Introduction

Heart Failure (HF) is a major public health problem and the number of persons affected steadily increases (1,2). Results from randomised controlled trials have demonstrated the efficacy of specific care components in reducing HF morbidity and mortality, e.g., treatment with Angiotensin Converting Enzyme/Angiotensin II antagonist (ACE/ATII) inhibitors and betablockers (2-4). However, the effectiveness of these interventions outside the very controlled and standardized settings of clinical trials is more uncertain. Furthermore, a direct link with important clinical outcomes has yet to be established for many processes of modern HF care including physical training and patient education. Comprehensive efforts have been made to develop and implement clinical guidelines for management of patients with HF (5,6). Still little is understood about the relationship between quality of care and HF outcomes in general medical settings as available data are sparse and inconclusive (5,6). In general, previous studies have been unable to demonstrate a consistent relationship between the quality of specific care components and clinical outcomes among HF patients, which potentially undermines the implementation of clinical guidelines and other initiatives to improve quality of care.

To fill this gap in knowledge, we examined the association between the quality of care as reflected by fulfilment of process performance measures and 1-year mortality among Danish patients with incident HF in a nationwide registry-based follow-up study.

Methods

The Danish Heart Failure Registry (DHFR) is part of the Danish Clinical Registries – a nationwide initiative to monitor and improve the quality of care for specific diseases including HF (7). The initiative does this by developing evidence-based performance measures related to the structure, process, and outcome of health care and, subsequently, by monitoring and systematically auditing the fulfillment of these measures. Participation is mandatory for all hospitals in Denmark treating patients with HF and is not associated with economic incentives.

All Danish residents have free access to hospital care provided by the tax-financed Danish National Health Service, who also refunds a variable proportion of prescription medication costs (8) . All acute medical conditions, including HF, are treated at public hospitals in Denmark. We conducted this study by linking data from the DHFR with other nationwide medical registries. Since 1968 every Danish citizen has been assigned a unique ten-digit civil registration number, which is used in all Danish registries, enabling unambiguous linkage between them (9).

Data sources

The DHFR was established in 2003 and holds prospectively collected data from all Danish hospitals, including both wards and outpatient clinics, treating patients with HF. A total of 41 hospitals and 54 departments reported data to the DHFR during the study period. The hospitals and departments eligible for reporting data to the DHFR were identified by the Danish Regions, which are responsible for running the hospitals. The completeness of patient registration have been reported to be 98-100% for the vast majority of departments according to comparisons with local hospital discharge registries and the Danish Registry of Patients (7). In addition to data on care, the DFHR also holds data on a range of sociodemographic, clinical and life style related variables including age, sex, comorbidity, left ventricular ejection fraction (LVEF) and NYHA classification as well as alcohol intake and smoking habits.

Information on comorbid disease was acquired from the DHFR as well as from the Danish National Registry of Patients, an administrative nationwide public registry which holds data on all admissions to somatic hospitals in Denmark since the 1st of January 1977 (10).

Information on vital status was acquired from the Civil Registration System, which since 1968 maintains electronic records of changes in the vital status of all Danish residents. Each record carries a unique 10-digit civil registration number and contains information on name, sex, date of birth, place of birth, place of residence, citizenship, and daily updated information on vital status (9).

We also obtained data regarding long-term use of pharmacological therapy from the Danish Medicines Agency´s Register of Medicinal Product Statistics, a national prescription registry that contains information on all redeemed prescriptions for reimbursable drugs dispensed from all pharmacies in Denmark since 1995 (11). The information includes type of drug (according to the Anatomic Therapeutic Chemical classification system) and the drugs dispensed. We identified all prescriptions for beta-blockers, alpha-beta blockers, ACE inhibitors, angiotensin II receptor blocker (ARB), statins, insulin and oral antidiabetics filled from hospital discharge until the end of follow-up. All drugs were available by prescription only.

Information about marital status, employment status, personal income, and educational level were ascertained from the integrated database for Labour Market Research at Statistics Denmark. This database contains socioeconomic information at the individual level of Danish citizens.

Study population

The study population included all patients registered in the DHFR for the period 2003 to 2010, who were for the first time ever either hospitalised or had a contact to an outpatient cardiology clinic with a primary diagnosis of HF identified by the following International Classification of Disease codes, 10th revision (ICD-10): I11.0, I13.0, I13.2, I42.0, I42.6, I42.7, I42.8, I42.9, I50.0, I50.1, I50.2, I50.3, I50.8, I50.9). The HF diagnosis was verified by a cardiologist to ensure the validity of the diagnosis (12). Patients were 18 years of age or older and Danish residents and were enrolled irrespective of their left ventricular function. Patients who have previously been admitted with other conditions as the primary diagnosis (e.g. myocardial infarction, atrial fibrillation or a chest infection) and HF as a secondary diagnosis will therefore also be eligible if they at any time during the course of their disease is admitted or seen as an outpatient with HF as the primary diagnosis. We identified a total of 24,504 patients registered in DHFR during the study period. Of these, 129 had been residents in Denmark for less than one year, 16 had died before registration began, 4 had unknown vital status and 47 had age unknown in our dataset (i.e. did not have a valid civil registration number), leaving us with a total of 24,308 patients for analyses.

Process performance measures of HF care

The process performance measures reflect recommendations from national and international clinical guidelines on the care of HF patients (Table 1) (2,13). For the DHFR, a national expert panel including physicians, nurses, physiotherapists and dietitians were assigned to identify the performance measures (13-15). The expert panel followed a structured process to develop pathways and tools to ensure standardised procedures. When selecting the measures, the feasibility of collecting the required data in routine clinical settings and the ability of the criteria to reflect the multidisciplinary efforts involved in HF care was also considered. A time frame was defined for each performance measure to capture the timeliness of the interventions (Table 1).

Data were collected using a standardised registration form with detailed written data specifications for each item and was prospectively collected from the time of patient admission to hospital or first contact with an outpatient cardiology clinic.

Two measures of care in DHFR, echocardiography and NYHA-classification, are monitored in all patients. The remaining processes of care (ACE/ATII inhibitors, betablockers, physical training, and patient education) are only monitored in patients with systolic HF (Left Ventricular Ejection

Fraction (LVEF) ≤ 40%). We computed an aggregated measure of the quality of care to reflect the overall quality of HF care. The score was calculated by dividing the number of fulfilled process performance measures with the total number of performance measures that the patient was eligible for. The score was categorized into quartiles, i.e., 0-25 % (low quality), 26-50 % (medium/low quality), 51-75 % (medium/high quality) and 76-100 % (high quality).

Mortality

We used the Danish Civil Registration System to obtain information on 1-year mortality for patients with HF. Follow-up time started on the date of first ever hospital admission or contact to the HF clinic and ended on the date of death, emigration or after 1 year, whichever came first. For all practical purposes follow-up on mortality using the Civil Registration system can be considered fully complete.

The study was approved by the Danish Data Protection Agency (J.nr. 2008-41-2072 cvr-nr. 11-88-37-29), the Danish National Indicator Project/ The Danish Clinical registers and the Ministry of Health.

Statistics

In and outpatients were followed from the data of admission until 1 year after admission or date of death, whichever came first. We first used multivariable Cox proportional hazards regression to assess the association between fulfilment of the individual process performance measures and 1-year mortality. We adjusted for patient baseline characteristics presented in Table 2 and then in an extended multivariable model also adjusted for treatment and care during follow-up, including drug use at the time of admission and during follow-up as well as mutual adjustment for other process performance measures. We repeated the analyses using the aggregated measure of overall quality of care (proportion of all performance measures being fulfilled) as exposure. Finally, all analyses were repeated after restricting to patients with LVEF ≤ 40%.

There were missing data for some of the variables, ranging from 0.1% for income to 38.6% for NYHA-classification. Patients with missing data for these variables were not included in the multivariable analyses.

Data were analysed using Stata 13.0 (StataCorp LP, College Station, Texas).

Results

Table 1 and 2 summarizes the patient characteristics of the 24.308 patients registered in the DHFR and the performance measures for the incident HF patients' respectively.

A total of 4159 patients died within 1 year after the date of diagnosis, corresponding to 17.1 %. As seen in Table 3, fulfilling the process performance measures was associated with a lower mortality. The adjusted Hazard Ratio (HR) ranged from 0.56 (95 % Confidence Interval ((CI) 0.51-0.62)) for patient education to 1.00 (CI 0.91-1.11) for initiation of betablocker therapy. Table 4 shows the association between meeting more processes of performance measures and 1 year mortality. Indications of a dose-response pattern were observed in this analysis, which used patients with 0 % -25 % of the measures fulfilled as reference. Patients, who received a care which fulfilled between 75% and 100% of the measures, had an adjusted HR of 0.28 (CI 0.24-0.32), whereas patients who received a care meeting 0% to 25% of the measures had an adjusted HR of 0.51 (CI 0.47-0.55). When restricting analyses to patients with LVEF ≤ 40% we found that fulfilment of the process measures were strongly associated with 1 year mortality, Table 4 and 4a. We did not include separate analyses for patients with LVEF > 40% as the sample was too small to provide a satisfactory statistical precision.

Discussion

In this nationwide follow-up study of patients with incident HF, we found that fulfillment of a range of process performance measures reflecting key elements of modern HF care was associated with lower mortality in real-world settings. The association which remained after adjustment for confounding factors appeared to follow a dose-response pattern.

The strengths of this study are the population-based design, the complete long-term follow-up, a large number of patients and consecutive inclusion of in-hospital and out-patients with a first time primary diagnosis. A potential limitation of our study is that the reliability of the DHFR data could have been limited by interobserver variability because the data are collected by many different clinicians during routine clinical work. However, extensive efforts are made to ensure the validity of the data in the DHFR. Structured audit processes are regularly carried out on national, regional and local bases to critically assess the quality of the data and results and provide continuous feed-back to the hospital units (7). Clinicians could get further verification of data accuracy and justification of the method of indicator calculation if wanted. Should the clinicians experience difficulty in accepting indicator feed-back it was possible to review the records of their indicator-failed patients as in the Brisbane Cardiac Consortium (16). The DHFR aims to include all incident patients admitted with HF as the primary diagnosis; consequently, the DHFR will not reflect the incidence of HF in the general Danish population. All patients are only included after approval by a cardiologist, which has reviewed the medical record. In light of consistency of the results and the dose-response effect it seems unlikely that the direction of the results could be attributed to bias and unaccounted confounding. Several precautions were taken to account for potential confounding, including multivariable adjustment for a wide range of prognostic factors and stratification. Furthermore, only patients considered eligible for care by the staff were included in the analysis and thereby minimizing the risk of confounding by indication. These initiatives are likely to have reduced the influence of confounding substantially and the majority of the associations presented in Table 3 seem clinically reasonable. However, the findings of betablockers and physical training indicate that some caution is warranted when interpreting the results for the individual process performance measures, e.g., the apparent lack of association between early initiation of betablocker therapy and 1-year mortality may potentially reflect a combination of non-persistence, use of betablocker therapy in the comparison group (but with a later start) and potential unaccounted confounding by indication (17,18)

The results of this study are supported by other studies that have addressed associations between processes of care and reduction in mortality (19-21). Still some studies find no or only little associations between performance measures and outcome for patients with HF (5,22). Heidenreich et al. found that hospitals receiving achievement awards from Get With the Guideline programmes have modest lower adjusted mortality, but also stated that the study provides evidence that quality improvement programmes that improve processes of care (performance measures) for heart disease may also improve patient outcome (23). Reasons for the discrepancies between studies could be differences in sampling, selection of the population, study designs, the chosen indicators (performance measures) (16,24). The importance of the chosen performance measures are supported by national and international guidelines (2,13) and the measures are at least partly in accordance with measures used by other quality improvements initiatives including the Get With the Guideline programme (24).

As for patient education, our findings extends findings from previous studies, which reported patient education to be associated with a lower risk of readmission or death (25-27), although not all previous studies have indicated such a strong effect (28,29). Patient education is also important as it influences quality of life after diagnosis of HF (30). Implementing patient education as a core measure for quality databases could help the teams taking care of HF patients to qualify the education and hereby enhance adherence to guidelines (31).

Conclusion

In conclusion, meeting process performance measures reflecting clinical guidelines recommendations for HF care was associated with substantially lower 1 year mortality among real-life incident HF patients in Denmark.

Acknowledgements

The multidisciplinary expert panel and the staff involved in the collection of data to the Danish Heart Failure Registry are thanked for making this study possible.

Sources of funding

This study was supported by grants from The Danish Heart Association [Grant number 08-4-R64-A1918-B252-22469] and [Grant number 09-04-R71-A2370_09-S1-22524F], Research Foundation of Health Science in the Central Denmark Region, and Fabrikant Karl G. Andersens Fond.

Conflicts of interest

None declared

References

(1) Roger VL. Epidemiology of heart failure. Circ Res 2013 Aug 30;113(6):646-659.

(2) Authors/Task Force Members, Document Reviewers. 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 J Heart Fail 2016 May 20.

(3) Kazi D, Deswal A. Role and optimal dosing of angiotensin-converting enzyme inhibitors in heart failure. Cardiol Clin 2008 Feb;26(1):1-14, v.

(4) Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005 Feb;26(3):215-225.

(5) Maeda JL. Evidence-based heart failure performance measures and clinical outcomes: a systematic review. J Card Fail 2010 May;16(5):411-418.

(6) Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). Circulation 2010 Aug 10;122(6):585-596.

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

(8) 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 Nov 17;7:449-490.

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

(10) Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999 Jun;46(3):263-268.

(11) Pottegard A, Schmidt SA, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol 2016 Oct 27.

(12) Zannad F, Stough WG, Pitt B, Cleland JG, Adams KF, Geller NL, et al. Heart failure as an endpoint in heart failure and non-heart failure cardiovascular clinical trials: the need for a consensus definition. Eur Heart J 2008 Feb;29(3):413-421.

(13) Egstrup K, Eiskjær H, Gustafson F, Hassager C, Hildebrandt P, Korup E, et al. Hjerteinsufficiens DCS vejledning 2007. Nr. 3. Dansk Cardiologisk Selskab, Hauser Plads 10, 1127 København K. [Heart Failure DCS guideline 2007. No. 3. The Danish Heart Association, Hauser Plads 10, 1127 København K]. 2007.

(14) Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009 Apr 14;119(14):1977-2016.

(15) Authors/Task Force Members, McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, 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 May 19.

(16) Hickey A, Scott I, Denaro C, Stewart N, Bennett C, Theile T. Using clinical indicators in a quality improvement programme targeting cardiac care. Int J Qual Health Care 2004 Apr;16 Suppl 1:i11-25.

(17) Passos LC, Oliveira MG, Duraes AR, Trindade TM, Barbosa AC. Initiation or maintenance of beta-blocker therapy in patients hospitalized for acute heart failure. Int J Clin Pharm 2016 Aug;38(4):802-807.

(18) Gislason GH, Rasmussen JN, Abildstrom SZ, Schramm TK, Hansen ML, Buch P, et al. Persistent use of evidence-based pharmacotherapy in heart failure is associated with improved outcomes. Circulation 2007 Aug 14;116(7):737-744.

(19) Jernberg T, Johanson P, Held C, Svennblad B, Lindback J, Wallentin L, et al. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. JAMA 2011 Apr 27;305(16):1677-1684.

(20) Panella M, Marchisio S, Demarchi ML, Manzoli L, Di Stanislao F. Reduced in-hospital mortality for heart failure with clinical pathways: the results of a cluster randomised controlled trial. Qual Saf Health Care 2009 Oct;18(5):369-373.

(21) Fitzgerald AA, Powers JD, Ho PM, Maddox TM, Peterson PN, Allen LA, et al. Impact of medication nonadherence on hospitalizations and mortality in heart failure. J Card Fail 2011 Aug;17(8):664-669.

(22) Patterson ME, Hernandez AF, Hammill BG, Fonarow GC, Peterson ED, Schulman KA, et al. Process of care performance measures and long-term outcomes in patients hospitalized with heart failure. Med Care 2010 Mar;48(3):210-216.

(23) Heidenreich PA, Lewis WR, LaBresh KA, Schwamm LH, Fonarow GC. Hospital performance recognition with the Get With The Guidelines Program and mortality for acute myocardial infarction and heart failure. Am Heart J 2009 Oct;158(4):546-553.

(24) Heidenreich PA, Hernandez AF, Yancy CW, Liang L, Peterson ED, Fonarow GC. Get with the guidelines program participation, process of care, and outcome for medicare patients hospitalized with heart failure. Circ Cardiovasc Qual Outcomes 2012 Jan 1;5(1):37-43.

(25) Koelling TM, Johnson ML, Cody RJ, Aaronson KD. Discharge education improves clinical outcomes in patients with chronic heart failure. Circulation 2005 Jan 18;111(2):179-185.

(26) Kfoury AG, French TK, Horne BD, Rasmusson KD, Lappe DL, Rimmasch HL, et al. Incremental survival benefit with adherence to standardized heart failure core measures: a performance evaluation study of 2958 patients. J Card Fail 2008 Mar;14(2):95-102.

(27) VanSuch M, Naessens JM, Stroebel RJ, Huddleston JM, Williams AR. Effect of discharge instructions on readmission of hospitalised patients with heart failure: do all of the Joint Commission on Accreditation of Healthcare Organizations heart failure core measures reflect better care? Qual Saf Health Care 2006 Dec;15(6):414-417.

(28) Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. JAMA 2007 Jan 3;297(1):61-70.

(29) Gwadry-Sridhar FH, Flintoft V, Lee DS, Lee H, Guyatt GH. A systematic review and meta-analysis of studies comparing readmission rates and mortality rates in patients with heart failure. Arch Intern Med 2004 Nov 22;164(21):2315-2320.

(30) Cameron J, Worrall-Carter L, Driscoll A, Stewart S. Measuring self-care in chronic heart failure: a review of the psychometric properties of clinical instruments. J Cardiovasc Nurs 2009 Nov-Dec;24(6):E10-22.

(31) Fonarow GC, Yancy CW, Heywood JT, ADHERE Scientific Advisory Committee, Study Group, and Investigators. Adherence to heart failure quality-of-care indicators in US hospitals: analysis of the ADHERE Registry. Arch Intern Med 2005 Jul 11;165(13):1469-1477.

Table 1. Process performance measures monitored in the Danish Heart Failure Registry

Process performance measure*	Definition
Echocardiography	Proportion of patients who undergo echocardiography, no more than 6 months before or within 7 days after 1st contact to either hospital or outpatient clinic
NYHA classification	Proportion of patients who undergo NYHA-classification, within 12 weeks from admission to either hospital or outpatient clinic
Medication (ACE/ATII inhibitors)	Proportion of patients with reduced systolic function (LVEF below 40 %) who is treated with ACE/ATII inhibitors, within 8 weeks from admission to either hospital or outpatient clinic
Medication (Betablockers)	Proportion of patients with reduced systolic function (LVEF below 40 %) who is treated with betablockers, within 12 weeks from admission to either hospital or outpatient clinic
Physical training	Proportion of patients with reduced systolic function (LVEF below 40 %) referred to individual physical training, within 12 weeks from admission to either hospital or outpatient clinic
Patient education	Proportion of patients with reduced systolic function (LVEF below 40 %) who started a structured patient education (inclusive nutrition, physical training, understanding medical treatment, risk factors and symptoms of the disease), within 12 weeks from admission to either hospital or outpatient clinic

NYHA: New York Heart Association, ACE/ATII Angiotensin converting enzyme/angiotensin II antagonist inhibitors, LVEF: Left Ventricular Ejection Fraction
*All performance measures must be documented in the medical record

Table 2. Descriptive characteristics for patients with incident heart failure in Denmark registered in the Danish Heart Failure Register from 2003 to 2010.

Patient characteristics (n = 24.308) (%)	
Age (year)	**N (%)**
18-65	7204 (29.6)
>65-80	10082 (41.5)
>80	7022 (28.9)
Sex	
Male	15462 (63,6)
Female	8846 (36,4)
Left ventricular ejection fraction	
LVEF≤40%	17758 (73.1)
LVEF>40%	3398 (13.9)
missing	3152 (13.0)
New York Heart Association classification	
NYHA-class I	1897 (7.8)
NYHA-class II	8151 (33.5)
NYHA-class III	4425 (18.2)
NYHA-class IV	456 (1.9)
missing	9379 (38.6)
Comorbid diseases*	
AMI	
Yes	8830 (36.3)
No	15478 (63.7)
Stroke	
Yes	3484 (14.3)
No	20824 (85.7)
COPD	
Yes	4171 (17.2)
No	20137 (82.8)
Hypertension[1]	
Yes	8859 (36.4)
No	15449 (63.6)
Diabetes[2]	
Yes	4918 (20.2)
No	19390 (79.8)
Alcohol intake	
≤14/21 drinks pr. Week for female/male	16556 (68.1)
>14/21 drinks pr. Week for female /male	1616 (6.7)
missing	6136 (25.2)

Smoking habits	
Smoker	7040 (29.0)
Nonsmoker	17221 (70.8)
missing	47 (0.2)
Marital Status	
Unmarried/Single	2628 (10.8)
Married/separated/registered partner	12030 (49.5)
Divorced/terminated partnership	3140 (12.9)
Widow/longest living partner	6510 (26.8)
Income (euro/year)	
Euro 0-17289	6061 (24.9)
Euro 17290-21845	6075 (25.0)
Euro 21846-30825	6076 (25.0)
Euro 30826 (more)	6076 (25.0)
missing	20 (0.1)
The proportions of performance measures fulfilled	
From 0 and up to 25 %	3725 (15.3)
From 26 % and up to 50 %	6456 (26.6)
From 51 % and up to 75 %	6117 (25.2)
From 75 % and up to 100 %	7990 (32.9)

LVEF: Left Ventricular Ejection Fraction, NYHA: New York Heart Association, AMI: Acute Myocardial Infarction, COPD: Chronic Obstructive Pulmonary Disease,
* Data are from the Danish National Registry of Patients
[1]Patients with a hospital diagnosis and/or in treatment with antihypertensive medication
[2] Patients with a hospital diagnosis and/or in treatment with antidiabetic medication

Table 3. Association between fulfillment of performance measures and 1-year mortality

Process performance measures	Patients who died N = yes/total (%)	Crude HR (95 % CI)	Adjusted HR* (95 % CI)	Adjusted HR** (95 % CI)
Indicator 1: Echocardiography	2639/16613 (15.9)	0.40 (0.38-0.43)	0.63 (0.59-0.68)	0.74 (0.69-0.81)
Indicator 2: NYHA classification	1604/13321 (12.0)	0.35 (0.33-0.37)	0.48 (0.44-0.51)	0.61 (0.57-0.66)
Indicator 3a: ACE/ATII inhibitors	1417/11037 (12.8)	0.45 (0.42-0.48)	0.72 (0.66-0.78)	0.79 (0.72-0.88)
Indicator 3b: Betablockers	1249/9927 (12.6)	0.47 (0.44-0.50)	0.78 (0.72-0.85)	1.00 (0.91-1.11)
Indicator 4: Physical training	189/2075 (9.1)	0.44 (0.38-0.50)	0.76 (0.65-0.88)	0.93 (0.81-1.10)
Indicator 5: Patient Education	766/9006 (8.5)	0.30 (0.28-0.33)	0.51 (0.47-0.56)	0.56 (0.51-0.62)

HR: Hazard Ratio, NYHA: New York Heart Association classification, ACE/ATII inhibitors: Angiotensin Converting Enzyme/Angiotensin II Antagonist inhibitors
HR*Adjusted for baseline characteristics in table 2
HR**Adjusted for baseline characteristics in table 2, use of ASA, clopidogrel, statins, diuretics, insulin, oral diabetic medication during follow-up and mutual adjustment for other process performance measures

Table 3a. Association between fulfillment of performance measures and 1-year mortality, LVEF ≤ 40%

Process performance measures	Patients who died N = yes/total (%)	Crude HR (95 % CI)	Adjusted HR* (95 % CI)	Adjusted HR** (95 % CI)
Indicator 1: Echocardiography	2179/14137 (15.4)	0.93 (0.81-1.08)	1.11 (0.96-1.28)	1.12 (0.97-1.29)
Indicator 2: NYHA classification	1283/11382 (11.3)	0.43 (0.40-0.47)	0.44 (0.40-0.48)	0.46 (0.43-0.51)
Indicator 3a: ACE/ATII inhibitors	1417/11037 (12.8)	0.59 (0.54-0.64)	0.69 (0.64-0.76)	0.70 (0.64-0.76)
Indicator 3b: Betablockers	1249/9927 (12.6)	0.62 (0.57-0.67)	0.75 (0.69-0.82)	0.77 (0.71-0.84)
Indicator 4: Physical training	189/2075 (9.1)	0.56 (0.49-0.66)	0.75 (0.65-0.87)	0.78 (0.68-0.91)
Indicator 5: Patient Education	766/9006 (8.5)	0.35 (0.32-0.38)	0.48 (0.44-0.53)	0.50 (0.46-0.55)

HR: Hazard Ratio, NYHA: New York Heart Association classification, ACE/ATII inhibitors: Angiotensin Converting Enzyme/Angiotensin II Antagonist inhibitors
HR*Adjusted for baseline characteristics in table 2
HR**Adjusted for baseline characteristics in table 2, use of ASA, clopidogrel, statins, diuretics, insulin, oral diabetic medication during follow-up and mutual adjustment for other process performance measures

Table 4. Association between proportion of fulfilled process performance measures and 1-year mortality.

Proportion of criteria fulfilled	Patients who died N = yes/total (%)	Crude HR (95 % CI)	Adjusted HR* (95 % CI)
0 % -25 %	1422/2303 (61.7)	Reference: 1	Reference:1
26 % - 50 %	1342/5111 (26.3)	0.41 (0.38 – 0.44)	0.51 (0.47 – 0.55)
51 % - 75 %	781/5333 (14.6)	0.20 (0.18 – 0.22)	0.32 (0.28 – 0.36)
76 % - 100 %	603/7386 (8.2)	0.18 (0.16 – 0.20)	0.28 (0.24 – 0.32)

HR Hazard Ratio,
HR* Adjusted for baseline characteristics listed in table 2, use of ASA, chlopidogrel, statins, diuretics, insulin and oral antidiabetics during follow-up

Table 4a. Association between proportion of fulfilled process performance measures and 1-year mortality, LVEF ≤ 40%

Proportion of criteria fulfilled	Patients who died N = yes/total (%)	Crude HR (95 % CI)	Adjusted HR* (95 % CI)
0 % -25 %	296/630 (47.0)	Reference: 1	Reference:1
26 % - 50 %	849/3364 (25.2)	0.57 (0.50 – 0.65)	0.64 (0.56 – 0.74)
51 % - 75 %	778/5315 (14.6)	0.34 (0.30 – 0.39)	0.48 (0.41 – 0.56)
76 % - 100 %	461/6057 (7.6)	0.18 (0.16 – 0.21)	0.30 (0.25 – 0.36)

HR Hazard Ratio,
HR* Adjusted for baseline characteristics listed in table 2, use of ASA, chlopidogrel, statins, diuretics, insulin and oral antidiabetics during follow-up

Reports/PhD theses from Department of Clinical Epidemiology

1. Ane Marie Thulstrup: Mortality, infections and operative risk in patients with liver cirrhosis in Denmark. Clinical epidemiological studies. PhD thesis. *2000*.

2. Nana Thrane: Prescription of systemic antibiotics for Danish children. PhD thesis. *2000*.

3. Charlotte Søndergaard. Follow-up studies of prenatal, perinatal and postnatal risk factors in infantile colic. PhD thesis. *2001*.

4. Charlotte Olesen: Use of the North Jutland Prescription Database in epidemiological studies of drug use and drug safety during pregnancy. PhD thesis. *2001*.

5. Yuan Wei: The impact of fetal growth on the subsequent risk of infectious disease and asthma in childhood. PhD thesis. *2001*.

6. Gitte Pedersen. Bacteremia: treatment and prognosis. PhD thesis. *2001*.

7. Henrik Gregersen: The prognosis of Danish patients with monoclonal gammopathy of undertermined significance: register-based studies. PhD thesis. *2002*.

8. Bente Nørgård: Colitis ulcerosa, coeliaki og graviditet; en oversigt med speciel reference til forløb og sikkerhed af medicinsk behandling. PhD thesis. *2002*.

9. Søren Paaske Johnsen: Risk factors for stroke with special reference to diet, Chlamydia pneumoniae, infection, and use of non-steroidal anti-inflammatory drugs. PhD thesis. *2002*.

10. Elise Snitker Jensen: Seasonal variation of meningococcal disease and factors associated with its outcome. PhD thesis. *2003*.

11. Andrea Floyd: Drug-associated acute pancreatitis. Clinical epidemiological studies of selected drugs. PhD thesis. *2004*.

12. Pia Wogelius: Aspects of dental health in children with asthma. Epidemiological studies of dental anxiety and caries among children in North Jutland County, Denmark. PhD thesis. *2004*.

13. Kort-og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg og Århus amter 1985-2003. *2004*.

14. Reimar W. Thomsen: Diabetes mellitus and community-acquired bacteremia: risk and prognosis. PhD thesis. *2004*.

15. Kronisk obstruktiv lungesygdom i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

16. Lungebetændelse i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

17. Kort- og langtidsoverlevelse efter indlæggelse for nyre-, bugspytkirtel- og leverkræft i Nordjyllands, Viborg, Ringkøbing og Århus amter 1985-2004. *2005*.

18. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg, Ringkøbing og Århus amter 1995-2005. *2005*.

19. Mette Nørgaard: Haematological malignancies: Risk and prognosis. PhD thesis. *2006*.

20. Alma Becic Pedersen: Studies based on the Danish Hip Arthroplastry Registry. PhD thesis. *2006*.

    Særtryk: Klinisk Epidemiologisk Afdeling - De første 5 år. *2006*.

21. Blindtarmsbetændelse i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

22. Andre sygdommes betydning for overlevelse efter indlæggelse for seks kræftsygdomme i Nordjyllands, Viborg, Ringkjøbing og Århus amter 1995-2005. *2006*.

23. Ambulante besøg og indlæggelser for udvalgte kroniske sygdomme på somatiske hospitaler i Århus, Ringkjøbing, Viborg, og Nordjyllands amter. *2006*.

24. Ellen M Mikkelsen: Impact of genetic counseling for hereditary breast and ovarian cancer disposition on psychosocial outcomes and risk perception: A population-based follow-up study. PhD thesis. *2006*.

25. Forbruget af lægemidler mod kroniske sygdomme i Århus, Viborg og Nordjyllands amter 2004-2005. *2006*.

26. Tilbagelægning af kolostomi og ileostomi i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

27. Rune Erichsen: Time trend in incidence and prognosis of primary liver cancer and liver cancer of unknown origin in a Danish region, 1985-2004. Research year report. *2007*.

28. Vivian Langagergaard: Birth outcome in Danish women with breast cancer, cutaneous malignant melanoma, and Hodgkin's disease. PhD thesis. *2007*.

29. Cynthia de Luise: The relationship between chronic obstructive pulmonary disease, comorbidity and mortality following hip fracture. PhD thesis. *2007*.

30. Kirstine Kobberøe Søgaard: Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study. Research year report. *2007*.

31. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1995-2006. *2007*.

32. Mette Skytte Tetsche: Prognosis for ovarian cancer in Denmark 1980-2005: Studies of use of hospital discharge data to monitor and study prognosis and impact of comorbidity and venous thromboembolism on survival. PhD thesis. *2007*.

33. Estrid Muff Munk: Clinical epidemiological studies in patients with unexplained chest and/or epigastric pain. PhD thesis. *2007*.

34. Sygehuskontakter og lægemiddelforbrug for udvalgte kroniske sygdomme i Region Nordjylland. *2007*.

35. Vera Ehrenstein: Association of Apgar score and postterm delivery with neurologic morbidity: Cohort studies using data from Danish population registries. PhD thesis. *2007*.

36. Annette Østergaard Jensen: Chronic diseases and non-melanoma skin cancer. The impact on risk and prognosis. PhD thesis. *2008*.

37. Use of medical databases in clinical epidemiology. *2008*.

38. Majken Karoline Jensen: Genetic variation related to high-density lipoprotein metabolism and risk of coronary heart disease. PhD thesis. *2008*.

39. Blodprop i hjertet - forekomst og prognose. En undersøgelse af førstegangsindlæggelser i Region Nordjylland og Region Midtjylland. *2008*.

40. Asbestose og kræft i lungehinderne. Danmark 1977-2005. *2008*.

41. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1996-2007. *2008*.

    Sandra Kruchov Thygesen. Atrial fibrillation in patients with ischemic stroke: A population-based study. Research year report. *2008*.

42. Akutte indlæggelsesforløb og skadestuebesøg på hospiter i Region Midtjylland og Region Nordjylland 2003-2007. Et pilotprojekt. *Not published*.

43. Peter Jepsen: Prognosis for Danish patients with liver cirrhosis. PhD thesis. *2009*.

44. Lars Pedersen: Use of Danish health registries to study drug-induced birth defects – A review with special reference to methodological issues and maternal use of non-steroidal anti-inflammatory drugs and Loratadine. PhD thesis. *2009*.

45. Steffen Christensen: Prognosis of Danish patients in intensive care. Clinical epidemiological studies on the impact of preadmission cardiovascular drug use on mortality. PhD thesis. *2009*.

46. Morten Schmidt: Use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs and risk of cardiovascular events and death after intracoronary stenting. Research year report. *2009*.

47. Jette Bromman Kornum: Obesity, diabetes and hospitalization with pneumonia. PhD thesis. *2009*.

48. Theis Thilemann: Medication use and risk of revision after primary total hip arthroplasty. PhD thesis. *2009*.

49. Operativ fjernelse af galdeblæren. Region Midtjylland & Region Nordjylland. 1998-2008. *2009*.

50. Mette Søgaard: Diagnosis and prognosis of patients with community-acquired bacteremia. PhD thesis. *2009*.

51. Marianne Tang Severinsen. Risk factors for venous thromboembolism: Smoking, anthropometry and genetic susceptibility. PhD thesis. *2010*.

52. Henriette Thisted: Antidiabetic Treatments and ischemic cardiovascular disease in Denmark: Risk and outcome. PhD thesis. *2010*.

53. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme. Region Midtjylland og Region Nordjylland 1997-2008. *2010*.

54. Prognosen efter akut indlæggelse på Medicinsk Visitationsafsnit på Nørrebrogade, Århus Sygehus. *2010*.

55. Kaare Haurvig Palnum: Implementation of clinical guidelines regarding acute treatment and secondary medical prophylaxis among patients with acute stroke in Denmark. PhD thesis. *2010*.

56. Thomas Patrick Ahern: Estimating the impact of molecular profiles and prescription drugs on breast cancer outcomes. PhD thesis. *2010*.

57. Annette Ingeman: Medical complications in patients with stroke: Data validity, processes of care, and clinical outcome. PhD thesis. *2010*.

58. Knoglemetastaser og skeletrelaterede hændelser blandt patienter med prostatakræft i Danmark. Forekomst og prognose 1999-2007. *2010*.

59. Morten Olsen: Prognosis for Danish patients with congenital heart defects - Mortality, psychiatric morbidity, and educational achievement. PhD thesis. *2010*.

60. Knoglemetastaser og skeletrelaterede hændelser blandt kvinder med brystkræft i Danmark. Forekomst og prognose 1999-2007. *2010*.

61. Kort- og langtidsoverlevelse efter hospitalsbehandlet kræft. Region Midtjylland og Region Nordjylland 1998-2009. *2010*.

62. Anna Lei Lamberg: The use of new and existing data sources in non-melanoma skin cancer research. PhD thesis. *2011*.

63. Sigrún Alba Jóhannesdóttir: Mortality in cancer patients following a history of squamous cell skin cancer – A nationwide population-based cohort study. Research year report. *2011*.

64. Martin Majlund Mikkelsen: Risk prediction and prognosis following cardiac surgery: the EuroSCORE and new potential prognostic factors. PhD thesis. *2011*.

65. Gitte Vrelits Sørensen: Use of glucocorticoids and risk of breast cancer: a Danish population-based case-control study. Research year report. *2011*.

66. Anne-Mette Bay Bjørn: Use of corticosteroids in pregnancy. With special focus on the relation to congenital malformations in offspring and miscarriage. PhD thesis. *2012*.

67. Marie Louise Overgaard Svendsen: Early stroke care: studies on structure, process, and outcome. PhD thesis. *2012*.

68. Christian Fynbo Christiansen: Diabetes, preadmission morbidity, and intensive care: population-based Danish studies of prognosis. PhD thesis. *2012*.

69. Jennie Maria Christin Strid: Hospitalization rate and 30-day mortality of patients with status asthmaticus in Denmark – A 16-year nationwide population-based cohort study. Research year report. *2012*.

70. Alkoholisk leversygdom i Region Midtjylland og Region Nordjylland. 2007-2011. *2012*.

71. Lars Jakobsen: Treatment and prognosis after the implementation of primary percutaneous coronary intervention as the standard treatment for ST-elevation myocardial infarction. PhD thesis. *2012*.

72. Anna Maria Platon: The impact of chronic obstructive pulmonary disease on intensive care unit admission and 30-day mortality in patients undergoing colorectal cancer surgery: a Danish population-based cohort study. Research year report. *2012*.

73. Rune Erichsen: Prognosis after Colorectal Cancer - A review of the specific impact of comorbidity, interval cancer, and colonic stent treatment. PhD thesis. *2013*.

74. Anna Byrjalsen: Use of Corticosteroids during Pregnancy and in the Postnatal Period and Risk of Asthma in Offspring - A Nationwide Danish Cohort Study. Research year report. *2013*.

75. Kristina Laugesen: In utero exposure to antidepressant drugs and risk of attention deficit hyperactivity disorder (ADHD). Research year report. *2013*.

76. Malene Kærslund Hansen: Post-operative acute kidney injury and five-year risk of death, myocardial infarction, and stroke among elective cardiac surgical patients: A cohort study. Research year report. *2013*.

77. Astrid Blicher Schelde: Impact of comorbidity on the prediction of first-time myocardial infarction, stroke, or death from single-photon emission computed tomography myocardial perfusion imaging: A Danish cohort study. Research year report. *2013*.

78. Risiko for kræft blandt patienter med kronisk obstruktiv lungesygdom (KOL) i Danmark. (Online publication only). *2013*.

79. Kirurgisk fjernelse af milten og risikoen for efterfølgende infektioner, blodpropper og død. Danmark 1996-2005. (Online publication only). *2013*.

    Jens Georg Hansen: Akut rhinosinuitis (ARS) – diagnostik og behandling af voksne i almen praksis. *2013*.

80. Henrik Gammelager: Prognosis after acute kidney injury among intensive care patients. PhD thesis. *2014*.

81. Dennis Fristrup Simonsen: Patient-Related Risk Factors for Postoperative Pneumonia following Lung Cancer Surgery and Impact of Pneumonia on Survival. Research year report. *2014*.

82. Anne Ording: Breast cancer and comorbidity: Risk and prognosis. PhD thesis. *2014*.

83. Kristoffer Koch: Socioeconomic Status and Bacteremia: Risk, Prognosis, and Treatment. PhD thesis. *2014*.

84. Anne Fia Grann: Melanoma: the impact of comorbidities and postdiagnostic treatments on prognosis. PhD thesis. *2014*.

85. Michael Dalager-Pedersen: Prognosis of adults admitted to medical departments with community-acquired bacteremia. PhD thesis. *2014*.

86. Henrik Solli: Venous thromboembolism: risk factors and risk of subsequent arterial thromboembolic events. Research year report. *2014*.

87. Eva Bjerre Ostenfeld: Glucocorticoid use and colorectal cancer: risk and postoperative outcomes. PhD thesis. *2014*.

88. Tobias Pilgaard Ottosen: Trends in intracerebral haemorrhage epidemiology in Denmark between 2004 and 2012: Incidence, risk-profile and case-fatality. Research year report. *2014*.

89. Lene Rahr-Wagner: Validation and outcome studies from the Danish Knee Ligament Reconstruction Registry. A study in operatively treated anterior cruciate ligament injuries. PhD thesis. *2014*.

90. Marie Dam Lauridsen: Impact of dialysis-requiring acute kidney injury on 5-year mortality after myocardial infarction-related cardiogenic shock - A population-based nationwide cohort study. Research year report. *2014*.

91. Ane Birgitte Telén Andersen: Parental gastrointestinal diseases and risk of asthma in the offspring. A review of the specific impact of acid-suppressive drugs, inflammatory bowel disease, and celiac disease. PhD thesis. *2014*.

    Mikkel S. Andersen: Danish Criteria-based Emergency Medical Dispatch – Ensuring 112 callers the right help in due time? PhD thesis. *2014*.

92. Jonathan Montomoli: Short-term prognosis after colorectal surgery: The impact of liver disease and serum albumin. PhD thesis. *2014*.

93. Morten Schmidt: Cardiovascular risks associated with non-aspirin non-steroidal anti-inflammatory drug use: Pharmacoepidemiological studies. PhD thesis. *2014*.

94. Betina Vest Hansen: Acute admission to internal medicine departments in Denmark - studies on admission rate, diagnosis, and prognosis. PhD thesis. *2015*.

95. Jacob Gamst: Atrial Fibrillation: Risk and Prognosis in Critical Illness. PhD thesis. *2015*.

96. Søren Viborg: Lower gastrointestinal bleeding and risk of gastrointestinal cancer. Research year report. *2015*.

97. Heidi Theresa Ørum Cueto: Folic acid supplement use in Danish pregnancy planners: The impact on the menstrual cycle and fecundability. PhD thesis. *2015*.

98. Niwar Faisal Mohamad: Improving logistics for acute ischaemic stroke treatment: Reducing system delay before revascularisation therapy by reorganisation of the prehospital visitation and centralization of stroke care. Research year report. *2015*.

99. Malene Schou Nielsson: Elderly patients, bacteremia, and intensive care: Risk and prognosis. PhD thesis. *2015*.

100. Jens Tilma: Treatment Injuries in Danish Public Hospitals 2006-2012. Research year report. *2015*.

101. Thomas Lyngaa: Intensive care at the end-of-life in patients dying of cancer and non-cancer chronic diseases: A nationwide study. Research year report. *2015*.

102. Lone Winther Lietzen: Markers of immune competence and the clinical course of breast cancer. PhD thesis. *2015*.

103. Anne Høy Seemann Vestergaard: Geographical Variation in Use of Intensive Care in Denmark: A Nationwide Study. Research year report. *2015*.

104. Cathrine Wildenschild Nielsen: Fecundability among Danish pregnancy planners. Studies on birth weight, gestational age and history of miscarriage. PhD thesis. *2015*.

105. Kathrine Dyhr Lycke: Preadmission use of antidepressants and quality of care, intensive care admission and mortality of colorectal cancer surgery – a nationwide population-based cohort study. Research year report. *2015*.

106. Louise Bill: Hyponatremia in acute internal medicine patients: prevalence and prognosis. PhD thesis. *2015*.

107. Kirstine Kobberøe Søgaard: Risk and prognosis of venous thromboembolism in patients with liver disease. PhD thesis. *2015*.

108. Rikke Nørgaard Pedersen: Reoperation due to surgical bleeding in breast cancer patients and breast cancer recurrence: A Danish population-based cohort study. Research year report. *2015*.

109. Thomas Deleuran: Cirrhosis of the liver and diseases of the large joints. PhD Thesis. *2016*.

110. Anne Mette Falstie-Jensen: Hospital accreditation – what's in it for the patients? PhD thesis. *2016*.

111. Sandra Kruchov Thygesen: Respiratory distress syndrome in moderately late and late preterm infants and selected long-term neurodevelopmental outcomes. PhD thesis. *2016*.

112. Alma Bečić Pedersen: Total hip replacement surgery - occurrence and prognosis. Doctoral dissertation. *2016*.

113. Anil Mor: Type 2 Diabetes and Risk of Infections. PhD thesis. *2016*.

114. Aske Hess Rosenquist: Behavioral Development Following Early Life Organochlorine Exposure. Research year report. *2016*.

115. Simon Ramsdal Sørensen: Anti-platelet and Anti-coagulant Prescriptions and Breast Cancer Recurrence: a Danish Nationwide Prospective Cohort Study. Research year report. *2016*.

116. Regional Differences in Treatment of Patients with Inflammatory Bowel Disease in Denmark

117. Clara Reece Medici: Impact of preadmission anti-inflammatory drug use on risk of depression and anxiety after intensive care requiring mechanical ventilation. Research year report. *2016*.

118. Johan Frederik Håkonsen Arendt. Clinical implications and biochemical understanding of high plasma vitamin B12 levels. PhD thesis. *2016*.
119. Manual for using the LABKA database for research projects. *2016*.

120. Søren Christiansen: Timing of renal replacement therapy and long-term risk of chronic kidney disease and death in intensive care patients with acute kidney injury. Research year report. *2017*.

121. Ellen Hollands Steffensen: Preadmission antidepressant use and bladder cancer: a population-based cohort study of stage at diagnosis, time to surgery, and surgical outcomes. Research year report. *2017*.

122. Sara Søndergaard Schwartz: Incidence and mortality of pulmonary hypertension in adults with congenital heart disease. Research year report. *2017*.

123. Jesper Smit: Community-acquired Staphylococcus aureus bacteremia: Studies of risk and prognosis with special attention to diabetes mellitus and chronic heart failure. PhD thesis. *2017*.

124. Carina Nørskov Bagge: Risk of Dementia in Adults with Congenital Heart Disease: A Nationwide Population-Based Cohort Study. Research year report. *2017*.

125. Pia Kjær Kristensen: Hip fracture in Denmark: Quality of in-hospital care and clinical outcomes. PhD thesis. *2017*.

126. Anne Nakano Jensen: Incident heart failure in Denmark: Studies on a nationwide quality improvement initiative. PhD thesis. *2017*.