Prevalence and treatment of patients with heart failure with special emphasis on diuretics

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'Heavy hearts, like heavy clouds in the sky, are best relieved by the letting of a little water'
Christopher Morley

To my family

ABSTRACT

Background: Heart failure (HF) is a major health problem worldwide with an estimated prevalence of about 1-2% in the Western world. The temporal trend for prevalence of HF has never been investigated in a nationwide population. In patients with HF diuretic treatment is recommended for relief of congestive symptoms. Over 80% of all patients with HF are estimated to be treated with diuretics. However, information about the temporal trend for diuretic treatment in a nationwide population is lacking and the prognostic effect of diuretic treatment in patients with HF has never been studied in a randomized clinical trial. Diuretics have been associated with increased mortality in selected populations with HF but the association of diuretics with mortality in unselected Western world patients discharged from a hospitalization for HF or in unselected outpatients with HF has not been studied.

Aim: The aims of this thesis was to study trends for prevalence of patients hospitalized with HF 1990-2007, trends for diuretic treatment in patients hospitalized for HF 2004-2011, the association of diuretic treatment at hospital discharge from a hospitalization for HF with short- and long-term mortality, and to evaluate diuretic treatment as a prognostic predictor for long-term mortality in outpatients with HF.

Methods and results: Data from several different Swedish registries were linked in these studies. Patients hospitalized with a primary or secondary diagnosis of HF aged 19-99 years 1990-2007 were included in Paper I. An increase in age-adjusted prevalence of HF until 1995 and a decrease from 2002 to 2007 was observed. Prevalence of HF in people aged less than 55 years increased throughout the observational period. In absolute numbers, patients with HF older than 85 years increased by 77% from 1990 to 2007 (Paper I). Patients with a first-time hospitalization for HF that survived for 18 months or more after discharge were included in Paper II. Post-discharge diuretic treatment and doses decreased 2005-2014 and coincided with increased neuro-hormonal antagonist treatment rates (Paper II). Patients recorded in the Swedish HF registry 2004-2011 with known diuretic treatment status were included in Paper III and IV. Diuretic treatment at hospital discharge had a neutral association with short-term mortality but was associated with increased long-term mortality (Paper III). Diuretic treatment in unselected outpatients with HF was independently associated with increased long-term mortality but did not improve a previously known model for prediction of 3-year mortality (Paper IV).

Conclusions: The prevalence of HF decreased 2002-2007 but may increase in the future due to increased prevalence in young persons and the demographic transition. If the observed trend for decreased post-discharge diuretic treatment rates and doses in patients with HF 2005-2014 was related to the observed coinciding increase of treatment with neuro-hormonal antagonists was not answered by this study. If the observed associations of diuretic treatment with increased long-term mortality in real-life patients with HF was related to a direct prognostic effect of diuretic treatment or to diuretic treatment as a marker for HF disease severity remains unknown.

Keywords: heart failure, epidemiology, pharmaco-epidemiology, diuretics, mortality

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LIST OF PAPERS

This thesis is based on the following papers.

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II Parén P, Rosengren A, Zverkova Sandström T, Schaufelberger M. Temporal trends in loop diuretic treatment and neurohormonal antagonists after hospitalization for heart failure in Sweden from 2005-2014.
Submitted

III Parén P, Dahlström U, Edner M, Lappas G, Rosengren A, Schaufelberger M. Association of diuretic treatment at hospital discharge in patients with heart failure with all-cause short- and long-term mortality: A propensity score-matched analysis from SwedeHF.
Submitted

IV Parén P, Rosengren A, Dahlström U, Edner M, Lappas G, Schaufelberger M. Diuretic treatment as a prognostic predictor for long-term mortality in 17,518 real-life outpatients with heart failure after adjustment for MAGGIC mortality predictors.
Submitted

CONTENTS

ABBREVIATIONS

ACCF/AHA	American College of Cardiology Foundation/American Heart Association
ADHF	acute decompensated heart failure
AHF	acute heart failure
ARB	angiotensin receptor blockers
ARNI	angiotensin receptor neprilysin inhibitor
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
CDR	Cause of Death Register
CHF	chronic heart failure
DDD	Defined Daily Dose
DIG	Digitalis Investigation Group
EAPC	estimated annual percentual change
ESC	The European Society of Cardiology
FHS	Framingham Heart Study
HF	heart failure
HHF	hospitalization for HF
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 Diseases
IPR	Swedish National Inpatient Register
MAGGIC	Meta-Analysis Global Group in Chronic Heart Failure
MRA	mineralocorticoid receptor antagonist
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
PCWP	pulmonary capillary wedge pressure
PIN	personal identity number
PRA	plasma renin activity
PS	propensity score
RAAS	renin angiotensin aldosterone system
RAS	renin angiotensin system
RCT	randomized clinical trial
ROC	receiver operating characteristic
SPDR	The Swedish Prescribed Drug Register
SwedeHF	The Swedish Heart Failure Registry
WHO	World Health Organisation

INTRODUCTION

The definition of heart failure

Several definitions of heart failure (HF) have been suggested. One of the most frequently used was presented by Eugen Braunwald in 1967, 'a clinical syndrome characterized by well-known symptoms and physical signs. . . . [It is] the pathological state in which an abnormality of myocardial function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues during ordinary activity' (1). A developed and modernized version was suggested by Milton Packer in 1988, 'HF represents a clinical syndrome characterized by abnormalities of left ventricular function and neuro-hormonal regulation which are accompanied by effort intolerance, fluid retention and reduced longevity'.

Causes and comorbidities in patients with heart failure

There are many different causes of HF, e.g. ischaemic heart disease, hypertension, diabetes mellitus, infectious diseases, valvular diseases, tachyarrhythmia, abuse of alcohol or drugs, chemotherapy, and 'idiopathic' dilated cardiomyopathy (where about 25% have a genetic basis) (2). The causes of HF vary in importance in different parts of the world. In the individual patient with HF, the exact cause or causes of HF, and the distinction between cause and comorbidity, may be difficult to establish. Examples of frequently occurring comorbidities in patients with HF are ischemic heart disease, hypertension, diabetes mellitus, atrial fibrillation and chronic kidney dysfunction (3).

The pathophysiology of decompensated heart failure

The pulmonary and peripheral oedema seen in HF is the result of multiple physiologic disturbances. Decreased cardiac output leads to a relative renal hypoperfusion that stimulates neuro-hormonal activation of the renin angiotensin aldosterone axis. This activation results in increased activity of the renal sympathetic nerve, increased activity of the renin angiotensin aldosterone system, and increased secretion of vasopressin. Increased secretion of vasopressin contributes to venous congestion through aquaporin mediated retention of water (4). Retention of free water and sodium results in increased volume and pressure in capacitance vessels. Hydrostatic pressure elevation leads to fluid extravasation into peripheral tissues and lungs. In acute decompensated HF (ADHF), the heart is not able to effectively increase stroke volume when exposed to elevated filling pressures. Acute elevation of left ventricular preload (end-diastolic) pressure directly leads to elevated left atrial pressure, elevated pulmonary capillary wedge pressure (PCWP) and eventually pulmonary oedema (5). Fluid retention and congestion are estimated to be present in 95% of patients with acute HF (AHF) (2). Clinical signs and symptoms of congestion are the most common findings in patients at admission to hospital for ADHF (6). However, sub-clinical signs of congestion have been observed in patients with HF both before and after an episode of clinical decompensation. Increased intrathoracic fluid documented by intrathoracic impedance monitoring has been observed as early as 18 days before hospitalization for HF (7).

Increased weight (8) and elevated PCWP (9) have been observed several days before clinical pulmonary oedema and hospitalization for HF. Residual sub-clinical congestion documented by pulmonary ultrasound has been observed in patients at discharge from a HF hospitalization (10) and clinically unrecognized hypervolemia has been observed in non-oedematous patients with chronic HF (CHF) (11).

In addition, congestion has been found to be the most important hemodynamic factor driving the worsening renal function (WRF) observed in patients with HF (12). HF and WRF constitute the cardio-renal syndrome. The cardio-renal syndrome was defined by the National Heart, Lung, and Blood Institute in 2004 as a condition in which therapy to relieve congestive symptoms of HF is limited by a decline in renal function as manifested by a reduction in glomerular filtration rate.

The diagnosis of heart failure

Diagnoses in medical records are registered with classification codes. The World Health Organisation (WHO) Nomenclature Regulations, adopted in 1967, stipulated that Member States should use the most current International Classification of Diseases (ICD) revision for mortality and morbidity statistics. Since 1967, the ICD has been continuously revised and published in a series of editions to reflect advances in health and medical science over time. The current version, ICD-10, was endorsed in May 1990.

Signs and symptoms seen in HF may resemble signs and symptoms seen in other diseases. These signs and symptoms can be hard to identify and distinguish in obese persons, in the elderly, and in patients with chronic pulmonary disease. Several sets of diagnostic criteria for HF, based on a combination of clinical signs, symptoms, and examination findings have been proposed. In the era when non-invasive techniques for assessing systolic and diastolic dysfunction were not yet widely available, the Framingham (13), Duke (14), Boston (15) and Gothenburg (16) criteria were proposed in 1971, 1977, 1985, and 1987, respectively. Of these, the Boston criteria have the highest combined sensitivity (50%) and specificity (78%) for HF (17, 18). The European Society of Cardiology (ESC) proposed their first diagnostic criteria for HF in 1995 (19). Since then the ESC criteria for HF have been gradually updated. The latest algorithm, based on clinical findings, measurement of N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and results from echocardiographic examination was presented in 2016 (2).

Classification of heart failure related to time course

HF may be subdivided into AHF or CHF. AHF can be either “new-onset” HF or decompensated CHF. Patients who have had HF for some time are said to have CHF (2). The term ‘hospitalization for HF’ (HHF) has been proposed for patients with HF considered in need of hospitalization (20). HHF comprises patients with: 1) worsening CHF (~80%); 2) de novo HF (15%); and 3) advanced or end-stage HF (5%). AHF, CHF and HHF are stages of the HF syndrome. There are no separate classification codes that differentiate between AHF, CHF and HHF in the ICD coding system.

Classification of heart failure related to ejection fraction

The present main terminology used to further categorize HF is based on the measurement of left ventricular ejection fraction (EF). Mathematically, EF is the stroke volume (the end-diastolic volume minus the end-systolic volume) divided by the end-diastolic volume. HF comprises a wide range of patients, from those with normal LVEF (≥50%), described as HF with preserved EF (HFpEF), to those with reduced LVEF (<40%), described as HF with reduced EF (HFrEF), in current guidelines (2, 21). Differences between HFrEF and HFpEF have been observed on both macroscopic and cellular levels (22). Compared to patients with HFrEF, a larger proportion of patients with HFpEF are older, women and with a history of hypertension or atrial fibrillation, while a history of myocardial infarction is less common (23, 24). A majority of patients with HFrEF are estimated to die from cardiovascular causes, e.g. progressive HF, arrhythmias and ischaemic events whereas a majority of patients with HFpEF are estimated to die from non-cardiovascular causes (25). However, diastolic dysfunction may be difficult to assess and the proportion of patients with HF that have been classified with preserved EF have ranged from 22% to 73% in different studies (2).

Patients with EF in the range of ≥40–49% represent a 'grey area', or 'mid-range', defined as HF with mid-range EF (HFmrEF) in the latest update of ESC guidelines (2) and as 'HFpEF, borderline', in the latest update of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines (21). EF in patients with HFrEF may improve with time, usually as an effect of treatment. The term 'HFpEF, improved', has been suggested in the latest ACCF/AHA guidelines for patients with a current EF≥40% and a previous EF<40%. The phenotype of HFmrEF has been found to resemble HFrEF more than HFpEF (24). Long-term mortality rates have been reported to be somewhat higher in HFrEF than in HFpEF (26). A recent analysis from the European HF registry has reported highest one-year mortality rates in HFrEF, intermediate in HFmrEF and lowest in HFpEF (24). There are no separate classification codes that differentiate between HFrEF, HFmrEF and HFpEF in the ICD coding system.

Classification of heart failure related to symptomatology

The terminology most frequently used to describe symptomatic severity in patients with HF is the New York Heart Association (NYHA) classification that was introduced in 1964. Patients in NYHA class I, II, III, and IV are said to have no, mild, moderate or severe symptoms, respectively. NYHA classification is dynamic and may change with time and clinical course.

Treatment in acute heart failure

The first-line recommended treatment in international guidelines for patients with ADHF is diuretics (2, 21). If the diuretic response is inadequate despite a combination of different diuretics, ultrafiltration (27) for congestive relief may be considered. In patients with AHF and respiratory distress, non-invasive positive pressure ventilation should be considered. Furthermore, intravenous vasodilators should be considered as

the initial treatment in hypertensive AHF and, if symptomatic hypotension is absent, as an adjuvant to diuretic therapy for relief of dyspnoea. In patients with AHF and inadequate peripheral perfusion fluid challenge, inotropes and mechanical circulatory support may be considered.

Treatment with tolvaptan, a vasopressin V_2 receptor antagonist (28), rolofylline, an adenosine receptor blocker (29), nesiritide, a synthetic natriuretic peptide (30), ularitide, a vasodilator (31), and serelaxin, recombinant human relaxin-2, (https://www.escardio.org/The-ESC/Press-Office/Press-releases/serelaxin-fails-to-meet-primary-endpoints-in-phase-3-relax-ahf-2-trial) in patients with AHF has been evaluated in large randomize clinical trials (RCTs) without any signs of prognostic benefits (30). Results from studies on inotropes have led to debate and concerns that they may increase mortality in patients with AHF (32).

Neuro-hormonal blocking treatment in chronic HFrEF

Treatment in chronic HFreF with prognostic benefits proven in RCTs is available. The era of neuro-hormonal blocking treatment in chronic HFrEF is modern and began in the 1980s when it was established that inhibition of the renin angiotensin system (RAS) with the angiotensin-converting–enzyme (ACE) inhibitor enalapril reduced overall mortality in HF (33, 34). In addition, it was shown that enalapril was superior to vasodilating treatment with the combination of hydralazine and isosorbide dinitrate (35). The 1990s was a successful decade when new treatments for chronic HFrEF with prognostic benefits were discovered. It was shown that the benefits of enalapril in reducing hospitalizations for HF also applied to asymptomatic patients (36).

The use of beta-blocker therapy, nowadays considered as a cornerstone of HF treatment, once was contraindicated in HF because of the negative inotropic and chronotropic effects that were thought to affect patients with systolic dysfunction in a negative way. However, evidence of a mortality benefit emerged for three beta-blockers, bisoprolol (37), carvedilol (38), and sustained-release metoprolol (39). Spironolactone, a mineralocorticoid-receptor antagonist (MRA), was proven to reduce mortality in patients with severe symptoms already receiving an ACE-inhibitor and a loop diuretic but where only 10% of the included patients were treated with a beta-blocker (40). Treatment with angiotensin receptor blocker (ARB) therapy for HF was introduced in the beginning of the 21st century (41), but because treatment with ARBs is not superior to treatment with ACE inhibitors, ARBs have generally been reserved for patients who cannot tolerate ACE inhibitors because of cough or angiooedema. In 2011, it was demonstrated that treatment with the MRA eplerenone decreased mortality in patients with mild symptoms (42). In 2014, ARB and neprilysin inhibition with a combination of sacubitril and valsartan was shown to reduce cardiovascular and all-cause mortality on top of standard of care, as compared to enalapril (43).

Other treatment with prognostic benefit in chronic HFrEF

In the 1980s, vasodilating treatment with hydralazine plus isosorbide dinitrate, as compared to either placebo or prazosin, was shown to reduce mortality (44). In 1997, the it was demonstrated that treatment with digoxin when compared to placebo did

not reduce overall mortality, but reduced the rate of hospitalization, both overall and for worsening heart failure in patients with left ventricular systolic dysfunction (45). However, the role of digoxin in the contemporary treatment of HF has been debated. In the beginning of the 21st century it was shown that cardiac resynchronization therapy (46) and implantable cardioverter-defibrillators (47) decreased mortality in selected patients with HFrEF. In addition, cardiac resynchronization therapy has been proven to reduce the risk for hospitalization for HF in selected patients with HFrEF and mild symptoms (48). In 2010, it was shown that treatment with the sinus node inhibitor ivabradine reduced the composite endpoint of cardiovascular death or hospital admission for worsening heart failure in selected patients with HFrEF (49).

Treatment in chronic HFpEF

Guidelines recommend symptomatic treatment in patients with HFpEF. Treatment with beta-blocker (50), ARB (51) and MRA (52) in patients with HFpEF have been evaluated in large randomized clinical trials but without any signs of prognostic benefits.

Salt and water reduction in heart failure

The latest ESC recommendations for self-care management of HF consider the evidence for the optimal fluid management in the patient with HF limited (53). However, it is recommended that salt and water reduction may be considered in patients with severe symptoms.

The history of diuretic treatment in heart failure

In the 18th century it was observed that the diuretic action of digitalis was increased when digitalis was combined with calomel, a mercury chloride mineral. Almost a hundred year later the diuretic effect of calomel alone was shown when the administration of repeated small doses of calomel per os resulted in diuresis in patients with oedema (54). The majority of observers at that time favoured the view that calomel acted directly on the kidney. However, warnings were expressed that treatment with calomel was associated with renal damage (55). Novasurol, an organic compound containing mercury, was introduced as an anti-syphilitic drug in the beginning of the 20th century. The first studies of Novasurol as a diuretic (56) and for the relief of oedema in patients with HF (57) were performed soon thereafter. However, mercurial diuretics were difficult to use and found to have toxic effects. In 1937, the diuretic effect of sulphonamides was investigated and one year later oral therapy with sulphonamides became available (58). In 1953, Diamox, a carbonic hydrase inhibitor, was introduced as an oral diuretic in patients with HF (59). A few years later, thiazides and thiazide-like diuretics were introduced (60) and observed to reduce oedema in patients with HF (61). In the 1960s, furosemide, a loop diuretic, was synthesized. The diuretic effect of furosemide was found to be superior to thiazides in patients with oedema and even more effective in patients with oedema due to heart disease (62). Since then, loop diuretics has been the first line treatment for congestive relief in patients with HF. Currently, the loop diuretics furosemide, bumetanide, and torasemide are available for prescription. It has been shown that torasemide has a better decongestive effect

than furosemide and there have been indications that torasemide also has prognostic advantages when compared to furosemide (63). Nevertheless, furosemide is still the most frequently used loop diuretic in real life clinical practice. Diuretic treatment is recommended in international guidelines for relief of congestive symptoms in patients with HF, both in HFrEF and HFpEF. In addition, dose reduction or discontinuation, if clinically feasible, is recommended (2, 21).

Table 1. The history of diuretic treatment

Year	
1799	Increased diuretic action of digitalis when given in combination with calomel (mercury) was observed
1886	Diuretic effects of calomel (mercury) alone was observed
1920	Diuretic effects of Novasurol (mercury) was observed
1925	Novasurol (mercury) was used for relief of oedema in HF
1937	Diuretic effects of sulphonamides was observed
1938	The first oral sulphonamide was introduced
1953	Carbonic anhydrase inhibitors were introduced as oral diuretics in HF
1958	Thiazides and thiazide-like diuretics were introduced
1960s	The loop diuretic furosemide was synthesized and introduced for treatment of oedema in HF

Pharmacodynamics of loop diuretic treatment

Loop diuretics inhibit chloride resorption in the ascending limb of Henle's loop in the kidney. This results in increased secretion of chloride coinciding with increased secretion of sodium, calcium, magnesium, and potassium. The resulting diuresis is accompanied by a weak reduction in blood pressure. Due to variations in bioavailability after oral administration of furosemide, intravenous administration of furosemide is preferred in patients with ADHF. The threshold dose for obtaining diuretic effect after administration of furosemide is higher in patients with impaired renal function when compared to persons with normal renal function (64) and the ceiling dose is lower in patients with HF when compared to persons with chronic kidney disease (65). The diuretic effect of furosemide begins 10-30 minutes after intravenous administration and 1-1.5 hours after oral administration. In addition, loop diuretics induce synthesis of prostaglandins, resulting in renal and peripheral vascular smooth muscle relaxation and venous dilatation. Decrease in the dose-response diuretic effect for the given dose of loop diuretics over time is called diuretic resistance (66). Diuretic resistance is thought to be related to increased reabsorption of sodium and water in the distal tubules. It can to some extent be counteracted if loop diuretics are combined with thiazides.

Effects of diuretic treatment in patients with heart failure

In a study of patients with severe HF, it was shown that in the first 20 minutes after intravenous administration a fall in stroke volume index and increases in left ventricu-

lar filling pressure, heart rate, mean arterial pressure, systemic vascular resistance, plasma renin activity, plasma norepinephrine level, and plasma arginine vasopressin level occured (67). Later effects in that study were diuresis, reduction of the intravascular volume, decreased central venous pressure, decreased right and left heart filling pressures, and decreased pulmonary vascular pressures. A recent observational study showed that early when compared to late administration of furosemide after admission to hospital was associated with decreased mortality in patients with ADHF (68). When diuretic bolus doses were compared to continuous infusion and high doses of diuretics were compared to low doses in the randomized DOSE trial no differences between these strategies were observed in the primary endpoints of patients' global assessment of symptoms and changes in renal function (6).

Despite the reported high diuretic treatment rates in patients hospitalized for HF (69) many patients are discharged from a hospitalization for HF with residual congestion (10, 70). Residual clinical congestion at discharge from a hospitalization for HF has been associated with an increase in the composite endpoint of 60-day mortality, hospitalization and emergency department visits (70). Residual congestion measured with pulmonary ultrasound at hospital discharge has been associated with an increase in the composite endpoint of 3-month all-cause death or HF hospitalization (10). In addition, higher BNP when compared to lower BNP at discharge from a hospitalization for HF has been associated with increased long-term mortality (71). Diuretic treatment when compared to no diuretic treatment at hospital discharge has been associated with increased long-term mortality in a study from the Japanese HF registry (72). However, differences in comorbidities and prognosis between Japanese and Western world patients with HF have been observed, why generalization may be difficult to make (73).

Clinical side effects e.g. fatigue, decreased exercise capacity, and hypotension may occur in patients with CHF treated with diuretics (74). In addition, diuretic treatment has been associated with increased activity of the RAS system (75), WRF (76), hypokalaemia (77), and hypomagnesaemia (78) in patients with CHF. These conditions have directly, or indirectly, been associated with increased mortality in patients with CHF. Diuretic treatment has been associated with increased long-term mortality in selected outpatients with HF in a secondary analysis from the Digitalis Investigation group (DIG) study (79).

Temporal trends for treatment in patients with chronic heart failure

Trends for increased beta-blocker, RAS inhibitor and MRA treatmnet rates have been observed in selected cohorts with CHF (80-85) coinciding in time with the gradual introduction of these drugs in guideline recommendations. Contemporary treatment patterns for beta-blockers, RAS inhibitors and MRAs in patients with HF have been considered in adherence to guideline recommendations (69). In contrast, adherence to guideline recommendations on device treatment has been considered low, at least in Sweden (85). However, beta-blockers and RAS inhibitors may still be underused in women when compared to men and in older when compared to younger persons (86, 87).

In theory, successful treatment with neuro-hormonal antagonists may decrease the degree of fluid retention (88) and, consequently, decrease the need for diuretic treatment in patients with CHF. Nevertheless, diuretic treatment rates observed in selected cohorts with CHF have decreased only slightly last decades (80-85).

Observational research

In observational studies, results are obtained either retrospectively or prospectively from a population that is not under the control of the investigator. Incidence is a measure of the probability of occurrence of a given medical condition in a population within a specified period of time. Prevalence is the number of people estimated to have a defined condition divided by the total number of people studied. Mortality is a measure of the number of deaths (all-cause, or due to a specific cause) in a particular population, per unit of time. Incidence, prevalence, and mortality are usually expressed as fractions, percentages or the number of cases per 10,000 or 100,000 people. The prevalence of a chronic disease depends on the incidence of the disease and all-cause mortality. Temporal trends for prevalence of a chronic disease depend on trends for risk factors, incidence, treatment, mortality, and demography (the composition of a population). In the ideal epidemiological investigation, a representative cohort, where results may be generalized to other populations, is studied. However, there may be selection bias involved in observational research, mainly due to practical reasons, why the characteristics of the included cohort are important for interpretation of results.

The epidemiology of heart failure

HF is a major health problem worldwide with an estimated prevalence of about 1-2% in the Western world based on studies of selected cohorts with geographical or age-realted limitations (2, 89, 90). Studies of prevalence of HF are important due to the high mortality (89) and morbidity (91) observed in patients with HF and, in addition, because of high economic costs related to HF care (92). Both incidence of HF and mortality in HF decreased in the 1990s (93). The prevalence of HF has been reported to be higher in older persons when compared to younger persons (89, 90). It has been observed that women have been older when diagnosed with HF, have survived longer after onset of HF, and more often have been classified with HFpEF when compared to men (94). Warnings of a HF 'epidemic' have been expressed (95), not at least due to the demographic transition in Western societies.

Swedish registries

Sweden has a long history of registry holding. Swedish church congregations registered births, marriages and deaths in church books from the beginning of the 17th century. Records from the 18th century are almost complete. In parallel there were census lengths kept by the Swedish tax agency. The first tax census was performed in 1571 and yearly tax registration of citizens that were considered taxable has been performed since 1652. From 1946 tax registration was based on church records until 30 June 1991 when tax and church registries were merged and the responsibility of the Swedish Population Registry was transferred to the Swedish Tax Agency. From 1947 all persons that have resided in Sweden have been assigned an individual personal

identity number (PIN) that is used in all official registries (96). Until year 2000, PINs were sometimes assigned to individuals who had not been registered in the Swedish Population Registry. From 2001, individuals that do not qualify for a PIN receive a personal coordination number.

The Swedish Hospital Discharge Register (also called the Swedish National Inpatient Register (IPR)) contains individual data for all inpatient hospital discharges in Sweden since 1987. This data include primary diagnosis, up to five secondary diagnoses, admission dates, and discharge dates. The IPR has been in operation since the 1960s and on a nationwide basis since 1987. From 1984 to 1986, data was available from 19 of 24 Swedish counties, comprising about 85% of the Swedish population. In recent years, more than 99% of hospital stays are registered in IPR, and the overall validity of a diagnosis in IPR is 85–95% (97). The validity of an ICD diagnosis of HF in the first position in IPR against the ESC criteria for HF is 95%, irrespectively of clinic (98). The validity for an ICD diagnosis of HF in any position at an internal medicine or cardiology clinic against the ESC criteria for HF is 86% and 91%, respectively. In contrast, the validity of a HF diagnosis in Swedish primary health care records against the ESC criteria for HF is 30% (99).

The Swedish Heart Failure Registry (SwedeHF) is a nationwide registry with approximately 80 variables on aetiology, diagnostic evaluation, treatment and follow-up (100). SwedeHF was created as a pilot in 2000 and introduced throughout Sweden in 2003. Inclusion criteria are clinician-judged HF. Patients are registered either at hospital discharge or in outpatient clinics. Establishment of the registry, and registration and analysis of the data are approved by a multisite ethics committee. Individual patient consent is not required or obtained.

The Swedish Prescribed Drug Register (SPDR) holds records of all dispensed drugs in Sweden since 1999, and since July 2005 with PIN (101). For drug dispensations, the registration is complete (although demographic data are missing in 0.02–0.6% of cases).

The Swedish Cause of Death Register (CDR) has been in operation since 1961. Until 2011, all deceased persons who by the time of death were registered in Sweden, irrespectively if death occurred in Sweden or abroad, were included in CDR. From 2012, all persons that die in Sweden, irrespectively if they were registered in Sweden or not have been included in CDR.

Missing data

There is a risk of missing data in observational databases. Missing data can introduce a substantial amount of bias (102). The process of replacing missing data with substituted values is called imputation. The method of 'Multiple Imputation' was developed in 1987. The imputed values are drawn *m* times from a distribution rather than just once. At the end of this step, there should be *m* completed datasets. Each of the *m* datasets is analysed. At the end of this step there should be *m* analyses. The *m* results are consolidated into one result by calculating the mean, variance, and confidence interval of the variable of concern.

Estimations of survival and risk in observational research

To study the effects of given treatments the golden standard is considered to be RCTs. However, there may be limitations with RCTs related to selection bias, ethics, or practical reasons. In these cases, observational research may be used. Selection bias in observational research may influence the outcome (103) and associations reported in observational research do not prove that there are causal relationships.

In 1958 the Kaplan–Meier estimation was presented. In medical research, it is often used to measure the fraction of patients living for a certain time after treatment. An advantage of the Kaplan–Meier curve is that this method can take into account some types of censored data, particularly right-censoring, which occurs if a patient withdraws from a study, is lost to follow-up, or is alive without event occurrence at last follow-up. However, the Kaplan-Meier method is limited in its ability to estimate survival adjusted for covariates.

For comparison of observed risks in two different groups, the proportional hazard model was proposed in 1972. The proportional hazard model (Cox regression) evaluates the effect of covariates independently of the underlying baseline hazard function and reports these effects as a hazard ratio (HR) for a specified outcome, 0 or 1. The HR associated with a categorical variable compares the risk in patients with and without the variable and the HR of a continuous variable is the proportional scaling of the hazard related to an increase of one unit of the variable.

However, confounding factors may influence the results in risk estimations. A confounder is a variable that influences both the dependent variable and independent variable causing a false association. Different methods how to adjust for confounding factors have been proposed. In a multi-variate Cox regression model, risk after adjustment for confounding factors may be estimated. In 1983, another method how to adjust for potential selection bias, confounding, and differences between treatment groups in observational studies using logistic regression called ‘Propensity Score’ was proposed. The propensity score (PS) confers the propensity from 0 to 1 to receive a specific treatment in a specific cohort based on a set of known baseline variables. Treated and untreated patients with the closest PS can be matched. A small accepted difference in PS between treated and untreated patients in a PS matched cohort increase similarities in baseline variables between treated and untreated patients but to the cost of more patients being excluded from the original cohort. The standarized difference is the difference between the means for treated and untreated patients divided by mutual standard deviation. For comparison of descriptive data between the original and matched cohorts, standardized differences in both cohorts may be calculated. Quantifications of the effects of hypothetical unmeasured confounders necessary to change the results of an estimation of relative risk may be performed (104).

Potential confounders in estimations of mortality risk in chronic heart failure

Several clinically usable risk models or scores have evaluated risk predictors for long-time mortality in patients with CHF. Potential confounders in estimations of associa-

tions between diuretic treatment and long-term mortality in patients with CHF may be selected from these models. The Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) score is based on a meta-analysis of individual data on 39,372 patients with CHF, including both reduced and preserved left-ventricular EF, from 30 cohort studies, six of which were clinical trials (105). The MAGGIC risk score evaluated 31 different variables for long-term all-cause mortality in HF and identified 13 independent and two interaction risk predictors.

Models for prediction of risk

The accuracy of a predictive model may be measured in how well a model separates the group being examined into those with and without the specified outcome. The area under the receiver operating characteristic (ROC) curve, known as the AUC, is currently considered to be the standard method to assess the accuracy of predictive models. Predictive models for specific outcomes based on risk scores for patients with CHF are available. An area of 1 represents a perfect model; an area of 0.5 and below represents that the result is by chance.

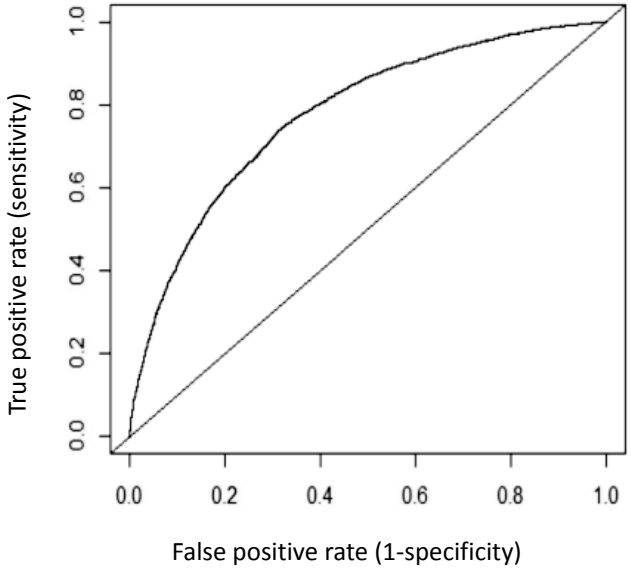


Figure 1. Example of receiver operatin characteristic curve.

THE RATIONALE OF THE THESIS

Paper I

No study has previously investigated trends in prevalence of patients hospitalized with HF in a nationwide cohort.

Paper II

Temporal trends for diuretic treatment and coinciding neurohormonal antagonist treatment rates after a first-time hospitalization for HF have never been studied in a nationwide cohort.

Paper III

The association of diuretic treatment with mortality has previously been studied in selected cohorts with HF with limited possibilities to adjust for confounders. Congestion is the main reason for hospitalization for HF (2) Higher mortality rates have been observed in patients hospitalized for HF when compared to outpatients with HF (103). The association of diuretic treatment at hospital discharge with short- term all-cause mortality in unselected real-life patients with HF has never been studied. The association of diuretic treatment at hospital discharge with long-term all-cause mortality has never been studied in unselected Western world real-life patients with HF.

Paper IV

Diuretic treatment is a strong predictor for long-term mortality in HF scores but has not been considered as an additional risk predictor in the HF score with the largest underlying database; the MAGGIC score.

AIMS

The overall aims of this thesis was:

I to estimate trends for prevalence of patients hospitalized with HF in a nationwide cohort, by sex and age

II to estimate trends for diuretic treatment and coinciding neuro-hormonal antagonist treatment rates after a first-time hospitalization for HF in a nationwide cohort, by sex and age

III to estimate the association of diuretic treatment at hospital discharge with all-cause short- and long-term mortality in unselected real-life patients with HF

IV to evaluate diuretic treatment as a predictor for long-term all-cause mortality in unselected real-life outpatients with HF.

METHODS

Paper I

All patients hospitalized in Sweden for any reason at least once during 1980-2007 with a principal or contributory diagnosis of HF and aged between 19 and 99 years at any time during the period 1990–2007 were eligible for inclusion in this study. A person in this study is considered to have a diagnosis of HF during the period between the incident year when he, or she, for the first time was hospitalized with a first or contributory diagnosis of HF and the year of death. ICD version 8 (ICD-8) was used until 1986, ICD-9 between 1987 and 1996, and ICD-10 from 1997 onwards. The discharge codes applied to HF were 427.00, 427.10 (ICD-8), 428A, 428B, 428X (ICD-9), and I50 (ICD-10). Data from IPR and CDR was merged. Prevalence of patients aged 19-99 with an ICD diagnosis of HF at hospital discharge for each calendar year 1990-2007 and temporal trends for prevalence in the total cohort, by sex and age were estimated. Predefined age groups were 19-54, 55-64, 75-84, and 85-99 years. In order to estimate the prevalence for a specific age X on a specific year Y, to the actual incident cases year Y the 1-year survivors among the incident cases of age X-1 at year Y-1 and the 2-year survivors among incident cases of age X-2 at year Y-2 are added and so on. The counting method was described more formally by Gail (106). Population data for the Swedish population for the corresponding age and/or sex-specified group and calendar year was used as reference populations in all prevalence estimates. This data was provided by the Swedish governmental agency Statistics Sweden. The Swedish general population in year 2000 was used as the reference for age-adjusted prevalence rates that were computed by using direct standardization. Temporal trends were estimated with "Joinpoint regression". A two-sided P value <0.05 was considered statistically significant. SAS software version 9.2 (SAS, Cary, NC, USA) and R software version 2 (R Development Core Team) were used for data analysis. Joinpoint Regression Program 4.0.4 – May 2013 (Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute) was used for joinpoint analysis. The study was approved by the Regional Ethical Review Board of University of Gothenburg.

Paper II

Patients that survived for 18 months or more after a first-time hospitalization for HF 2005-2014 were eligible for inclusion in this study. We defined a hospital admission registered 2005-2014 in the IPR with HF as the primary diagnosis with no previous admission for HF in the past seven years as a first-time hospitalization for HF. The discharge codes applied to HF in this study were I11.0, I13.0, I13.2, I42.0, I42.3-9, I50.0-1, and I50.9 (ICD10). The discharge codes applied to comorbidities in this study are shown in Table 2.The Anatomical Therapeutic Chemical (ATC) codes used for classification of HF treatment investigated in this study are shown in Table 3. Diuretic in combined preparations were thiazides. At least one dispensed prescription of a drug class during a specified period was defined as treatment with that drug class during that period. The Defined Daily Dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults and defined by WHO

Table 2. ICD codes used for comorbidities at hospital discharge

Comorbidity	ICD10 codes
Ischaemic heart disease	I20-I22, I24, I25
Valvular disease	I34-I37
Stroke	I60-I64, I69
Periferial arterial disease	I70, I73.9
Chronic obstructive pulmonary disease	J44
Renal failure	N17.0-N17.2, N17.8-N17.9, N18
Sleep apnoea syndrome	G47.3
Diabetes mellitus	E10, E11, E12, E13, E14
Obesitas	E66.0-E66.2, E66.8-E66.9
Hypertension	I10, I11.9, I12.0-I12.9, I13.1-I13
Atrial fibrillation	I48

Table 3. Anatomical Therapeutic Chemical codes for treatment for heart failure

Drug class	Drug	ATC code
Loop diuretics	furosemide	C03CA01
	bumetanide	C03CA02
	torasemide	C03CA04
Digitalis	digitoxin	C01AA04
	digoxin	C01AA05
MRA	spironolactone	C03DA01
	eplerenone	C03DA04
Beta-blockers	metoprolol	C07AB02
	bisoprolol	C07AB07
	carvedilol	C07AG02
	atenolol	C07AB03
	metoprolol and felodipine	C07FB02
RAS antagonists	captopril	C09AA01
	enalapril	C09AA02
	lisinopril	C09AA03
	perindopril	C09AA04
	ramipril	C09AA05
	fosinopril	C09AA09
	enalapril and diuretics	C09BA02
	lisinopril and diuretics	C09BA03
	ramipril and diuretics	C09BA05
	quinapril and diuretics	C09BA06
	losartan	C09CA01
	eprosartan	C09CA02
	valsartan	C09CA03
	irbesartan	C09CA04
	candesartan	C09CA06
	telmisartan	C09CA07
	losartan and diuretics	C09DA01
	eprosartan and diuretics	C09DA02
	valsartan and diuretics	C09DA03
	irbesartan and diuretics	C09DA04
	candesartan and diuretics	C09DA06
	telmisartan and diuretics	C09DA07
	valsartan and amlodipine	C09DB01
I_f channel antagonist	ivabradine	C01EB17

Collaborating Centre for Drug Statistics Methodology (https://www.whocc.no/ddd/definition_and_general_considera/ 170314). The DDD is 40 mg for furosemide, 1 mg for bumetanide and 15 mg for torasemide. Registry data from IPR, SPDR and CDR was merged. Temporal trends for treatment rates were evaluated with the Cochran-Armitage test. Temporal trends for DDD were evaluated with linear regression. Significance level was set at 0.05. SAS software version 9.2 (SAS, Cary, NC, USA) and R software version 2 (R Development Core Team) were used for data analysis. The study was approved by the Regional Ethical Review Board of Gothenburg University.

Paper III and IV

Patients registered in SwedeHF 2005-2011 with known diuretic treatment status were eligible for inclusion in these studies. Data from SwedeHF and the Swedish Population Registry was merged. The cohort was separated into two study populations - patients registered at hospital discharge (Paper III) and outpatients (Paper IV). In each study population, multiple imputation (n=10) was performed for missing data in baseline variables. In Paper III, propensity scores based on 46 baseline variables for the propensity between 0 and 1 for each included patient to be treated with diuretics were estimated using logistic regression. In Paper IV the corresponding propensity scores were based on the 15 MAGGIC risk predictors. We created 1:1 PS matched cohorts with accepted maximal differences in PS of 0.01 between a patient treated with diuretics and a patient not treated with diuretics. For descriptive analyses original data was used. Continuous variables were presented as mean (standard deviation) or median (interquartile range) if non-normally distributed. Categorical variables were presented as counts and percentages. Comparisons between groups were made using the chi-square test for categorical variables, the independent samples t-test for normally distributed continuous variables, and the Mann–Whitney U test for continuous variables with a skewed distribution. Standardized differences were calculated. For survival analyses, multiple imputed data was used. Kaplan-Meier estimates of long-time survival in patients with and without diuretics in the original and matched cohorts were performed. All-cause mortalities at end of follow-up for patients with or without diuretics at baseline were compared with the log rank test in the original and matched cohorts, respectively. The unadjusted relative risk of all-cause mortality, the relative risk for all-cause mortality adjusted for PS, and the relative risk for all-cause mortality in the PS matched cohorts associated with diuretics were estimated. In Paper IV, the relative risk for all-cause mortality associated with diuretics adjusted for the 15 MAGGIC mortality risk predictors was estimated. In Paper IV, time-dependent ROC curves (89) for the ability to predict 3-year mortality of the MAGGIC mortality risk predictors and the ability to predict 3-year mortality of the MAGGIC mortality risk predictors with diuretic treatment as an additional covariate were computed by using the patients' risk scores and areas under the ROC curves were calculated.

A two-sided P value <0.05 was considered statistically significant. Statistical Package for the Social Sciences (SPSS; version 22.0, SPSS Inc., Chicago, IL) and R software version 2.12.0 (R Development Core Team) were used for data analyses. Establishment of the SwedeHF registry, and registration and analysis of the data were approved by a multisite ethics committee.

RESULTS

Paper I

Absolute numbers of patients who had been hospitalized with a HF diagnosis and were aged 19-99 years increased from 105,449 in 1990 to 144,925 in 2007, with a 77% increase in patients aged 85–99 years. The overall prevalence in 1990 was 1.61% and increased with an estimated annual percentual change (EAPC) of 4.9% (95% confidence interval (CI): 4.4% to 5.4%) from 1990 until 1995, with no further significant change until 2001 (Table 4). Prevalence peaked in year 2001 with 2.12% and then declined slowly (EAPC: -0.6 (95% CI: −0.9% to −0.2%) to 2.03% in 2007. In 1990, the age-adjusted prevalence of patients who had been hospitalized with HF in Sweden was 1.70% in men and 1.77% in women. The prevalence in both sexes then increased to 2.13% in men and 2.14% in women around 1998–2000. Subsequently, the prevalence decreased to 2.03% in men and 1.93% in women. In persons <65 years no decrease in prevalence was found, instead, an increase was seen during the observation period.

Table 4. Joinpoint analysis: trends in prevalence of patients hospitalized with heart failure. Rates in the total population, sex-specific and age-specific.

	Period 1 Years	EAPC (95% CI)	Period 2 Years	EAPC (95% CI)	Period 3 Years	EAPC (95% CI)
Total population	1990-95	4.3* (3.6 to 4.9)	1995-2002	0.1 (-0.4 to 0.6)	2002-7	-1.1* (-1.5 to –0.6)
Gender						
Men	1990-96	4.4* (3.9 to 4.9)	1996-2007	-0.3* (-0.5 to -0.1)		
Women	1990-96	3.8* (3.4 to 4.3)	1996-2003	-0.4* (-0.8 to -0.1)	2003-7	-1.6* (-2.2 to -1.1)
Age						
19-54	1990-93	3.6* (2.7 to 4.6)	1993-97	5.7* (5.1 to 6.2)	1997-2007	1.3* (1.2 to 1.4)
55-64	1990-95	4.9* (4.2 to 5.6)	1995-2004	-0.5* (-0.8 to –0.2)	2004-7	1.3* (0.2 to 2.5)
65-74	1990-95	6.2* (5.5 to 6.9)	1995-2000	0.4 (-0.2 to 1.1)	2000-7	-1.9* (-2.2 to –1.5)
75-84	1990-95	5.2* (4.6 to 5.8)	1995-2002	0.0 (-0.3 to 0.3)	2002-7	-1.4* (-1.8 to –1.0)
85-99	1990-96	2.4* (1.7 to 3.1)	1996-2004	0.2 (-0.3 to 0.7)	2004-7	-1.3 (-2.9 to 0.4)

EAPC, estimated annual percentage change, *significantly different from 0

Paper II

In Paper II 81,531 patients with a first-time hospitalization for HF who survived for 18 months or longer post-discharge were included (Figure 2). Age, sex and comorbidities at hospital discharge are shown in Table 5. Between 2005 and 2014, in the period 0-3 months after discharge, loop diuretic drug treatment rates decreased from 87.2% to 82.3% and median loop diuretic DDD decreased from 2.22 (interquartile range 1.11-3.21) to 1.98 (interquartile range 1.11-2.50) (p for trend <0.001 and 0.002, respectively), coinciding with a trend for increased treatment with RAS inhibitors and beta-blockers during the period (Table 6). Corresponding figures for the period 6-18 months post-discharge were 89.0% and 82.1% and median loop diuretic DDD 1.37 (interquartile range 1.82-2.19) and 1.10 (interquartile range 0.82-2.05) (p for trends <0.001) (Table 7). The median loop diuretic DDD 6-18 months post-discharge was lower than the median loop diuretic DDD 0-3 months post-discharge in every calendar year during the study period. Beta-blocker, RAS inhibitor and MRA treatment rates were higher 6-18 months post-discharge than 0-3 months post-discharge (data

not shown) whereas only small changes, predominantly increases, were observed for the coinciding diuretic treatment rates (Table 6). Post-discharge diuretic treatment rates were higher in women when compared to men and in older patients when compared to younger patients.

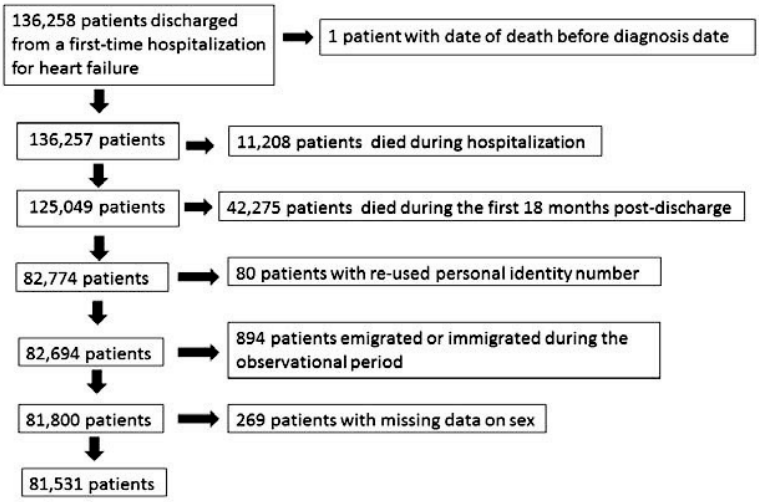


Figure 2. Flow chart of inclusion of patients.

Table 5. Age, sex and comorbidities at hospital discharge

All patients, n (%)	81,531 (100)
Age and sex	
Age, mean (SD), years	76.0 (12.2)
Sex, n (%)	
Men	43,665 (53.6)
Women	37,866 (46.4)
Age group (years), n (%)	
18-54	4,916 (6.0)
55-64	8,730 (10.7)
65-74	16,916 (20.7)
75-84	29,021 (35.6)
85-99	21,948 (26.9)
Comorbidities, n (%)	
Ischaemic heart disease	34,173 (41.9)
Valvular disease	10,362 (12.7)
Stroke	11,560 (14.2)
Periferal arterial disease	5,169 (6.3)
Chronic obstructive pulmonary disease	8,355 (10.2)
Renal failure	5,961 (7.3)
Sleep apnea syndrome	1,916 (2.4)
Diabetes mellitus	21,222 (26)
Obesitas	4,063 (5.0)
Hypertension	47,092 (57.8)
Atrial fibrillation	40,406 (49.6)

Table 6. Loop diuretic treatment rates in patients alive for 18 months or more after discharge from a first-time hospitalization for HF in Sweden 2005-2014

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	P-value
	Oct-Dec									Jan-Jun	for trend
Number of patients (%)											
All	2,188	9,002	9,146	9,319	9,404	9,471	9,545	9,434	9,301	4,721	
	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	
Men	1,243	4,878	4,913	5,060	4,983	5,020	5,129	5,014	4,955	2,470	
	(56.8)	(54.2)	(53.7)	(54.3)	(53.0)	(53.0)	(53.7)	(53.1)	(53.3)	(52.3)	
Women	945	4,124	4,233	4,259	4,421	4,451	4,416	4,420	4,346	2,251	
	(43.1)	(45.8)	(46.3)	(45.7)	(47.0)	(47.0)	(46.3)	(46.9)	(46.7)	(47.7)	
Aged 18-54	126	558	591	538	523	574	586	596	539	285	
	(5.7)	(6.2)	(6.5)	(5.8)	(5.6)	(6.1)	(6.1)	(6.3)	(5.8)	(6.0)	
Aged 55-64	284	995	1,070	1,023	1,025	970	988	983	937	455	
	(13.0)	(11.1)	(11.7)	(11.0)	(10.9)	(10.2)	(10.4)	(10.4)	(10.1)	(9.6)	
Aged 65-74	424	1,814	1,855	1,892	1,867	1,880	2,026	2,081	2,027	1,050	
	(19.4)	(20.2)	(20.3)	(20.3)	(19.9)	(19.9)	(21.2)	(22.1)	(21.8)	(22.2)	
Aged 75-84	826	3,358	3,337	3,448	3,391	3,339	3,375	3,165	3,183	1,599	
	(37.8)	(37.3)	(36.9)	(37.0)	(36.1)	(35.2)	(35.4)	(33.5)	(34.2)	(33.9)	
Aged 85-99	528	2,277	2,293	2,418	2,598	2,708	2,570	2,609	2,615	1,332	
	(24.1)	(25.3)	(25.1)	(25.9)	(27.6)	(28.6)	(26.9)	(27.7)	(28.1)	(28.2)	
Month 0-3 before admission											
All	49.9	48.2	49.4	48.3	48.1	47.9	48.1	47.3	46.3	45.7	<0.001
Men	47.1	43.9	45.2	44.4	44.8	44.4	43.8	42.9	42.2	42.8	<0.001
Women	53.4	53.3	54.3	52.9	51.9	51.8	53.0	52.3	51.0	48.9	<0.001
Age 18-54	23.8	22.8	2679	16.9	16.8	19.0	18.4	19.8	20.0	20.0	0.023
Age 55-64	37.3	32.6	33.5	37.1	34.1	33.9	36.5	32.3	32.7	32.3	0.330
Age 65-74	48.4	46.5	48.1	44.3	44.4	44.3	45.4	44.0	43.0	41.7	<0.001
Age 75-84	51.8	51.8	52.7	52.6	52.5	52.4	52.8	50.7	51.1	49.2	0.042
Age 85-99	61.1	57.3	58.9	56.9	56.9	56.0	55.1	57.8	53.4	54.7	<0.001
Month 0-3 after discharge											
All	87.2	86.6	85.9	84.6	85.3	84.8	83.9	83.0	81.9	82.3	<0.001
Men	86.2	85.4	84.8	83.7	83.9	83.2	83.2	81.3	80.7	81.1	<0.001
Women	88.6	87.9	87.2	85.6	86.9	86.5	84.8	84.9	83.2	83.7	<0.001
Age 18-54	74.6	74.6	67.5	65.8	66.3	66.4	66.0	61.2	61.2	65.3	<0.001
Age 55-64	83.8	79.6	77.9	76.1	73.8	73.9	74.2	72.0	70.4	71.2	<0.001
Age 65-74	86.8	83.7	85.1	82.5	83.2	82.2	79.7	79.2	78.0	75.8	<0.001
Age 75-84	87.0	88.8	88.9	87.8	88.2	87.1	87.6	86.6	85.3	86.6	0.010
Age 85-99	92.6	91.4	90.9	89.3	91.3	91.4	90.3	90.7	89.0	89.8	<0.001
Month 6-18 after discharge											
All	89.0	88.5	87.9	86.3	86.2	85.0	84.3	82.7	82.2	82.1	<0.001
Men	86.8	86.2	86.3	84.5	83.9	82.8	82.1	80.5	80.7	79.2	<0.001
Women	92.0	91.3	89.7	88.4	88.8	87.5	86.8	85.3	84.0	85.2	<0.001
Age 18-54	65.9	67.9	65.0	57.6	57.2	58.4	52.6	54.9	54.9	61.8	<0.001
Age 55-64	78.9	76.8	75.5	76.1	71.6	70.3	68.0	67.3	66.6	65.5	<0.001
Age 65-74	89.2	86.1	86.8	83.2	82.5	81.3	81.4	78.3	77.9	75.4	<0.001
Age 75-84	91.8	92.6	92.0	90.0	90.6	89.2	89.5	87.5	86.3	87.1	<0.001
Age 85-99	95.6	94.5	94.5	94.0	94.8	93.2	93.0	92.6	91.8	91.3	<0.001

Table 7. Diuretic doses in patients alive for 18 months or more after discharge from a first-time hospitalization for HF in Sweden 2005-2014

Year	2005 Oct-Dec	2006	2007	2008	2009	2010	2011	2012	2013	2014 Jan-Jun	p-value for trend
DDD per day, 0-3 months after discharge, median (IQR)											
All	2.22 (1.11-3.21)	2.22 (1.11-3.06)	2.22 (1.11-3.06)	2.18 (1.11-2.78)	2.18 (1.11-2.78)	2.18 (1.11-2.78)	2.18 (1.11-2.78)	1.94 (1.11-2.60)	1.94 (1.11-2.50)	1.98 (1.11-2.50)	0.002
Men	2.22 (1.11-3.33)	2.22 (1.11-3.19)	2.22 (1.11-3.27)	2.20 (1.11-2.78)	2.18 (1.11-2.78)	2.20 (1.11-2.78)	2.21 (1.11-2.80)	2.10 (1.11-2.76)	2.18 (1.11-2.76)	2.18 (1.11-2.77)	0.010
Women	2.22 (1.11-2.78)	2.22 (0.11-3.00)	2.22 (1.11-2,90)	2.11 (1.11-2.78)	2.02 (1.11-2.78)	1.94 (1.11-2.78)	1.99 (1.11-2.78)	1.83 (1.11-2.51)	1.74 (1.11-2.40)	1.94 (1.11-2.42)	<0.001
Age 18-54	1.69 (1.11-2.22	1.67 (1.11-2.50)	2.18 (1.11-2.78)	1.67 (1.11-2.22)	2.18 (1.11-2.78)	1.67 (1.11-2.22)	1.67 (1.11-2.39)	1.67 (1.11-2.22)	1.67 (1.11-2.22)	2.22 (1.11-2.50)	0.729
Age 55-64	2.22 (1.11-2.78)	2.22 (1.11-3.02)	2.22 (1.11-3.17)	2.20 (1.11-2.78)	2.18 (1.11-2.78)	2.22 (1.11-2.78)	1.87 (1.11-2.72)	2.19 (1.11-2.22)	1.67 (1.11-2.22)	1.91 (1.11-2.39)	0.019
Age 65-74	2.22 (1.11-3.33)	2.22 (1.11-3.10)	2.22 (1.11-3.31)	2.20 (1.11-2.78)	2.18 (1.11-2.78)	2.20 (1.11-3.03)	2.22 (1.11-3.29)	2.20 (1.11-2.78)	2.18 (1.11-2.78)	2.22 (1.11-2.78)	0.345
Age 75-84	2.22 (1.11-3.33)	2.22 (1.11-3.17)	2.22 (1.11-3.17)	2.20 (1.11-2.83)	2.18 (1.11-2.78)	2.22 (1.11-2.78)	2.20 (1.11-2.78)	2.18 (1.11-2.76)	2.12 (1.11-2.78)	1.95 (1.11-2.68)	0.018
Age 85-99	2.22 (1.11-2.80)	2.22 (1.11-3.06)	2.18 (1.11-2.78)	1.94 (1.11-2.71)	2.02 (1.11-2.78)	1.81 (1.11-2.51)	1.94 (1.11-2.75)	1.82 (1.11-2.50)	1.79 (1.11-2.29)	1.87 (1.11-2.22)	<0.001
DDD per day, 6-18 months after discharge, median (IQR).											
All	1.37 (0.82-2.19)	1.37 (0.82-2.19)	1.37 (0.82-2.19)	1.35 (0.82-2.16)	1.36 (0.82-2.19)	1.25 (0.82-2.11)	1.32 (0.82-2.18)	1.17 (0.82-2.08)	1.12 (0.82-2.05)	1.10 (0.82-2.05)	<0.001
Men	1.40 (0.82-2.33)	1.37 (0.82-2.19)	1.37 (0.82-2.19)	1.30 (0.82-2.18)	1.36 (0.82-2.19)	1.23 (0.82-2.16)	1.23 (0.82-2.19)	1.10 (0.82-2.13)	1.10 (0.82-2.05)	1.10 (0.81-2.04)	<0.001
Women	1.37 (0.82-2.19)	1.37 (0.82-2.19)	1.37 (0.82-2.19)	1.37 (0.82-2.14)	1.37 (0.82-2.18)	1.33 (0.82-2.07)	1.36 (0.82-2.15)	1.23 (0.82-2.07)	1.22 (0.82-2.05)	1.10 (0.82-2.05)	<0.001
Age 18-54	1.10 (0.82-1.92)	1.10 (0.55-1.78)	1.09 (0.59-1.90)	0.91 (0.50-1.64)	0.89 (0.55-1.64)	0.89 (0.54-1.64)	1.03 (0.55-1.64)	0.92 (0.55-1.64)	0.89 (0.54-1.64)	0.83 (0.42-1.57)	0.009
Age 55-64	1.10 (0.82-2.19)	1.10 (0.82-2.18)	1.10 (0.82-1.92)	1.10 (0.81-2.05)	1.10 (0.70-2.04)	1.10 (0.68-1.99)	1.10 (0.68-2.06)	1.10 (0.55-1.92)	1.09 (0.55-1.69)	1.09 (0.55-1.76)	0.025
Age 65-74	1.37 (0.82-2.26)	1.36 (0.82-2.19)	1.36 (0.82-2.19)	1.23 (0.82-2.15)	1.23 (0.82-2.18)	1.10 (0.82-2.18)	1.23 (0.82-2.19)	1.10 (0.82-2.19)	1.10 (0.68-2.07)	1.10 (0.74-2.11)	<0.001
Age 75-84	1.37 (0.82-2.19)	1.37 (0.85-2.19)	1.37 (0.82-2.19)	1.37 (0.82-2.19)	1.37 (0.82-2.19)	1.37 (0.82-2.19)	1.37 (0.82-2.19)	1.23 (0.82-2.16)	1.22 (0.82-2.10)	1.12 (0.82-2.08)	0.006
Age 85-99	1.63 (1.00-2.47)	1.51 (1.00-2.33)	1.51 (1.00-2.24)	1.37 (0.92-2.08)	1.50 (0.98-2.19)	1.37 (0.88-2.11)	1.37 (0.96-2.18)	1.36 (0.82-2.09)	1.29 (0.82-2.05)	1.15 (0.82-2.05)	<0.001

DDD, daily defined dose; IQR, interquartile range.

Paper III and IV

In Paper III 26,218 patients discharged from a hospitalization for HF and registered in SwedeHF 2005-2011 (mean age 77.1 ± 16.1 years) were included, of whom 87% were treated with diuretics and 13% were not treated with diuretics at hospital discharge (Figure 3).

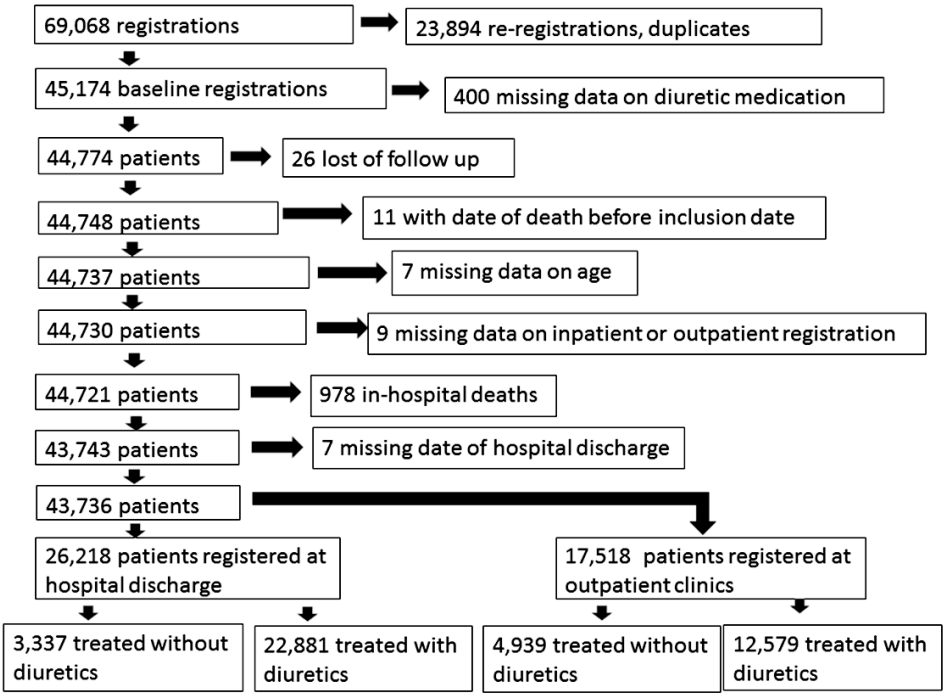


Figure 3. Flow chart of inclusion of patients.

Table 8. Baseline characteristics at hospital discharge in the original and 1:1 propensity score-matched cohorts .

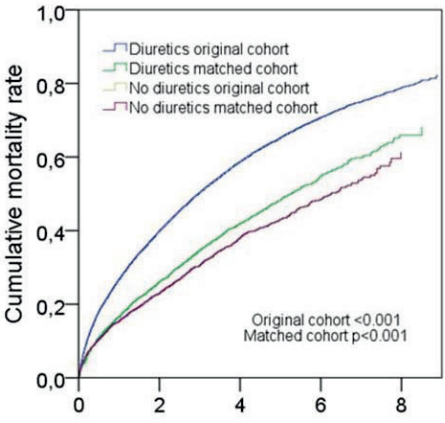
		Original cohort (n=26218)				PS- matched cohort (n=6564)			
	Missing %	No diuretics (n=3337)	Diuretics (n=22881)	Standardized Difference (%)[a]	*P*-value	No diuretics (n=3282)	Diuretics (n=3282)	Standardized Difference (%)[a]	*P*-value
Follow-up period, median, years (min-max)	0	2.92 (0-9.00)	2.06 (0-9.03)			2.97 (0-9.00)	2.77 (0-9.02)		
All-cause mortality, numbers (Deaths per 1000 person years)	0	1240 (120)	13370 (232)			1237 (121)	1377 (140)		
Baseline demographics									
Age, mean (SD), years[b]	0	72.5 (13.2)	77.8 (11.2)	43	<.001	72.8 (13.0)	72.5 (13.6)	2	.404
Sex[b]	0								
Men, N (%)		2068 (62)	12772 (56)	13	<.001	2030 (62)	2042 (62)	1	.760
Women, N (%)		1277 (38)	10109 (44)			1251 (38)	1252 (38)		
Marital status[b]	6.4								
Single, No (%)		1316 (43)	10962 (51)	17	<.001	13062 (43)	1355 (45)	3	.186
Married/cohabitating, N. (%)		1779 (57)	10488 (49)			1738 (57)	1684 (55)		
Living arrangements[b]	26								
Independent, N (%)		2244 (93)	15240 (90)	10	<.001	2236 (93)	2182 (92)	1	.293
Institution, N (%)		177 (7.3)	1731 (10)			177 (7.3)	192 (7.5)		
Specialty[b]	0								
Geriatrics or internal medicine, N (%)		1515 (45)	11180 (49)	7	<.001	1496 (46)	1474 (45)	1	.585
Cardiology, N (%)		1822 (55)	11701 (51)			1786 (54)	1808 (55)		
Registration year[b]	0								
2004-2007, N (%)		1098 (33)	8585 (38)	10	<.001	1098 (33)	1099 (33)	0	.979
2008-2011, N (%)		2239 (67)	14296 (62)			2184 (67)	218398 (67)		
HF duration[b]	0.9								
<6 months, N (%)		2179 (66)	10797 (48)	38	<.001	2132 (66)	2170 (67)	2	.483
≥6 months, N (%)		1108 (34)	11888 (52)			1102 (34)	1081 (33)		
Former HF inpatient[b], N (%)	78	143 (18)	2002 (40)	49	<.001	141 (19)	185 (24)	11	.037
Baseline clinical parameters									
NYHA class[b], N (%)	39								
I-II, N (%)		1265 (68)	7188 (51)	36	<.001	1231 (68)	1292 (66)	4	.253
III-IV, N (%)		592 (32)	6947 (49)			589 (32)	669 (34)		
LVEF (%)[b]	18								
≥40%, N (%)		1257 (44)	8776 (47)	8	<.001	1240 (44)	1224 (45)	2	.515
<40%, N (%)		1631 (56)	9734 (53)			1596 (56)	1521 (55)		
Blood pressure									
Systolic[b], mean (SD), mm Hg	<0.1	130 (22.4)	128 (22.0)	5	.007	130 (22.4)	130 (22.8)	2	.478
Diastolic[b], mean (SD), mm Hg	<0.1	74.5 (12.9)	73.0 (12.7)	12	<.001	74.5 (12.9)	74.6 (13.0)	1	.563
Heart rate mean (SD), b.p.m.[b],	8.4	75.8 (17.3)	76.5 (15.9)	4	.028	75.9 (17.3)	75.9 (16.2)	0	.914
QRS width mean (SD), ms[b]	32	106 (25.8)	110 (29.4)	13	<.001	107 (25.8)	108 (28.0)	5	.078
BMI mean (SD), kg/m^2[b]	55	26.1 (9.03)	26.6 (7.00)	7	.029	26.1 (9.10)	26.8 (7.12)	9	.015
Pulmonary congestion on X-ray during hospitalization[b], No (%)	22	641 (29)	8780 (48)	40	<.001	640 (29)	843 (33)	8	.005

Baseline characteristics in the original and 1:1 PS matched cohorts are shown in Table 8. Differences in baseline characteristics were in general smaller in the matched cohort when compared to the original cohort.

Baseline laboratory									
Hb mean (SD), g/L[b]	0	132 (17.5)	138 (17.6)	23	<.001	132 (17.5)	132 (17.7)	1	.705
eGFR mean (SD), mL/min[b]	0	74.4 (30.7)	60.5 (28.0)	47	<.001	73.6 (29.9)	73.0 (34.2)	2	.397
Potassium mean (SD), mmol/L[b]	52	4.15 (0.448)	4.07 (0.467)	17	<.001	4.18 (1.08)	4.13 (1.79)	3	.355
Sodium mean (SD), mmol/L[b]	84	139 (3.17)	140 (3.64)	8	.080	139 (3.17)	139 (3.24)	2	.780
NT-proBNP median (IQR), ng/L[b]	76	2840 (1250-6110)	4056 (1880-8628)	17	<.001	2974 (1282-6230)	2879 (1286-6048)	7	>0.05
Baseline medical history									
Hypertension[b], N (%)	2.8	1400 (43)	11394 (51)	17	<.001	1389 (43)	1408 (44)	1	.664
Diabetes[b], N (%)	1.1	578 (18)	6332 (28)	25	<.001	577 (18)	582 (16)	0	.853
Atrial fibrillation[b], N (%)	0.9	1341 (41)	12131 (54)	26	<.001	1337 (41)	1321 (41)	1	.634
Ischemic heart disease[b], N (%)	4.1	1570 (49)	10852 (49)	1	.452	1541 (49)	14898 (47)	3	.319
Former myocardial infarction [b], N (%)	77	282 (35)	1835 (35)	0	.968	263 (35)	263 (32)	5	.326
Valvular disease[b], N (%)	6.1	487 (15)	4869 (23)	19	<.001	486 (16)	465 (15)	1	.556
Dilated cardiomyopathy[b], N (%)	5.7	322 (10)	2023 (9.4)	2	.198	315 (10)	331 (11)	2	.390
Hypertrophic cardiomyopathy[b], N (%)	29	59 (2.5)	404 (2.5)	0	.989	59 (2.5)	59 (2.6)	1	.826
Pulmonary disorder[b]	3.2	474 (15)	4528 (20)	15	<.001	471 (15)	464 (15)	1	.800
Smoking[b]	31								
Never, N (%)		1071 (44)	6963 (45)	2	.376	1047 (44)	1030 (43)	1	.740
Former or Active, N (%)		1374 (56)	8593 (55)			1348 (56)	1352 (57)		
Alcohol consumption[b]	60								
Never, N (%)		165 (12)	1256 (14)	6	.049	158 (12)	168 (12)	1	.855
Yes, N (%)		1236 (88)	7909 (86)			1207 (88)	1256 (88)		
Baseline history of interventions									
Valvular surgery[b], N (%)	1.9	157 (4.8)	1256 (5.6)	4	.060	156 (4.8)	147 (4.6)	1	.589
Revascularization[b], N (%)	2.8	900 (28)	4997 (22)	12	<.001	874 (27)	806 (25)	5	.064
CRT[b], N (%)	0	45 (1.3)	451 (2.0)	5	.014	44 (1.3)	44 (1.3)	0	1.00
ICD[b], N (%)	0	91 (2.7)	486 (2.1)	4	.027	84 (2.6)	73 (2.2)	3	.374
Pacemaker[b], N (%)	0	243 (7.3)	2443 (11)	12	<.001	243 (7.4)	2417 (7.3)	0	.925
Baseline concomitant medications									
RAS inhibition[b], N (%)	0.4	2616 (79)	16989 (75)	10	<.001	2564 (78)	2561 (78)	0	.940
Beta blocker[b], N (%)	0.6	2784 (84)	18910 (83)	2	.362	2733 (84)	2735 (84)	1	.749
MRA[b], N (%)	0.8	463 (14)	7216 (32)	43	<.001	463 (14)	523 (16)	5	.042
Long-acting nitroglycerin[b], N (%)	0.8	493 (15)	4892 (22)	17	<.001	490 (15)	512 (16)	2	.476
Platelet inhibitor[b], N (%)	0.6	1932 (58)	12519 (55)	7	<.001	1898 (58)	1909(59)	1	.839
Anticoagulant[b], N (%)	0.7	1019 (31)	7867 (35)	8	<.001	1011 (31)	982 (30)	2	.384
Digoxin[b], N (%)	0.5	458 (14)	4650 (20)	18	<.001	458 (14)	456 (14)	0	.911
Statin[b], N (%)	0.5	1531 (46)	8844 (39)	15	<.001	1497 (46)	1446 (44)	3	.193
Amiodarone[b], N (%)	24	65 (2.6)	442 (2.5)	1	.851	65 (2.6)	69 (2.8)	1	.649

Numbers are presented as N (%) for categorical variables and mean (standard deviation) for continuous variables and median (interquartile range) for continuous variables with a skew distribution (NT-proBNP). *P*-values are shown for differences between the groups by independent samples *t*-test for continuous variables, χ^2 test for categorical variables and Mann-Whitney *U* test for continuous variables with skewed distribution (NT-proBNP). HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; BMI, body mass index; eGFR, estimated glomerular filtration rate; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; RAS, renin angiotensin system; MRA, mineralocorticoid receptor antagonist; PS, propensity score. [a]The standardized difference is expressed as a percentage and is the difference between the means for the two groups divided by mutual standard deviation. [b]Variables included in the propensity score for the propensity of diuretic treatment

Cumulative mortality rates for the original and the 1:1 PS matched cohorts are shown in Figure 4.



Numbers at risk					
Diuretics original cohort	22,881	11,720	5,209	1,497	232
No diuretics original cohort	3,337	2,206	1,066	289	24
Diuretics matched cohort	3,282	2,059	970	297	39
No diuretics matched cohort	3,282	2,185	1,064	289	24

Figure 4. Cumulative mortality rates for patients with heart failure treated with or without diuretics at hospital discharge in original and 1:1 propensity score matched cohorts.

The unadjusted relative risk of 90-day all-cause mortality associated with diuretics at hospital discharge in the original cohort was increased, HR 1.62 (95% CI 1.42–1.85). Over a median follow-up of 2.18 years (IQR 0,98-3.91), the unadjusted relative risk of long-term all-cause mortality associated with diuretics at hospital discharge was increased, HR 1.94 (95% CI 1.82-2.07). After adjustment for PS, the relative risk of 90-day all-cause mortality associated with diuretics was no longer significantly increased, HR 0.98 (95% CI 0.94–1.02) whereas the long-term all-cause mortality associated with diuretics remained moderately increased, HR 1.16 (95% CI 1.14–1.18). In the 1:1 PS matched cohort the association of diuretic treatment at hospital discharge with 90-day all-cause mortality was neutral, HR 0.89 (95% CI 0.74–1.07). In the matched cohort, over a median follow-up of 2.85 years (IQR 1.44-4.42) the relative risk of long-term all-cause mortality (median follow-up: 2.85 years) was increased, HR 1.15 (95% CI 1.06-1.24).

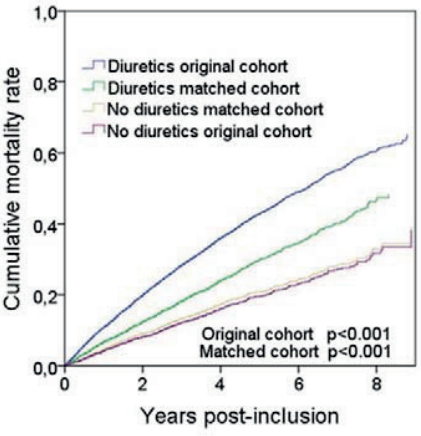
In Paper IV 17,518 outpatients (mean age 71.7 years ± 12.0 years), 72% treated with diuretics, were included (Figure 3). Baseline demographics in the original and 1:1 propensity score matched cohorts are shown in Table 9. Differences in baseline characteristics were in general smaller in the matched cohort when compared to the original cohort.

Table 9. Baseline characteristics in outpatients with heart failure treated with or without diuretics at baseline in the original and 1:1 propensity score matched cohorts.

Variable	Original cohort (n=17,518)					1:1 Propensity score matched cohort (n=8,494)				
	Missing data (%)	No diuretic treatment (n=4,939)	Diuretic treatment (n=12,579)	Standardized difference, %[a]	P-value	Missing data (%)	No diuretic treatment (n=4,247)	Diuretic treatment (n=4,247)	Standardized difference, %[*]	P-value
Follow-up period, median (min-max)	0	3.45 (0-9.02)	2.86 (0-9.01)			0	3.67 (0-9.02)	3.42 (0-9.01)		
All-cause mortality, numbers (Deaths per 1000 person years)	0	788 (43.8)	4,523 (112)			0	763 (47.3)	1,043 (69.9)		
Age [b], years, mean (SD)	0	67.2 (12.9)	73.4 (11.1)	52	<0.001	0	69.4 (11.4)	68.9 (11.2)	4	0.065
Male sex [b], %	0	71.6	64.4	15	<0.001	0	69.5	70.4	2	0.356
BMI [b], kg/m^2, mean (SD)	58.6	26.3 (5.02)	27.9 (10.4)	19	<0.001	56.1	26.4 (5.14)	27.9 (5.60)	28	<0.001
Current smoker [b], %	17.9	14.1	10.9	10	<0.001	15.8	13.6	13.3	1	0.709
SBP [b], mm Hg, mean (SD)	1.89	130 (20.5)	128 (21.2)	12	<0.001	1.6	1301 (20.5)	131 (21.5)	0	0.929
Diabetes [b], %	0.5	13.8	24.6	28	<0.001	0.5	15.6	14.6	1	0.769
NYHA class [b], %	16.5					14.2				
I		23.7	8.3	43	<0.001		17.2	17.1	0	0.119
II		57.5	48.0	19			60.8	60.4	1	
III		18.4	48.7	53			21.7	21.8	0	
IV		0.3	1.9	15			0.3	0.7	6	
Ejection fraction [b], %	5.0					4.0				
≥50		15.1	17.2	6	<0.001		16.4	16.5	0	0.547
40-49		27.2	18.8	20			25.9	25.0	2	
39-40		32.1	25.1	16			33.6	33.1	1	
<30		19.8	29.5	23			24.1	25.4	3	
Pulmonary disease [b], %	2.1	11.4	18.5	20	<0.001	2.1	13.0	12.6	1	0.583
HF duration	0.4					0.4				
<6 months		56.0	42.3	28	<0.001		52.9	53.6	1	0.547
>6 months		44.0	57.7				47.1	46.4		
Creatinine [b] µmol/L, mean (SD)	0.07	88.4 (37.3)	107 (45.9)	45	<0.001	0.04	90.7 (39.3)	91.5 (31.2)	2	0.279
Beta-blocker [b], %	0.2	83.9	85.3	4	0.021	0.2	84.6	84.1	1	0.510
ACE-I/ARB [b], %	0.1	92.3	89.1	11	<0.001	0	91.5	91.2	1	0.694
Hemoglobin g/L, mean (SD)	0.1	139	134	29	<0.001	0.2	138	138	3	0.160
Atrial fibrillation , %	0.6	31.4	48.6	36	<0.001	0,6	33.2	42.9	22	<0.001
Hypertension , %	3.3	37.1	51.3	29	<0.001	3.1	38.6	48.9	21	<0.001
Ischaemic heart disease, %	4.6	45.8	46.5	1	0.63	4.8	47.7	39.4	17	<0,001
NT-proBNP ng/L, median (IQR)	61	1085 (460-2227)	2180 (984-4510)	43	<0.001	62	1214 (530-2427)	1708 (741-3708)	23	<0.001

Numbers are presented as n (%) for categorical variables and mean (standard deviation) for continuous variables and median (interquartile range) for continuous variables with a skew distribution (NT-proBNP). *P*-values are shown for differences between the groups by independent samples *t*-test for continuous variables, χ^2 test for categorical variables and Mann-Whitney U test for continuous variables with skewed distribution (NT-proBNP). ACE, angiotensin converting enzyme; ARB, aldosterone receptor blocker; BMI, body mass index; HF, heart failure; NYHA, New York Heart Association; SBP, systolic blood pressure. [a]The standardized difference is expressed as a percentage and is the difference between the means for the two groups divided by mutual standard deviation. [b]Variables included in the propensity score for the propensity of diuretic treatment

Cumulative mortality rates for the original and the 1:1 PS matched cohorts are shown in Figure 5.



Numbers at risk

Diuretics original cohort	12,579	8,307	3,943	1,325	244
No diuretics original cohort	4,939	3,741	1,997	616	89
Diuretics matched cohort	4,247	3,113	1,573	530	99
No diuretics matched cohort	4,247	3,319	1,863	611	88

Figure 5. Cumulative mortality rates for outpatients with heart failure treated with or without diuretics at baseline in original and 1:1 propensity score matched cohorts.

Over a median follow-up of 2.99 years (IQR 1.74-4.69), the unadjusted relative risk for long-term all-cause mortality associated with diuretic treatment was increased, HR 2.57 (95% CI 2.51–2.63) and remained significantly increased after adjustment for MAGGIC mortality risk predictors in a multi-variate Cox regression model, HR 1.47 (95% CI 1.43–1.51). After adjustment for PS, the relative risk for long-term all-cause mortality associated with diuretic treatment in the total cohort was increased, HR 1.46 (95% CI 1.42–1.50). In the 1:1 propensity score-matched cohort, over a median follow-up of 3.46 years (IQR 2.03-5.00) the relative risk for long-term all-cause mortality associated with diuretics was increased, HR 1.48 (95% CI 1.35–1.63). For prediction of 3-year mortality in our study population a model based on MAGGIC mortality risk predictors had an area under the ROC curve (AUC) of 0.78 (0.778). A model based on the MAGGIC mortality risk predictors with diuretic treatment as an additional covariate had an AUC of 0.78 (0.776).

DISCUSSION

The prevalence of heart failure

In Paper I, we observed that the prevalence of patients hospitalized with HF in Sweden was higher in year 2007 when compared to year 1990 but with a trend for a slight decrease in prevalence between 2002 and 2007. Thus, our findings did not support that a HF epidemic occurred during the final years of our observation period. However, the observed increase in the number of patients hospitalized with HF aged >85 years during our observational period and the coinciding increase in prevalence of patients hospitalized with HF in younger ages suggest a possible future increase in the overall prevalence of HF.

The point prevalence of HF has been studied in different cohorts with different methodologies since the 1940s. Data collection for Framingham Heart Study (FHS) began in 1948 when 5,209 residents of Framingham, Massachusetts, the United States, aged 28 to 62 years were enrolled in a prospective epidemiologic study (107). In 1971, children of the original study participants and spouses of these children, aged 6 to 70 years, were entered in the Framingham Offspring Study. In the combined cohort of the FHS cohort and the Framingham Offspring Study cohort, the estimated prevalence of HF 1948-1988, based on the Framingham diagnostic criteria, was 2.5% in persons aged >45 years (89).

The NHANES-I program included 23,808 non-institutionalized persons 1 to 74 years old from the Unites States (90). In the NHANES-I cohort the estimated prevalence of HF 1971-1975, based on Framingham diagnostic criteria, was 2% in participants aged 25-74 years. In Nottinghamshire, United Kingdom, the prevalence of HF 1991-1992, based on furosemide prescription data, was estimated to be somewhere between 1.0% - 1.6% (108). In the district of Ommoord in Rotterdam, the Netherlands, the estimated prevalence of HF 1990-1993, based on assessment of symptoms and signs (shortness of breath, ankle oedema and pulmonary crackles) and use of HF medication in 5,540 invited participants aged 55-95 years in the Rotterdam Study, was 3.9% (109). The FHS, NHANES-I, Nottinghamshire and Rotterdam studies reported similar prevalence of HF in men and women and higher prevalence of HF in older than in younger persons (89, 90, 108, 109). However, estimations in these studies were made on data collected before or in the beginning of the modern era of treatment for cardiovascular diseases including HF.

Trends for decreased prevalence of cardiovascular risk factors from the 1960s (110), decreased incidence of HF 1988-2000 (93) and decreased mortality in HF 1987-2003 (111) have been reported in studies based on registry data from Sweden. Other studies have reported trends for increased prevalence of HF between 1994 and 2003, based on data from medical records of patients 65 years or older covered by Medicare (112), and increased prevalence of HF between 2000 and 2005, based on data from medical records of medically insured in- and outpatients in the south-eastern United States (113). The validity of a diagnosis of HF in the medical records used in the Medicare study was not reported. The validity of an ICD-9 diagnosis of HF in the medical re-

cords used in the study of insured patients against Framingham clinical criteria was 97% for inpatients but was not reported for outpatients. In both these studies a higher prevalence of HF in men than in women was observed (112, 113).

Between 1987 and 2001, an increased proportion of all patients hospitalized for HF were classified with HFpEF and a trend for improved survival in HFrEF but not in HFpEF was observed (26). However, observed trends for increased prevalence of HFpEF may have been associated with an increased awareness of HFpEF, development of new methods how to assess diastolic dysfunction, and an increased tendency to use these methods.

Since the end of the 1990s, the proportion of patients with HF treated with medications with proven prognostic benefit in both HFrEF and other cardiovascular diseases than HF have increased (82). Between 2000 and 2010, trends for decreased incidence of both HFrEF and HFpEF, but more pronounced for HFrEF, was observed (114). A coinciding trend for decreased incidence of HF in both men and women, but more pronounced for women, and particularly pronounced for HFrEF in women, were observed. In addition, recent studies have suggested that the trend for decreased mortality observed in patients with HF during the 1990s decelerated in the beginning of the 21st century (80, 84). No differences were observed in all-cause mortality rates between 1998–2002 and 2003–2007 in patients with a first hospitalization for HF (84) or in all-cause mortality rates between 2003 and 2012 in patients with chronic HFrEF (80).

These observations suggested a potential difference between trends for prevalence of HF before and after the turn of the millennium. Our study on trends for prevalence of patients hospitalized with HF between 1990 and 2007 (Paper I) showed two main trends; increased prevalence until 1990-1995 and a slight decrease 2002-2007. The decreased prevalence of HF in the total cohort coincided with a decrease in women but not in men. In consistency with our results, decresed prevalence of HF between 2006 and 2010 was observed in women, but not in men, in a study based on data from the region of Stockholm, Sweden (115).

No data on EF was available in the registries used in this study (Paper I). A possible increase in the proportion of patients with HFrEF and decrease in the proportion of patients with HFpEF may have occured in our study cohort during the observation period. Beginning around 1995-2000 trends for increased prevalence of HFpEF, decreased prevalence of HFrEF, and no significant change in the prevalence of total HF (both HFrEF and HFpEF) in older adults have been reported in a recently published meta-analysis (116). In addition, it has been reported in European Registry Data that both all-cause hospitalizations and hospitalizations for HF may be more common in patients with HFrEF when compared to patients with HFmrEF or HFpEF (24).

The contemporary incidence of HF in Sweden is 3.8/1000 person-years in adults (both women and men), 3.2/1000 person-years in women and 3.0/1000 person-years in men (115). The contemporary one-year all-cause mortality rate in Europe is 17.4% in patients with AHF and 7.2% in patients with CHF (103) whereas the 5-year mortality rate n Sweden in adults is approximately 50% (115).

The current demographic transition in combination with the increased prevalence observed for many risk factors for HF, e.g. diabetes (Global burden of diabetes, In: Diabetic Atlas 5th ed. Brussels: International Diabetes Federation; 2011. Available at http://www.idf.org/diabetesatlas (Accessed 30th April 2013), obesity (117), atrial fibrillation (118), and a sedentary lifestyle (21) may predispose for a future increase in the prevalence of HF.

Treatment with diuretics in patients with heart failure

In our study (Paper II) a trend for increased post-discharge neuro-hormonal antagonist treatment rates coincided with a trend for decreased diuretic treatment rates and diuretic doses between 2005 and 2014 in patients with a first-time hospitalization for HF. In every calendar year during our observation period, neuro-hormonal antagonist treatment rates were higher 6-18 months post-discharge when compared to 0-3 months post-discharge suggesting that neuro-hormonal antagonist optimization after a first-time hospitalization for HF did occur in our cohort. The coinciding changes in diuretic treatment rates and diuretic doses suggested that neuro-hormonal antagonist optimization after a first-time hospitalization for HF coincided with diuretic dose reduction more frequently than with diuretic discontinuation.

The trends for increased post-discharge neuro-hormonal antagonist treatment rates between 2005 and 2014 that were observed in our study are in consistency with results in previous studies of more selected cohorts with geographical or age-related limitations (80-85). In our study, lower treatment rates for RAS inhibitors and beta-blockers were observed in women when compared to men and in older persons when compared to younger persons in consistency with previous findings on treatment patterns in patients with HF (86, 87). Trends for decreased diuretic treatment rates 0-3 months post-discharge between 2005 and 2014 were observed in our study whereas previous studies of more selected cohorts with follow-up until 2010 have reported trends for unchanged or relatively constant early post-discharge diuretic treatment rates (82, 83). The trends for decreased diuretic treatment rates 6-18 months post-discharge observed in our study were in consistency with results in previous studies of more selected cohorts with CHF and follow-up until 2012 (81, 84, 85). In addition, we observed higher diuretic treatment rate in women when compared to men and in older persons when compared to younger persons.

Diuretic discontinuation in patients with HF that were considered clinically stable has been investigated in some smaller clinical trials (119, 120). In those studies, many patients needed reintroduction of diuretics. In our study, in every calendar year, loop diuretic treatment rates decreased between 0-3 months and 6-18 months post-discharge in patients aged <65 years whereas they increased in patients aged >65 years. This suggests that the possibilities for successful diuretic discontinuation may differ with age. In contrast, diuretic dose decreased between 0-3 months and 6-18 months post-discharge irrespective of age in every calendar year during our observation period.

However, if there was a direct relationship between improved treatment with neuro-hormonal antagonists, decreased degree of fluid retention and decreased need for diuretic treatment was not answered by this observational study. We had no data on

symptomatic severity. The trend for decreased treatment with diuretics in HF may have coincided with a possible trend for less severe HF with a lower degree of congestive symptoms.

The association of diuretic treatment at hospital discharge with short- and long-term mortality in patients with heart failure

The association of diuretic treatment at hospital discharge with short-term mortality has never previously been investigated. In our study (Paper III), the association of diuretic treatment at hospital discharge with 90-day (short-term) mortality was neutral. In all other settings and lengths of follow-up in patients with HF diuretic treatment has been associated with increased mortality. In theory, a possible mechanistic link between diuretics at discharge and short-term mortality may be related to the observations that a large proportion of patients have residual clinical or sub-clinical congestion at discharge from a hospitalization for HF (10, 70) and that residual congestion at discharge has been associated with increased short-term mortality (10, 70). The hypothesis that the relative risk of short-term mortality associated with diuretic treatment in HF may differ between patients with congestion when compared to patients without congestion needs to be verified in a RCT, if possible. The association of diuretic treatment at hospital discharge with increased long-term mortality observed in our study of a Western world cohort with 26,218 patients (46) was in consistency with results from a report from the Japanese HF registry (n=2,549, mean follow-up 2.1 years) (72).

In consistency with our results, studies of selected cohorts of patients with CHF have reported associations between diuretic treatment and increased long-term mortality; a higher dose of diuretics when compared to a lower dose at baseline has been associated with increased long-term mortality both in patients with low (121-123) and in patients with high beta-blocker treatment rates (124) and non-potassium sparing diuretic treatment has been associated with increased long-term mortality in patients with chronic HFrEF and low beta-blocker treatment rates (125). Several pathophysiological mechanisms have been proposed to link diuretic treatment mechanistically with an increased long-term mortality in CHF, including increased activity of the renin angiotensin aldosterone and the sympathetic nervous systems (67, 75), impairment of renal function (126, 127) and arrhythmias induced by serum electrolyte disturbance (128). Successful withdrawal of diuretics in patients with CHF has been associated with decreased PRA and aldosterone levels, unchanged norepinephrine levels and increased natriuretic peptide levels (119, 120). The observed coinciding changes in diuretic treatment and changes in levels of neuro-hormones suggest that there may be a direct relationship between diuretic treatment and the neuro-hormones that have been associated with increased mortality in patients with HF.

The association of diuretic treatment with long-term mortality in outpatients with heart failure

In our study (Paper IV), diuretic treatment was associated with increased long-term mortality in a cohort of 17,518 unselected real-life outpatients with HF after adjustment for the 15 MAGGIC mortality predictors. However, an additional covariate

would have needed a stronger association with mortality than the one we estimated for diuretics in this cohort to improve the ability to predict 3-year mortality of the original MAGGIC predictors.

The observed association of diuretic treatment with increased long-term mortality in outpatients with HF was in consistency with results reported in a secondary retrospective analysis of a selected cohort from the Digitalis Investigation Group (DIG) study (79). The secondary DIG analysis included 7,788 outpatients with HF in sinus rhythm (median follow-up 40 months). It was based on data collected 1991–1993 and did not report the concomitant beta-blocker treatment rate (but it was probably low). Diuretic treatment as an independent predictor of long-term mortality has been evaluated in CHF risk scores other than MAGGIC, and, in consistency with our results, has been shown to be an independent risk predictor. In the Seattle HF mortality risk score, based on 1,125 patients with HF with EF<30% and NYHA III-IV from the Prospective Randomized Amlodipine Survival Evaluation (PRAISE1), diuretic dose was the strongest predictor for increased long-term mortality (129) and in the Barcelona HF score, based on 864 consecutive outpatients with HF according to ESC criteria treated at a single-centre multidisciplinary HF unit, diuretic treatment was a strong predictor for increased long term-mortality (130).

Possible confounders in estimations of the association of diuretic treatment with mortality in patients with heart failure

Diuretic treatment in real-life patients at discharge from a hospitalization for HF or in real-life outpatients with HF may be a marker for congestion or HF disease severity (131). Congestion and HF disease severity are very complicated to measure (132). Out of diuretic treatment, congestion and HF disease severity, diuretic treatment is, by far, the easiest variable to measure. Therefore, we consider our findings in Paper III and IV of importance even if the prognostic effects of diuretics remain unknown.

If the observed association between diuretic treatment and increased mortality depended on a direct mechanistic link between diuretics and mortality (Paper III and IV), the observed temporal trends for decreased diuretic treatment rates and doses (Paper II) may have influenced the observed temporal trend for decreased prevalence of HF (Paper I). However, if diuretic treatment is considered as a marker of HF disease severity (Paper III and IV), the observed temporal trend for decreased diuretic treatment (Paper II) and the observed trend for decreased prevalence of patients hospitalized with HF (Paper I) may have been signs of a temporal trend for decreased HF severity. To clarify the prognostic effects of diuretics, RCTs on diuretic treatment and/or diuretic discontinuation and/or diuretic dose reduction are needed.

Strengths and limitations

In Paper I all real-life patients hospitalized with a first or contributory diagnosis of HF recorded in a nationwide hospital discharge register were included. Thus, patients without hospitalizations were not included. In theory, changed indications for hospitalizations or changed frequencies of diagnosis setting in medical records may have influenced our results. In Sweden, the number of secondary diagnoses per case in

inpatient care increased during the 1990s after the introduction of diagnosis-related group-based prospective payment systems. Most of this increase took place in the early 1990s. However, no other major changes in the Swedish hospital or reimbursement systems occurred during our observation period. In addition, the validity of a diagnosis of HF in Swedish inpatients has been shown to be higher than in Swedish outpatients. No data on EF was available in the registries used in Paper I.

In Paper II all patients that survived 18 months post-discharge after a first-time hospitalization for HF 2005-2014 recorded in a nationwide hospital discharge register were included. That all patients in this study were included after a first-time hospitalization for HF probably limited the impact of a possible HF duration bias. The sickest patients who died during the first 18 months post-discharge were not included in this study. Nevertheless, 81,531 patients (mean age 76.0 $\pm$ 12.2 years), of whom 46% were women, were included. One limitation in this study was that no data on EF was recorded in the registries that were used in Paper II. However, the trends for increased treatment with neuro-hormonal antagonists were solid during our observation period why it was assumed that no major changes in the distribution of EF occurred. Data on the severity of HF was not recorded in the registries used in Paper II. Thus, it remains unknown if the temporal trends for decreased loop diuretic treatment rates and doses may have been a temporal trend for decreased HF severity.

In Paper III and IV patients were included form a nationwide HF register, SwedeHF. Participation in SwedeHF is voluntary, why there is a risk of selection bias. However, SwedeHF has a high coverage rate of hospitals and heart failure outpatient clinics in Sweden. We consider our studies on the association of diuretics with mortality the most ambitious so far in the number of included patients and in attempts to adjust for measured confounders and quantify the possible impact of unmeasured confounders. The MAGGIC mortality risk predictors used as co-variates in Paper IV has previously been validated to perform very well in predicting survival in the SwedeHF cohort (133). In our studies (Paper III and IV) the PS matching process selected the least sick patients treated with diuretics from the original cohort to match patients not treated with diuretics in the 1:1 PS matched cohort. This may limit extrapolation of our findings to patients with a more severe degree of HF than the patients included in our analyses. However, we consider it likely that in real-life clinical practice the clinical choice to treat or not treat with diuretics is more probable in patients with a less severe HF.

Information on what kind of diuretic agent that was used and diuretic dose was not recorded in SwedeHF before 2011. In data from 2011, 96% of all registered diuretics in SwedeHF were loop diuretics. The preferred loop diuretic in Sweden during our observation period was furosemide. We had no information on the reason of diuretic treatment or on changes in diuretic dose during follow-up. The latest verified EF available at registration was recorded in SwedeHF. However, there was no information on whether the patient had been classified with HFrEF, HFmrEF or HFpEF available in the registry. Information on causality of death is not provided in SwedeHF.

CONCLUSIONS

The overall aims of this thesis was to study temporal trends for prevalence of patients with HF, temporal trends for diuretic treatment in patients with HF and the association between diuretic treatment and mortality in patients with HF. The conclusion in Paper I was that the prevalence of patients hospitalized with HF increased between 1990 and 2007 in Sweden but with a slight but statistically significant decreasing trend in prevalence since 2001, mainly driven by a decreasing trend in women. The prevalence of HF increased gradually in patients <65 years. In absolute numbers, patients with HF older than 85 years increased by 77% during the study period. The current demographic transition in the Western world will most likely lead to increased numbers of very old patients with HF and probably result in increased costs for HF care in the future. When the temporal trends for prevalence of HF had been estimated (Paper I) we proceeded to study the temporal trends of diuretic treatment in patients with HF (Paper II). The conclusion of Paper II was that trends for decreased loop diuretic treatment rates and doses coincided with increased neuro-hormonal antagonist treatment rates in patients with a first-time hospitalization for HF between 2005 and 2014. Furthermore, we observed that post-discharge diuretic dose reduction coincided with neuro-hormonal antagonist optimization every calendar year during the observation period.

Thus, in Paper I and II we observed a temporal trend for decreased prevalence of HF (Paper I) and a temporal trend for decreased treatment with diuretics in patients with HF (Paper II). In Paper II it was also observed that a vast majority of Swedish patients were treated with diuretics after discharge from a first time hospitalization for HF during the observation period. However, the association of diuretic treatment at discharge from a hospitalization for HF and the association of diuretic treatment in outpatients with CHF with all-cause mortality in an unselected real-life nationwide cohort were not known. For this reason we continued with the studies presented in Paper III and IV. The conclusions of Paper III were that there was no significant difference in relative risk for 90-day all-cause mortality between patients with and without diuretic treatment at hospital discharge whereas an association between diuretic treatment at hospital discharge and increased long-term mortality was observed. The conclusion of Paper IV was that diuretic treatment in outpatients was associated with increased relative risk for long-term mortality but that a previously known model for prediction of 3-year mortality was not improved when diuretic treatment was an additional covariate. Whether the findings in Paper III and IV were the results of independent associations of diuretic treatment with mortality or related to measured or unmeasured confounders remains unknown. However, we suggest that diuretic treatment may be considered as a risk marker for incresed relative risk of all-cause mortality in unselected real-life patients with HF.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Hjärtsvikt är en sjukdom där hjärtats pumpförmåga är nedsatt. Den nedsatta pumpförmågan vid hjärtsvikt beror på att antingen hjärtmuskelns pumpkraft och/eller förmåga till avslappning av något skäl är påverkad. Förekomsten av hjärtsvikt har beräknats till c:a 1-2% men har aldrig undersökts i ett helt lands befolkning. Hjärtsvikt är ett allvarligt tillstånd med hög sjuklighet och hög dödlighet. Personer med hjärtsvikt drabbas ofta av vätskeansamling i kroppen. Vanliga tecken vid vätskeansamling på grund av hjärtsvikt är andfåddhet och bensvullnad. För att lindra dessa symptom rekommenderas vattendrivande behandling (diuretika). Trots att diuretika av olika slag har använts i flera hundra år och att över 80% av alla patienter med hjärtsvikt behandlas med diuretika är det okänt hur denna behandling påverkar dödligheten hos patienter med hjärtsvikt. Det övergripande syftet med denna avhandling var att undersöka trender i förekomsten av hjärtsvikt 1990-2007, trender i förekomsten av diuretikabehandling hos personer med hjärtsvikt 2005-2014 och sambandet mellan diuretikabehandling och dödlighet hos personer med hjärtsvikt. För att studera detta samkörde vi uppgifter från flera olika svenska register.

Delarbete I visade att av alla personer som var 19-99 år gamla i Sverige 1990-2007 var andelen med hjärtsvikt c:a 2%. Av alla personer som var 19-99 år gamla var andelen med hjärtsvikt högre 2007 än 1990 men minskade något mellan 2002 och 2007. Av alla personer som var yngre än 55 år var andelen med hjärtsvikt låg men ökade stadigt mellan 1990 och 2007. Antalet personer med hjärtsvikt som var äldre än 85 år ökade markant under hela perioden. Troligen kommer dessa trender att leda till en framtida ökning av både andelen och antalet personer med hjärtsvikt i Sverige samt ökade vårdbehov orsakade av hjärtsvikt.

I riktlinjer om hur man ska behandla hjärtsvikt anges att användningen av diuretika vid hjärtsvikt bör vara så låg som möjligt eftersom man inte vet hur diuretika påverkar dödligheten vid hjärtsvikt. Delarbete II visade att andelen personer med hjärtsvikt som behandlades med diuretika och deras diuretikadoser minskade mellan 2005 och 2014. Under samma period ökade andelen personer med hjärtsvikt som behandlades med andra läkemedel som bevisats minska sjuklighet och dödlighet vid hjärtsvikt. Vidare antydde resultaten i delarbete II att bara en liten andel av alla personer som hade sjukhusvårdats för första på grund av hjärtsvikt och påbörjat behandling med diuretika kunde bli av med denna behandling på sikt. Detta gällde särskilt personer med hjärtsvikt som var äldre än 65 år. Däremot verkade dosminskning av diuretika på sikt vara vanligt förekommande oavsett ålder.

Delarbete III och IV visade att diuretikabehandling hos personer med hjärtsvikt, både vid utskrivning från sjukhus och i öppenvården, hade ett samband med ökad dödlighet på lång sikt. Däremot visade sig diuretikabehandling vid utskrivning från sjukhus inte ha något samband med förändrad dödlighet på kort sikt. Dessa samband gällde även efter att hänsyn tagits till en mängd andra faktorer som kan påverka prognosen hos personer med hjärtsvikt. Om det finns något direkt orsakssamband mellan diuretika och dödlighet hos personer med hjärtsvikt är fortfarande okänt.

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REFERENCES

1. Braunwald E, Ross J, Jr., Sonnenblick EH. Mechanisms of contraction of the normal and failing heart. The New England journal of medicine. 1967;277(15):794-800 contd.

2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal. 2016;37(27):2129-200.

3. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, et al. EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). European journal of heart failure. 2010;12(10):1076-84.

4. Jonsson S, Agic MB, Narfstrom F, Melville JM, Hultstrom M. Renal neurohormonal regulation in heart failure decompensation. American journal of physiology Regulatory, integrative and comparative physiology. 2014;307(5):R493-7.

5. Picano E, Gargani L, Gheorghiade M. Why, when, and how to assess pulmonary congestion in heart failure: pathophysiological, clinical, and methodological implications. Heart failure reviews. 2010;15(1):63-72.

6. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. The New England journal of medicine. 2011;364(9):797-805.

7. Yu CM, Wang L, Chau E, Chan RH, Kong SL, Tang MO, et al. Intrathoracic impedance monitoring in patients with heart failure: correlation with fluid status and feasibility of early warning preceding hospitalization. Circulation. 2005;112(6):841-8.

8. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. Circulation. 2007;116(14):1549-54.

9. Adamson PB, Magalski A, Braunschweig F, Bohm M, Reynolds D, Steinhaus D, et al. Ongoing right ventricular hemodynamics in heart failure: clinical value of measurements derived from an implantable monitoring system. Journal of the American College of Cardiology. 2003;41(4):565-71.

10. Coiro S, Rossignol P, Ambrosio G, Carluccio E, Alunni G, Murrone A, et al. Prognostic value of residual pulmonary congestion at discharge assessed by lung ultrasound imaging in heart failure. European journal of heart failure. 2015.

11. Androne AS, Hryniewicz K, Hudaihed A, Mancini D, Lamanca J, Katz SD. Relation of unrecognized hypervolemia in chronic heart failure to clinical status, hemodynamics, and patient outcomes. The American journal of cardiology. 2004;93(10):1254-9.

12. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. Journal of the American College of Cardiology. 2009;53(7):589-96.

13. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. The New England journal of medicine. 1971;285(26):1441-6.

14. Harlan WR, Oberman A, Grimm R, Rosati RA. Chronic congestive heart failure in coronary artery disease: clinical criteria. Annals of internal medicine. 1977;86(2):133-8.

15. Carlson KJ, Lee DC, Goroll AH, Leahy M, Johnson RA. An analysis of physicians' reasons for prescribing long-term digitalis therapy in outpatients. Journal of chronic diseases. 1985;38(9):733-9.

16. Eriksson H, Caidahl K, Larsson B, Ohlson LO, Welin L, Wilhelmsen L, et al. Cardiac and pulmonary causes of dyspnoea--validation of a scoring test for clinical-epidemiological use: the Study of Men Born in 1913. European heart journal. 1987;8(9):1007-14.

17. Marantz PR, Tobin JN, Wassertheil-Smoller S, Steingart RM, Wexler JP, Budner N, et al. The relationship between left ventricular systolic function and congestive heart failure diagnosed by clinical criteria. Circulation. 1988;77(3):607-12.

18. Di Bari M, Pozzi C, Cavallini MC, Innocenti F, Baldereschi G, De Alfieri W, et al. The diagnosis of heart failure in the community. Comparative validation of four sets of criteria in unselected older adults: the ICARe Dicomano Study. Journal of the American College of Cardiology. 2004;44(8):1601-8.

19. Guidelines for the diagnosis of heart failure. The Task Force on Heart Failure of the European Society of Cardiology. European heart journal. 1995;16(6):741-51.

20. Gheorghiade M, Pang PS. Acute heart failure syndromes. Journal of the American College of Cardiology. 2009;53(7):557-73.

21. 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: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128(16):1810-52.

22. Katz AM, Rolett EL. Heart failure: when form fails to follow function. European heart journal. 2016;37(5):449-54.

23. Meta-analysis Global Group in Chronic Heart F. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. European heart journal. 2012;33(14):1750-7.

24. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. European journal of heart failure. 2017.

25. Chan MM, Lam CS. How do patients with heart failure with preserved ejection fraction die? European journal of heart failure. 2013;15(6):604-13.

26. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. The New England journal of medicine. 2006;355(3):251-9.

27. Bart BA. Treatment of congestion in congestive heart failure: ultrafiltration is the only rational initial treatment of volume overload in decompensated heart failure. Circulation Heart failure. 2009;2(5):499-504.

28. Konstam MA, Gheorghiade M, Burnett JC, Jr., Grinfeld L, Maggioni AP, Swedberg K, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA : the journal of the American Medical Association. 2007;297(12):1319-31.

29. Voors AA, Dittrich HC, Massie BM, DeLucca P, Mansoor GA, Metra M, et al. Effects of the adenosine A1 receptor antagonist rolofylline on renal function in patients with acute heart failure and renal dysfunction: results from PROTECT (Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function). Journal of the American College of Cardiology. 2011;57(19):1899-907.

30. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, et al. Effect of nesiritide in patients with acute decompensated heart failure. The New England journal of medicine. 2011;365(1):32-43.

31. Packer M, O'Connor C, McMurray JJV, Wittes J, Abraham WT, Anker SD, et al. Effect of Ularitide on Cardiovascular Mortality in Acute Heart Failure. The New England journal of medicine. 2017;376(20):1956-64.

32. Guglin M, Kaufman M. Inotropes do not increase mortality in advanced heart failure. International journal of general medicine. 2014;7:237-51.

33. Group CTS. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The New England journal of medicine. 1987;316(23):1429-35.

34. Investigators S, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The New England journal of medicine. 1991;325(5):293-302.

35. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. The New England journal of medicine. 1991;325(5):303-10.

36. Investigators S, Yusuf S, Pitt B, Davis CE, Hood WB, Jr., Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The New England journal of medicine. 1992;327(10):685-91.

37. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9-13.

38. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. The New England journal of medicine. 1996;334(21):1349-55.

39. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353(9169):2001-7.

40. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. The New England journal of medicine. 1999;341(10):709-17.

41. Cohn JN, Tognoni G, Valsartan Heart Failure Trial I. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. The New England journal of medicine. 2001;345(23):1667-75.

42. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. The New England journal of medicine. 2011;364(1):11-21.

43. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. The New England journal of medicine. 2014;371(11):993-1004.

44. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. The New England journal of medicine. 1986;314(24):1547-52.

45. Digitalis Investigation G. The effect of digoxin on mortality and morbidity in patients with heart failure. The New England journal of medicine. 1997;336(8):525-33.

46. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. The New England journal of medicine. 2005;352(15):1539-49.

47. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. The New England journal of medicine. 2005;352(3):225-37.

48. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. Journal of the American College of Cardiology. 2008;52(23):1834-43.

49. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376(9744):875-85.

50. van Veldhuisen DJ, Cohen-Solal A, Bohm M, Anker SD, Babalis D, Roughton 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). Journal of the American College of Cardiology. 2009;53(23):2150-8.

51. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. The New England journal of medicine. 2008;359(23):2456-67.

52. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. The New England journal of medicine. 2014;370(15):1383-92.

53. Lainscak M, Blue L, Clark AL, Dahlstrom U, Dickstein K, Ekman I, et al. Self-care management of heart failure: practical recommendations from the Patient Care Committee of the Heart Failure Association of the European Society of Cardiology. European journal of heart failure. 2011;13(2):115-26.

54. Jendrassik E. Das Calomel als Diureticum. Deut Arch f klin Med. 1886(xxxviii):499.

55. Cushny AR. The Secretion of Urine. 1st edition ed. London1917.

56. Saxl P, Heilig, R. . Ueber die diuretische Wirkung von Novasurol und anderen Quecksilberinjectionen. Wein klin Wchnschr. 1920(xxxiii):943.

57. Crawford JH, McIntosh JF. Observations on the Use of Novasurol in Edema Due to Heart Failure. The Journal of clinical investigation. 1925;1(4):333-58.

58. Strauss MB SH. Urinary changes due to sulfonamide administration. Bull Johns Hopkins Hosp 1938;63:41-5.

59. Friedberg CK, Taymor R, Minor JB, Halpern M. The use of diamox, a carbonic anhydrase inhibitor, as an oral diuretic in patients with congestive heart failure. The New England journal of medicine. 1953;248(21):883-9.

60. Freis ED, Wanko A, Wilson IM, Parrish AE. Treatment of essential hypertension with chlorothiazide (diuril); its use alone and combined with other antihypertensive agents. J Am Med Assoc. 1958;166(2):137-40.

61. Weissel W. [Treatment of cardiac edema with chlorothiazide]. Wiener Zeitschrift fur innere Medizin und ihre Grenzgebiete. 1959;40:281-91.

62. Kleinfelder H. [Experimental Studies and Clinical Trials of a New Diuretic]. Deutsche medizinische Wochenschrift. 1963;88:1695-702.

63. Cosin J, Diez J, investigators T. Torasemide in chronic heart failure: results of the TORIC study. European journal of heart failure. 2002;4(4):507-13.

64. Wilcox CS. New insights into diuretic use in patients with chronic renal disease. Journal of the American Society of Nephrology : JASN. 2002;13(3):798-805.

65. Ellison DH. Diuretic therapy and resistance in congestive heart failure. Cardiology. 2001;96(3-4):132-43.

66. MacFadyen RJ, Gorski JC, Brater DC, Struthers AD. Furosemide responsiveness, nonadherence and resistance during the chronic treatment of heart failure: a longitudinal study. British journal of clinical pharmacology. 2004;57(5):622-31.

67. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. Annals of internal medicine. 1985;103(1):1-6.

68. Matsue Y, Damman K, Voors AA, Kagiyama N, Yamaguchi T, Kuroda S, et al. Time-to-Furosemide Treatment and Mortality in Patients Hospitalized With Acute Heart Failure. Journal of the American College of Cardiology. 2017;69(25):3042-51.

69. Maggioni AP, Anker SD, Dahlstrom U, Filippatos G, Ponikowski P, Zannad F, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. European journal of heart failure. 2013;15(10):1173-84.

70. Lala A, McNulty SE, Mentz RJ, Dunlay SM, Vader JM, AbouEzzeddine OF, et al. Relief and Recurrence of Congestion During and After Hospitalization for Acute Heart Failure: Insights From Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF). Circulation Heart failure. 2015;8(4):741-8.

71. Kociol RD, Horton JR, Fonarow GC, Reyes EM, Shaw LK, O'Connor CM, et al. Admission, discharge, or change in B-type natriuretic peptide and long-term outcomes: data from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) linked to Medicare claims. Circulation Heart failure. 2011;4(5):628-36.

72. Hamaguchi S, Kinugawa S, Tsuchihashi-Makaya M, Goto D, Yamada S, Yokoshiki H, et al. Loop diuretic use at discharge is associated with adverse outcomes in hospitalized patients with heart failure: a report from the Japanese cardiac registry of heart failure in cardiology (JCARE-CARD). Circulation journal : official journal of the Japanese Circulation Society. 2012;76(8):1920-7.

73. Konishi M, Ishida J, Springer J, von Haehling S, Akashi YJ, Shimokawa H, et al. Heart failure epidemiology and novel treatments in Japan: facts and numbers. ESC heart failure. 2016;3(3):145-51.

74. van Kraaij DJ, Jansen RW, Bouwels LH, Hoefnagels WH. Furosemide withdrawal improves postprandial hypotension in elderly patients with heart failure and preserved left ventricular systolic function. Archives of internal medicine. 1999;159(14):1599-605.

75. Bayliss J, Norell M, Canepa-Anson R. Untreated heart failure: Clinical and neuroendocrine effects of introducing diuretics. British Heart Journal. 1987;57(1):17-22.

76. Packer M, Lee WH, Medina N, Yushak M, Kessler PD. Functional renal insufficiency during long-term therapy with captopril and enalapril in severe chronic heart failure. Annals of internal medicine. 1987;106(3):346-54.

77. Knight RK, Miall PA, Hawkins LA, Dacombe J, Edwards CR, Hamer J. Relation of plasma aldosterone concentration to diuretic treatment in patients with severe heart disease. Br Heart J. 1979;42(3):316-25.

78. Sheehan J, White A. Diuretic-associated hypomagnesaemia. Br Med J (Clin Res Ed). 1982;285(6349):1157-9.

79. Ahmed A, Husain A, Love TE, Gambassi G, Dell'Italia LJ, Francis GS, et al. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. European heart journal. 2006;27(12):1431-9.

80. Lee DS, Mamdani MM, Austin PC, Gong Y, Liu PP, Rouleau JL, et al. Trends in heart failure outcomes and pharmacotherapy: 1992 to 2000. The American journal of medicine. 2004;116(9):581-9.

81. Smith NL, Chan JD, Rea TD, Wiggins KL, Gottdiener JS, Lumley T, et al. Time trends in the use of beta-blockers and other pharmacotherapies in older adults with congestive heart failure. American heart journal. 2004;148(4):710-7.

82. de Peuter OR, Lip GY, Souverein PC, Klungel OH, de Boer A, Buller HR, et al. Time-trends in treatment and cardiovascular events in patients with heart failure: a pharmacosurveillance study. European journal of heart failure. 2011;13(5):489-95.

83. Joffe SW, Dewolf M, Shih J, McManus DD, Spencer FA, Lessard D, et al. Trends in the medical management of patients with heart failure. Journal of clinical medicine research. 2013;5(3):194-204.

84. Loh JC, Creaser J, Rourke DA, Livingston N, Harrison TK, Vandenbogaart E, et al. Temporal trends in treatment and outcomes for advanced heart failure with reduced ejection fraction from 1993-2010: findings from a university referral center. Circulation Heart failure. 2013;6(3):411-9.

85. Thorvaldsen T, Benson L, Dahlstrom U, Edner M, Lund LH. Use of evidence-based therapy and survival in heart failure in Sweden 2003-2012. European journal of heart failure. 2016;18(5):503-11.

86. 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;94(3):e10.

87. Ohlsson A, Lindahl B, Hanning M, Westerling R. Inequity of access to ACE inhibitors in Swedish heart failure patients: a register-basewd study. Journal of epidemiology and community health. 2015

88. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. The New England Journal of medicine. 199;341(8):577-85.

89. Ho KKL, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: The Framingham study. Journal of the American College of Cardiology. 1993;22(4 SUPPL. A):6A-13A.

90. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. Journal of the American College of Cardiology. 1992;20(2):301-6.

91. 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). Circulation Cardiovascular quality and outcomes. 2010;3(6):573-80.

92. Rydén-Bergsten T, Andersson F. The health care costs of heart failure in Sweden. Journal of Internal Medicine. 1999;246(3):275-84.

93. Schaufelberger M, Swedberg K, Koster M, Rosen M, Rosengren A. Decreasing one-year mortality and hospitalization rates for heart failure in Sweden; Data from the Swedish Hospital Discharge Registry 1988 to 2000. European heart journal. 2004;25(4):300-7.

94. Stromberg A, Martensson J. Gender differences in patients with heart failure. European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology. 2003;2(1):7-18.

95. Redfield MM. Heart failure--an epidemic of uncertain proportions. The New England journal of medicine. 2002;347(18):1442-4.

96. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. European journal of epidemiology. 2009;24(11):659-67.

97. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC public health. 2011;11:450.

98. Ingelsson E, Arnlov J, Sundstrom J, Lind L. The validity of a diagnosis of heart failure in a hospital discharge register. European journal of heart failure. 2005;7(5):787-91.

99. Dahlstrom U, Hakansson J, Swedberg K, Waldenstrom A. Adequacy of diagnosis and treatment of chronic heart failure in primary health care in Sweden. European journal of heart failure. 2009;11(1):92-8.

100. Jonsson A, Edner M, Alehagen U, Dahlstrom U. Heart failure registry: a valuable tool for improving the management of patients with heart failure. European journal of heart failure. 2010;12(1):25-31.

101. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiology and drug safety. 2007;16(7):726-35.

102. Barnard J, Meng XL. Applications of multiple imputation in medical studies: from AIDS to NHANES. Statistical methods in medical research. 1999;8(1):17-36.

103. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). European journal of heart failure. 2013;15(7):808-17.

104. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics. 1998;54(3):948-63.

105. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. European heart journal. 2013;34(19):1404-13.

106. Gail MH, Kessler L, Midthune D, Scoppa S. Two approaches for estimating disease prevalence from population-based registries of incidence and total mortality. Biometrics. 1999;55(4):1137-44.

107. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. American journal of public health and the nation's health. 1951;41(3):279-81.

108. Clarke KW, Gray D, Hampton JR. How common is heart failure? Evidence from PACT (prescribing analysis and cost) data in Nottingham. Journal of public health medicine. 1995;17(4):459-64.

109. Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A, et al. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. European heart journal. 1999;20(6):447-55.

110. Wilhelmsen L, Welin L, Svardsudd K, Wedel H, Eriksson H, Hansson PO, et al. Secular changes in cardiovascular risk factors and attack rate of myocardial infarction among men aged 50 in Gothenburg, Sweden. Accurate prediction using risk models. J Intern Med. 2008;263(6):636-43.

111. Shafazand M, Schaufelberger M, Lappas G, Swedberg K, Rosengren A. Survival trends in men and women with heart failure of ischaemic and non-ischaemic origin: data for the period 1987-2003 from the Swedish Hospital Discharge Registry. European heart journal. 2009;30(6):671-8.

112. Curtis LH, Whellan DJ, Hammill BG, Hernandez AF, Anstrom KJ, Shea AM, et al. Incidence and prevalence of heart failure in elderly persons, 1994-2003. Archives of internal medicine. 2008;168(4):418-24.

113. Goyal A, Norton CR, Thomas TN, Davis RL, Butler J, Ashok V, et al. Predictors of incident heart failure in a large insured population: a one million person-year follow-up study. Circulation Heart failure. 2010;3(6):698-705.

114. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA internal medicine. 2015;175(6):996-1004.

115. Zarrinkoub R, Wettermark B, Wandell P, Mejhert M, Szulkin R, Ljunggren G, et al. The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. European journal of heart failure. 2013;15(9):995-1002.

116. 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. European journal of heart failure. 2016;18(3):242-52.

117. James WP. The epidemiology of obesity: the size of the problem. J Intern Med. 2008;263(4):336-52.

118. Ball J, Carrington MJ, McMurray JJ, Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. International journal of cardiology. 2013;167(5):1807-24.

119. Galve E, Mallol A, Catalan R, Palet J, Mendez S, Nieto E, et al. Clinical and neurohumoral consequences of diuretic withdrawal in patients with chronic, stabilized heart failure and systolic dysfunction. European journal of heart failure. 2005;7(5):892-8.

120. van Kraaij DJ, Jansen RW, Sweep FC, Hoefnagels WH. Neurohormonal effects of furosemide withdrawal in elderly heart failure patients with normal systolic function. European journal of heart failure. 2003;5(1):47-53.

121. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. The American journal of cardiology. 2006;97(12):1759-64.

122. Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE, Cropp AB, et al. Diuretic resistance predicts mortality in patients with advanced heart failure. American heart journal. 2002;144(1):31-8.

123. Harjai KJ, Dinshaw HK, Nunez E, Shah M, Thompson H, Turgut T, et al. The prognostic implications of outpatient diuretic dose in heart failure. International journal of cardiology. 1999;71(3):219-25.

124. Dini FL, Ghio S, Klersy C, Rossi A, Simioniuc A, Scelsi L, et al. Effects on survival of loop diuretic dosing in ambulatory patients with chronic heart failure using a propensity score analysis. International journal of clinical practice. 2013;67(7):656-64.

125. Domanski M, Norman J, Pitt B, Haigney M, Hanlon S, Peyster E, et al. Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular Dysfunction (SOLVD). Journal of the American College of Cardiology. 2003;42(4):705-8.

126. Testani JM, Coca SG, McCauley BD, Shannon RP, Kimmel SE. Impact of changes in blood pressure during the treatment of acute decompensated heart failure on renal and clinical outcomes. European journal of heart failure. 2011;13(8):877-84.

127. Dupont M, Mullens W, Finucan M, Taylor DO, Starling RC, Tang WH. Determinants of dynamic changes in serum creatinine in acute decompensated heart failure: the importance of blood pressure reduction during treatment. European journal of heart failure. 2013;15(4):433-40.

128. Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ. Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. Circulation. 1999;100(12):1311-5.

129. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation. 2006;113(11):1424-33.

130. Lupon J, de Antonio M, Vila J, Penafiel J, Galan A, Zamora E, et al. Development of a novel heart failure risk tool: the barcelona bio-heart failure risk calculator (BCN bio-HF calculator). PloS one. 2014;9(1):e85466.

131. Felker GM, O'Connor CM, Braunwald E, Heart Failure Clinical Research Network I. Loop diuretics in acute decompensated heart failure: necessary? Evil? A necessary evil? Circulation Heart failure. 2009;2(1):56-62.

132. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, et al. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. European journal of heart failure. 2010;12(5):423-33.

133. Sartipy U, Dahlstrom U, Edner M, Lund LH. Predicting survival in heart failure: validation of the MAGGIC heart failure risk score in 51,043 patients from the Swedish heart failure registry. European journal of heart failure. 2014;16(2):173-9.