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Heart-kidney interactions in outpatients with heart failure

Reducing confounding by propensity score matching

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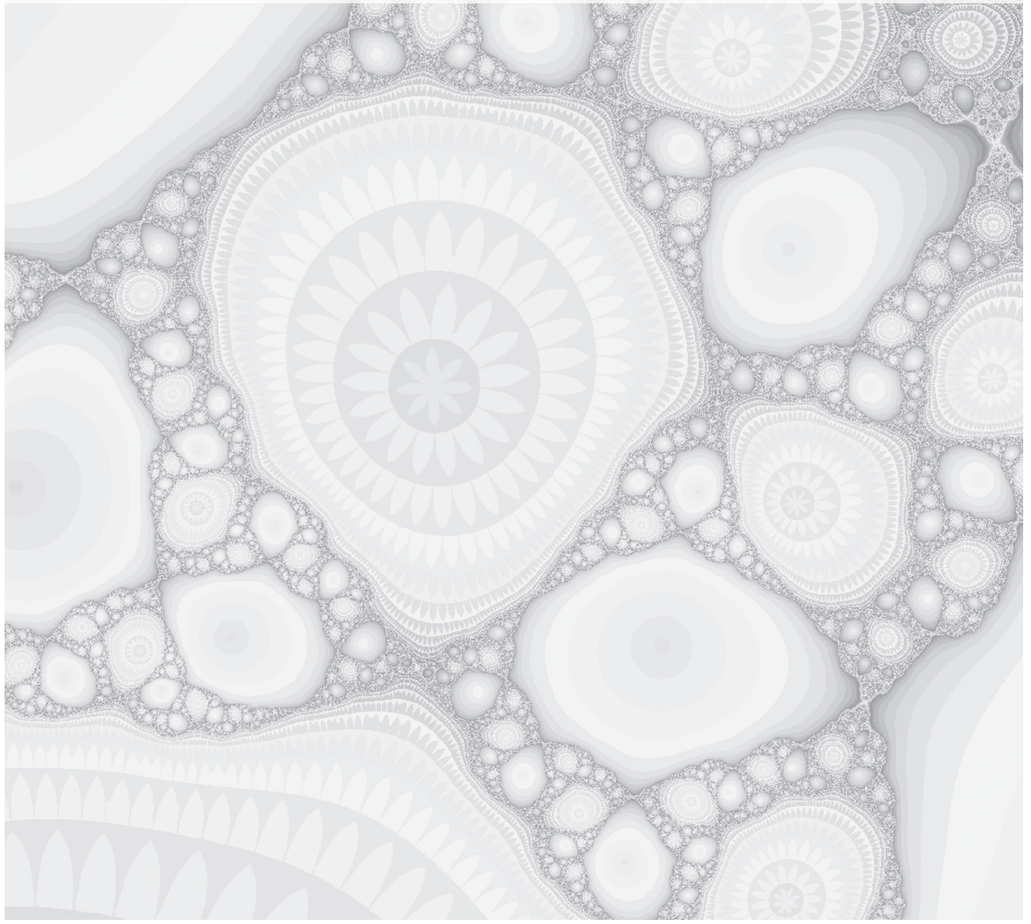

Faculty of Medicine

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Róbert Bielik

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Abbreviations

ACCF/AHA	American College of Cardiology Foundation/American Heart Association
ACEi	angiotensin-converting enzyme inhibitor
ADQI	Acute Dialysis Quality Initiative
AKI	acute kidney injury
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	confidence interval
CRS	cardiorenal syndrome
CV	cardiovascular
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
ESC	European Society of Cardiology
GFR	glomerular filtration rate
HbA1c	glycosylated haemoglobin
HF	heart failure
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved left ventricular ejection fraction

HFrEF	heart failure with reduced left ventricular ejection fraction
HR	hazard ratio
IHD	ischemic heart disease
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcome Quality Initiative
LVEF	left ventricle ejection fraction
MRA	mineralocorticoid receptor blocker
NO	nitric oxide
NYHA	New York Heart Association
RALES	Randomized Aldactone Evaluation Study
RAAS	renin-angiotensin-aldosterone system
RCT	randomized controlled trial
RRT	renal replacement therapy
SGLT-2	sodium-glucose cotransporter-2
SD	standard deviation
SUA	serum uric acid
UA	uric acid
XO	xanthine oxidase
WRF	worsening renal function

Summary

Heart disease and chronic kidney disease (CKD) are closely related and awareness about this relationship has increased the last decades. Nearly every other patient with chronic heart failure has reduced renal function (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2), which is 10-fold more than in the general population. Coexistence of the two conditions is detrimental for patient's prognosis, as presence of one deteriorates prognosis of the other.

Heart failure (HF) and CKD share risk factors such as diabetes mellitus, hypertension, ischemic heart disease and elevated serum uric acid (SUA). A complex cascade of pathophysiological mechanisms triggered by exposure to risk factors results in failing heart and kidneys. Still, the mechanisms of the interplay between heart and kidneys are not fully understood. The evidence of how to best treat patients with combined heart and kidney dysfunction is scarce as kidney patients are underrepresented in randomized controlled trials (RCTs) of cardiovascular interventions. The real world patients differ from the ones included in RCTs and the results may not be generalizable. Data from well-designed observational studies can provide valuable evidence from subgroups not addressed in the RCTs.

In all studies, it is crucial to reduce the effect of external factors (confounding variables) that can obscure the real effect of the exposure. Propensity score matching is an increasingly used statistical method to correct for confounding in observational studies. We utilized this method to balance baseline characteristics between the study groups to ensure that they were comparable.

Using the Norwegian national registry of patients with chronic HF, we explored the factors in the heart-kidney interplay. We investigated the independent effect of diabetes mellitus and elevated uric acid on all-cause mortality of HF outpatients. Furthermore, we explored if the effect was modified by reduced kidney function and other factors. The effect of spironolactone on survival of HF outpatients with reduced renal function was scrutinized as its safety is uncertain due to risk of hyperkalemia and deteriorating renal function.

We found that initiation of spironolactone in HF patients with reduced renal function was associated with improved survival compared to patients not treated with spironolactone, despite increased potassium levels and worsened renal function.

Diabetes mellitus was not found to be an independent predictor of all-cause mortality in HF outpatients and the effect was not modified neither by renal function, left ventricular ejection fraction or etiology of HF. However, the HF treatment of diabetic patients optimized by cardiologists at HF clinics was intensified more than HF treatment of non- diabetics.

In the study of the role of SUA in HF outpatients, we found SUA in the highest quartile to be an independent predictor of all-cause mortality. Importantly, the effect was gender-specific, with predictive value in women only but not in men. Renal function did not influence the relationship between high SUA and survival of HF outpatients.

HF is complex syndrome and its treatment should be tailored to assure maximum effect and minimum adverse outcomes. Our study shows that propensity score matching is a reliable method that contributes with new knowledge on the factors in the heart-kidney interactions. Results from the present study may contribute to identify the subgroups of HF outpatients with special characteristics to personalize the treatment and maximize its benefit in order to improve the outcomes of these high risk patients.

List of Papers

Paper I **Spironolactone Treatment and Effect on Survival in Chronic Heart Failure Patients with Reduced Renal Function: A Propensity-Matched Study.**
Viera Stubnova, Ingrid Os, Morten Grundtvig, Dan Atar, Bård Waldum-Grevbo

Cardiorenal medicine 2017, 7(2):128-136

Paper II **Prevalent Diabetes Mellitus: Mortality and Management in Norwegian Heart Failure Outpatients**.
Viera Stubnova, Ingrid Os, Morten Grundtvig, Bård Waldum-Grevbo

Cardiology 2016, 134(4):413-422

Paper III **Gender differences in association between uric acid and all-cause mortality in patients with chronic heart failure.**
Viera Stubnova, Ingrid Os, Aud Hoieggen, Marit D. Solbu, Morten Grundtvig, Arne S. Westheim, Dan Atar, Bård Waldum-Grevbo
BMC cardiovascular disorders 2019, 19(1):4

1. Background

The awareness of a close relationship between kidney and heart disease has existed for decades. Kidney disease and cardiovascular disease share many of the same risk factors. Furthermore, patients with kidney disease are at high risk of cardiovascular events and likewise, patients with cardiovascular disease are at high risk of kidney disease. Still, the mechanisms of the interplay between the two organ systems are not fully known and the evidence of how to best treat patients with combined heart and kidney dysfunction are scarce.

In this study we have used the Norwegian national registry of outpatients with chronic heart failure to explore topics in the heart-kidney interplay using propensity score matching to correct for confounding variables.

1.1 Chronic heart failure

Human heart is an organ that pumps blood through the body to deliver oxygen and nutrients to the tissues and to remove the metabolic waste [1, 2]. In the settings of altered structure or function, it fails to deliver oxygen at a rate required to meet the body's needs, leading to symptoms of heart failure.

HF is a growing public health problem as it is an important cause of cardiovascular and renal morbidity and mortality, and deteriorating health-related quality of life [3]. Despite improvements in HF management, it is still the most common diagnosis of hospitalization of patients above 65 years of age [4] and the 5-year mortality is about 50 % [5]. Together with other cardiovascular diseases (CVD) it accounts for the largest part of health expenditures in high-income countries, posing a substantial burden on health-care systems [6].

The pathophysiology of HF is complex and it is increasingly being recognized as a systemic disease comprising hemodynamic changes, neurohumoral activation and systemic metabolic derangements [7].

1.1.1 Definition of heart failure

The 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF defined HF as a clinical syndrome characterized by typical symptoms (e.g.

breathlessness, ankle swelling, fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema), caused by a structural and/or functional cardiac abnormality and resulting in a reduced cardiac output and/or elevated intracardiac pressure at rest or during stress [8]. It is mainly a chronic condition disrupted by episodes with acute exacerbations [9, 10].

HF is classified into three categories based on left ventricular ejection fraction (LVEF) - HF with preserved LVEF (HFpEF), HF with reduced (HFrEF) or HF with LVEF in the mid-range (HFmrEF). Previously, the ESC and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for management of HF patients varied in definition of the three types but the current guidelines are more uniform [8, 11, 12]. The 2016 ESC guidelines define HF as HFpEF if LVEF ≥ 50% , HFrEF if LVEF < 40% and HFmEF if LVEF is 40 - 49% (Table 1). Categorization of HF patients into those with HFrEF and HFpEF is important because of distinct differences in demographic features, risk factors, treatment options and prognosis [13].

Table 1. Definition of heart failure with reduced, mid-range and preserved LVEF, modified from 2016 ESC guidelines [8]

		Criteria		
Tyoe of heart failure	HFrEF	LVEF < 40%	Symptoms* ± signs**	
	HFmrEF	LVEF 40-49%	Symptoms* ± signs**	Elevated natriuretic peptides and either structural heart disease or diastolic dysfunction
	HFpEF	LVEF ≥ 50%	Symptoms* ± signs**	Elevated natriuretic peptides and either structural heart disease or diastolic dysfunction

* breathlessness, ankle swelling, fatigue
** elevated jugular venous pressure, pulmonary crackles and peripheral oedema

New York Heart Association (NYHA) classification

Severity of HF symptoms has been traditionally graded using NYHA classification [14]. Patients are classified into four categories based on the severity of functional limitation during physical activity – no symptoms at ordinary physical activity (NYHA I), slight limitation at activity but comfortable at

rest (NYHA II), marked limitation at activity but comfortable at rest (NYHA III), and disability to carry on any physical activity without discomfort and symptoms at rest (NYHA IV). The classification is subjective and some claim it insufficiently discriminates between the levels of functional impairment [15]. However, the classification has provided an important prognostic information in HF survival risk prediction models [16, 17], and it is broadly used both in research and clinical practice. In Norwegian HF outpatients, higher NYHA class was independently associated both with declining kidney function [18] and risk of death [19]. The current guidelines for HF management use the NYHA classification for treatment recommendations [8, 12].

1.1.2 Etiology and risk factors of heart failure

The etiology is heterogenous and varies among world regions [20, 21]. Ischemic heart disease (IHD) is the most common cause of HF in Western high-income countries as well as Central and Eastern Europe [21-23]. Non-ischemic cardiomyopathies, mostly infectious, lead most commonly to HF in sub-Saharan Africa, Latin America and the Caribbean, and rheumatic heart disease is the main cause of HF in East Asia [21]. However, there is a gradual shift from communicable to non-communicable causes worldwide [21]. Coronary artery disease, diabetes mellitus, hypertension, obesity and smoking are the risk factors responsible for about half of incident HF [24]. In Norway, IHD and hypertension are reported to be the cause of HF in nearly 66 % of chronic HF patients [18].

There are important differences in risk factors also between patients with HFrEF and HFpEF. While HF patients with reduced LVEF are more likely to be younger, males and with a history of ischemic heart disease, those with preserved LVEF are more likely to be older, women, to have atrial fibrillation and antecedent hypertension [9, 25]. The prognosis of HFpEF patients was earlier believed to be superior to those with HFrEF [25], but is now recognized to be as poor as in HFrEF [3].

1.1.3 Prevalence, incidence and prognosis of heart failure

The prevalence of HF is increasing worldwide, most likely due to a combination of ageing population and improved survival from acute CVD and HF [3]. Currently, there are 26-38 million people living with HF [26, 27]. In high-income countries the overall prevalence is about 2 %, increasing from 1 %

in those 55-64 years of age to over 10% in persons over 85 years [9, 28]. HF prevalence is projected to increase by 46 % from 2012 to 2030 [29].

The estimates of global incidence are limited by studied population and diagnostic criteria used [30], but it is estimated to be between 100 and 900 cases per 100 000 person-years [13]. Incidence in the high-income countries has stabilized or even declined over the past decades [30-33], which is mainly due to improved primary prevention of cardiovascular diseases and treatment of IHD [34, 35].

It is well-recognized that HF patients have poor prognosis. The Framingham Heart Study revealed 5-year mortality rate to be as high as 70% in patients diagnosed with HF in 1950-ies to 1960-ies [33]. Twenty years ago, the 5-year survival rate after first HF hospitalization was worse than all cancer types except for lung cancer in men and lung and ovarian cancer in women, observed in a Scottish population-based study [36]. Treatment of HF has improved substantially since then [37-44] and as a result, mortality rate in HF patients has also declined [33, 45, 46]. A recent study from Northwestern Europe has reported that 5-year mortality rate among patients enrolled to HF clinics between 2006-2015 had declined to 26 % [47], while US data still report an unchanged mortality [31].

1.2 Chronic kidney disease

The kidneys regulate body composition, excretion of metabolic end products and foreign substances, as well as production and secretion of enzymes and hormones [48]. Heterogeneous disorders can affect the kidney structure and function and lead to variable degree of progression, with premature death and kidney failure as the most serious outcome.

Chronic kidney disease is a part of the rising global burden of non-communicable diseases as important risk factors for CKD such as hypertension, diabetes and obesity are increasing [49]. In addition to burden for society, CKD is associated with impaired quality of life, multiple adverse outcomes and strongly decreased life expectancy [49].

1.2.1 Definition of chronic kidney disease

CKD is defined as abnormalities of kidney structure or function present for more than three months [50]. In 2002, the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) classified CKD into five stages based on glomerular filtration rate (GFR) and evidence of kidney damage [51]. Since both kidney function and albuminuria independently affect prognosis of CKD patients, the classification was revised in 2012 by Kidney Disease: Improving Global Outcomes (KDIGO) Work Group on Evaluation and Management of Chronic Kidney Disease and the currently used system was introduced [50, 52]. The revised classification categorized kidney function into six categories G1-G5 based on GFR and kidney damage into three categories A1-A3 based on the degree of albuminuria (Table 2). The diagnosis of CKD is established in the presence of either decreased kidney function (GFR < 60 ml/min/1.73 m^2) or markers of kidney damage (albuminuria) or both.

Table 2. Classification of chronic kidney disease by GFR and albuminuria, modified from KDIGO 2012 guidelines [50]

GFR category (ml/min/1.73 m^2)				Albuminuria category ACR (mg/mmol)			
	G1	Normal or high	⩾90		A1	Normal to mildly increased	< 3
	G2	Mildly decreased	60-89				
	G3a	Mildly to moderately decreased	45-59		A2	Moderately increased	3–30
	G3b	Moderately to severely decreased	30-44				
	G4	Severely decreased	15-29		A3	Severely increased	> 30
	G5	Kidney failure	<15				

1.2.2 Epidemiology of chronic kidney disease

CKD prevalence varies between 7-12 % in the different world regions [53]. It is estimated to be highest in the low- and middle-income countries, about 10-16 % [54]. In Norway, the prevalence of CKD 1-5 was about 11.1 % in 2006-08 [55], which is consistent with the reports from other high-income countries [56]. In parallel to increasing prevalence of HF, the prevalence of CKD is also increasing worldwide due to aging population, growing number of individuals with hypertension

and diabetes [49, 57] and decreasing competing causes of death such as cardiovascular diseases and stroke [58]. As a consequence, CKD is projected to affect 16.7 % of US population in 2030 [59].

Hypertension and diabetes are the most common causes of CKD particularly in high-income and middle-income countries, while glomerulonephritis and unknown causes are more common in low-income countries [58]. About 30-40 % of patients with diabetes are reported to have CKD [53]. In Norway, hypertensive nephrosclerosis is the leading cause of kidney failure in patients at initiation of renal replacement treatment (RRT), closely followed by diabetes. One third of patients initiating RRT have either diabetes kidney disease or diabetes as comorbidity [60].

The global burden of CKD is substantial due to increased risk of multiple adverse outcomes such as kidney failure, cardiovascular disease, cognitive impairment, and death [57]. In 2013, CKD was reported to be the 19th leading cause of death in the world [61]. In 2030, it is projected to ascend to the 5th place [62]. Mortality increases with decreasing kidney function and is highest in patients on dialysis. Compared to general population, the life-expectancy of dialysis patients is one third [53].

1.3 Heart-kidney interactions

Heart failure and chronic kidney disease frequently coexist. It is estimated that about 30-63 % of patients with HF have concomitant CKD [63-66]. A Norwegian study of HF outpatients reported 45 % patients with HF to have eGFR < 60 ml/min/1.73 m^2 [18], 10-fold more compared to about 4.7 % in general population in Norway (Table 3) [67].

Table 3. Prevalence of kidney disease in general population and HF outpatients in Norway

		Prevalence in Norwegian general population [67]	Prevalence among Norwegian HF outpatients [18]
eGFR category ml/min/1.73m^2	≥ 90	56.7 %	12.5 %
	60-89	38.2 %	42.6 %
	30-59	4.5 %	39.3 %
	15-29	0.16 %	5.5 %
	< 15	not known	

Both HF and CKD have poor prognosis and the concomitance of the two conditions is associated with even higher mortality and morbidity [66, 68, 69].

Kidney dysfunction has been consistently found to be associated with cardiovascular (CV) and all-cause mortality in high risk populations such as patients with diabetes mellitus, myocardial infarction, coronary artery interventions and heart valve surgery [70]. In HF patients, markers of renal function were found to be strong and independent predictors of mortality both in chronic HF [71, 72] and acute decompensated HF [73, 74].

Prevalence of cardiovascular disease (CVD) in CKD increases with decreasing kidney function [75-77]. The atherosclerotic process starts already in early CKD stages (CKD G1-G2) and inflammation and media calcification contribute to CVD as CKD progresses to later stages [53]. As CKD reaches the end stage renal disease (GFR < 15 ml/min/1.73 m^2), coronary heart disease and HF are present in 29 % and 19 % of Norwegian patients at initiation of renal replacement therapy (RRT) [60].

Similarly to kidney function being an independent predictor of poor outcome in CV patients, prevalent CVD is a strong independent predictor of outcome in CKD patients and may account for over 50 % of deaths in CKD patients [65]. Patients with CKD have 10- to 20-fold higher risk of cardiac death than age- and sex- matched cohorts. Although RRT (dialysis or kidney transplantation) is the most visible outcome of patients with CKD, patients with CKD are more likely to die from CVD than to progress to end-stage renal disease [78, 79].

The interplay between heart and kidneys is complex, more complex than earlier thought. An exposure to risk factors triggers a cascade of intricate pathophysiological pathways serving to preserve function of the affected organ but ultimately resulting in a vicious circle of damage to heart and kidneys. Hemodynamic changes, activation of sympathetic nervous system, activation of renin-angiotensin-aldosterone system (RAAS), activation of nitric oxide (NO) system, formation of reactive oxygen species, inflammation and other processes are involved [80].

The coexistence of a combined heart and kidney failure has been recognized as early as 1951 [81], but only later it was proposed that dysfunction in one organ may induce dysfunction in the other [82]. A clinical classification of cardiorenal syndromes based on primary organ dysfunction and time

course was introduced in 2008 [83]. Recently, a single cardiorenal syndrome was proposed, identifying fibrosis as the primary driver of pathogenesis [84].

1.3.1 Cardiorenal and renocardiac syndromes

In 2008, Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) proposed five distinct subtypes of cardiorenal syndromes (CRS) [83, 85]. The classification recognized the primary organ dysfunction by dividing the syndromes into cardiorenal (CRS type 1 and 2) and renocardiac (CRS type 3 and 4) and the clinical settings by dividing the syndromes into acute (CRS type 1 and 3) and chronic (CRS type 2 and 4). CRS type 5 is characterized by involvement of both heart and kidneys as a result of a systemic disease (Table 4).

Table 4. The subtypes of cardiorenal syndromes, modified from ADQI [83]

CRS type	Type 1	acute cardiorenal	Abrupt worsening of cardiac function leading to acute kidney injury
	Type 2	chronic cardiorenal	Chronic abnormalities in cardiac function causing progressive and permanent chronic kidney disease
	Type 3	acute renocardiac	Abrupt worsening of renal function causing acute cardiac dysfunction
	Type 4	chronic renocardiac	Chronic kidney disease resulting in decreased or worsening cardiac function
	Type 5	secondary	Systemic condition causing both cardiac and renal dysfunction

Cardiorenal syndromes type 1 and 3 are characterized by acute onset of organ dysfunction.

CRS type 1, an acute cardiorenal syndrome, is defined as abrupt worsening of cardiac function leading to acute kidney injury (AKI). Acute decompensated HF is usually triggered by ischemic heart disease such as acute coronary syndrome or non-ischemic heart disease such as pulmonary embolism or valve disease [80].

CRS type 3, acute renocardiac syndrome, is characterized by acute kidney injury precipitating acute cardiac injury [80]. AKI can result in fluid overload, electrolyte disturbances or metabolic acidosis which can lead to congestive HF, arrhythmias and impaired cardiac contractility.

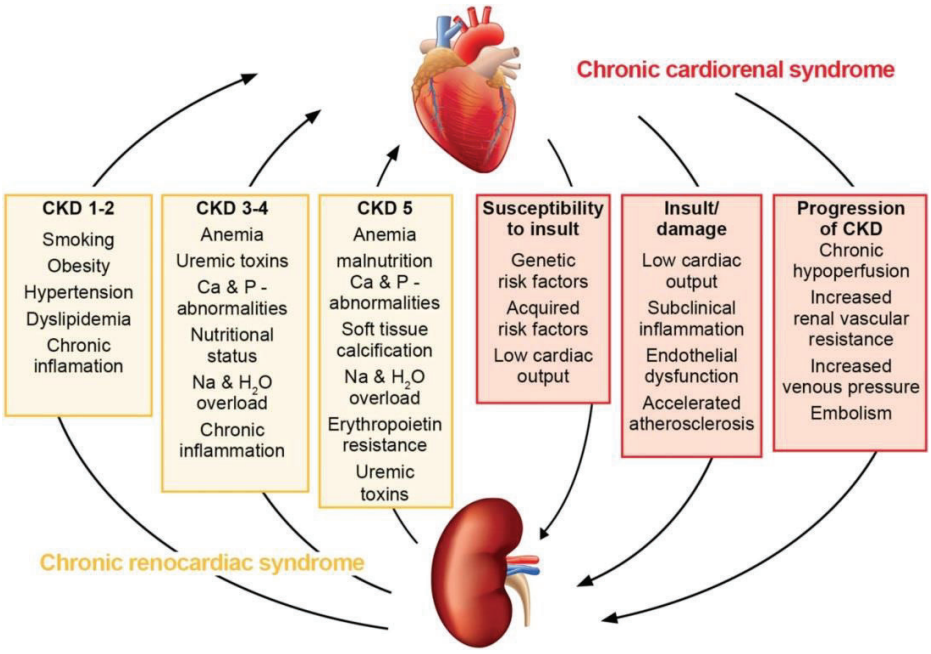
Chronic heart failure and chronic kidney disease

In cardiorenal syndromes type 2 and 4, chronic HF or CKD results in a gradual development of dysfunction in the other organ (Figure 1). However, distinguishing CRS type 2 from 4 may be challenging as primary organ dysfunction may be unclear. The chronological relationship between CVD and CKD as well as identification of causal relationship between the two is important to make a correct diagnosis.

CRS type 2, a chronic cardiorenal syndrome, is characterized by chronic abnormalities in cardiac function leading to progressive and permanent chronic kidney disease [85]. Chronic HF causally precedes the onset or progression of CKD.

CRS type 4, a chronic renocardiac syndrome, is defined as CKD leading to decreased or worsening cardiac function. The greatly increased risk for CVD in CKD patients is due to traditional cardiovascular risk factors such as diabetes, hypertension, obesity, smoking and dyslipidemia, as well as nontraditional, CKD-related risk factors such as hyperphosphatemia, anemia, volume overload and dialysis-related risk factors [77, 86].

Figure 1. Pathophysiology of chronic cardiorenal syndrome and chronic renocardiac syndrome



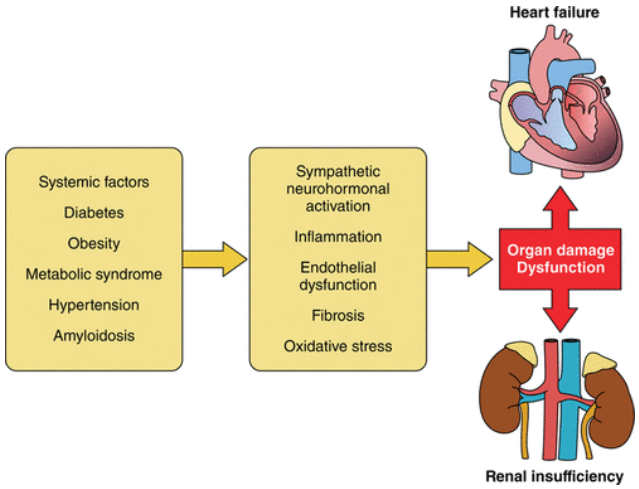
Ronco C, Adv Chronic Kidney Dis. 2018;25(5):382-390. Published with permission.

1.3.2 Common pathophysiological features in heart and kidneys

The current classification of cardiorenal syndromes is based on clinical presentation. It may often be difficult to determine the initial organ that was damaged and to distinguish CRS type 2 and 4. Also, in some patients an acute CRS type 1 might have preceded development of the chronic CRS [80].

CKD and HF share the same risk factors such as diabetes mellitus, hypertension, atherosclerosis, obesity and systemic diseases amyloidosis, vasculitis and others and share also the subsequent pathophysiological pathway. A novel approach by Zannad and Rossignol [84] encourages to move from the current classification of cardiorenal syndromes based on clinical presentation towards a model of a single cardiorenal syndrome reflecting the common pathophysiological pathways, identifying fibrosis as the primary driver of pathophysiology of CRS. Exposure to risk factors triggers a cascade of complex neurohormonal, inflammatory, immunologic and fibrotic pathophysiological processes that are common for both heart and kidneys but affect the two organs in various degree (Figure 2). The consequence is endothelial dysfunction and fibrosis which can affect heart in terms of diastolic dysfunction, HFrEF, HFpEF and ventricular hypertrophy and kidneys in terms of acute kidney injury or chronic kidney disease [66, 84]. The primary source of insult may often be difficult to decide.

Figure 2. Concept of a single cardiorenal syndrome. Concomitant heart and kidney damage result from common pathophysiological pathways triggered by systemic diseases.



Zannad and Rossignol, Circulation 2018;138:929–944.Published with permission.

1.4 Paper-specific topics in kidney-heart interactions

HF is a syndrome with frequent coexistence of other chronic diseases and conditions such as hypertension, CKD, diabetes mellitus, chronic lung disease, arthritis, anemia and hyperuricaemia. The co-existence has impact on outcome and may require modification of HF treatment and patient follow-up [12]. As most RCTs in HF do not enroll patients with multiple comorbidities, the recommendations cannot be generalized to real-world patients. In such cases, observational studies provide valuable evidence which cannot be obtained in RCTs, and RCTs and observational studies complement each other.

1.4.1 Treatment of heart failure in patients with CKD

The objective of HF treatment is to improve clinical status, functional capacity and quality of life and to prevent HF hospitalizations and reduce mortality. While HFrEF therapy is well-documented, there is a lack of evidence-based therapy for HFpEF. To reduce the risk of HF hospitalization and mortality, the current guidelines recommend use of angiotensin-converting enzyme inhibitors (ACEi) and β-blocker in all HFrEF patients unless contraindicated or not tolerated, and an addition of mineralocorticoid receptor blocker (MRA) in all symptomatic HFrEF patients despite treatment with ACEi and β-blocker. Diuretics are recommended to reduce the symptoms of congestion [8]. The recent years, new therapeutical agents angiotensin receptor neprilysin inhibitors (ARNI) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors have proved beneficial outcomes. Consequently, ARNI is now recommended in appropriate patients with HFrEF [8]. SGLT2i may prevent HF in patients with diabetes and ongoing trials may illuminate their role in the HF treatment in patients with and without diabetes mellitus, in both HFpEF and HFrEF [87].

However, several drugs used for HF treatment may have detrimental effect on kidney function. Associations between the use of ACEis, angiotensin receptor blockers (ARBs) and MRAs and the risk of hyperkalemia, worsening renal function (WRF) and acute kidney injury are well-documented [88-90]. As several studies have demonstrated an association between WRF and increased mortality in HF patients [72, 91] patients with kidney disease are less likely to receive recommended HF therapy [92]. However, there is evidence that WRF caused by recommended HF treatment may not lead to impaired outcome if patient's clinical status improves or stays equal [93-95]. It is thus

recommended in both acute and chronic HF that some increase in serum creatinine may be acceptable as long as the overall clinical status is improved or stable [96].

The HF treatment should be tailored for maximal benefit among appropriate patients and minimized in patients at risk for adverse events. Still, despite the great prevalence of CKD in HF patients [18], there's a lack of evidence-based treatment in CKD patients as they have been mainly excluded from the randomized clinical trials of cardiovascular interventions [97]. As a result, the current guidelines are mostly based on trials where kidney patients were grossly underrepresented. Although there is increased focus on inclusion of CKD patients in randomized clinical trials of novel therapies, it is unlikely that RCTS would be conducted to definitely resolve the role of already established HF treatment in kidney patients. Well-designed epidemiological studies are thus necessary to bring evidence on treatment efficacy in patient groups not thoroughly studied in RCTs, such as CKD patients.

1.4.2 Diabetes mellitus in heart failure and kidney disease

Diabetes is an important global health problem with increasing prevalence worldwide. The life expectancy of diabetic patients has increased but as a consequence, the rate of chronic diabetic complications is expected to increase as well. Diabetes is a well-recognized risk factor for development of HF [22, 98-100] and is the most common cause of CKD worldwide [101]. Diabetes is indeed highly prevalent in HF, affecting about 20 - 25% of patients [102, 103]. In Norway, about one in five HF outpatients [18] and one in three patients initiating renal replacement therapy [60] has prevalent diabetes.

Already 40 years ago, the Framingham study showed that women and men with diabetes had a 5- and 2-fold increased risk of developing HF than those without diabetes [104]. Comorbidities like hypertension and coronary artery disease have been commonly used to explain the increased risk of HF, but diabetes cardiomyopathy with altered myocardial metabolism and fibrosis has also been proposed [105, 106].

The coexistence of HF and diabetes is associated with poor prognosis and HF patients with diabetes experience increased risk of CV and all-cause mortality compared to those without diabetes [107-109]. Intensive glycemic control in patients with diabetes has not been shown to improve macrovascular outcomes [110]. Whether diabetes is an independent predictor of mortality in

patients with chronic HF or if it reflects a higher burden of comorbid conditions leading to impaired prognosis remains to be clarified. Furthermore, data are inconsistent concerning if diabetes could be an independent predictor of survival in specific subgroups of HF patients.

Diabetes is a common risk factor for both HF and CKD and the triade of these conditions frequently coexists. Complex pathophysiologic pathways result in a vicious circle where each condition can enhance progression of the other two [111]. Whether the prognostic effect of diabetes in HF patients is dependent on renal function is to our knowledge not decided. Ischemic heart disease is a more frequent cause of HF in patients with diabetes that in those without [112]. A differential impact of diabetes on mortality has been described; diabetes and ischemic heart disease may interact to accelerate the progression of myocardial dysfunction, but the data are inconsistent [112-114]. Furthermore, diabetes has primarily been reported to be a predictor of inferior survival in HFrEF patients [108, 115]. It is less clear if the impact of diabetes on HF prognosis differs depending on LVEF [109].

The current guidelines on HF management [8, 12] do not provide a specific recommendation for HF treatment of patients with diabetes. The evidence for pharmacological HF treatment of diabetic patients origins from either subgroup analyses of RCTs of HF interventions or subgroup analyses of HF patients from CV outcome trials of glucose lowering agents [116]. It is not clear how HF patients with concomitant diabetes respond to HF therapy. While diabetic patients with stable HF are reported to show similar response to HF treatment as patients without diabetes, those hospitalized with acute decompensated HF were found to have higher risk of adverse outcome and more side effects than patients without diabetes [107].

Treatment of the high risk HF patients with concomitant diabetes and CKD may be challenging. However, there are encouraging emerging data on cardiovascular and renal benefits of novel glucose-lowering drugs, SGLT-2 inhibitors. These drugs have been shown to have effects beyond glucose lowering and to reduce CV and all-cause mortality, hospitalization for HF as well as progression of albuminuria and decline of kidney function [117].

1.4.3 Uric acid in heart failure and kidney disease

Following the discovery that uric acid (UA) caused gout, UA was suspected to have a causal role in development of variety of cardiovascular diseases and renal disease [118, 119]. UA was overlooked

for decades, but the interest in it gained a revival in 50-ies and 60-ies [120, 121]. Since then, numerous studies have reported association between uric acid and CVD [122-126], hypertension [118], and chronic kidney disease [127, 128].

Uric acid is the final breakdown product of purine metabolism in humans. Endogenous and exogenous purines are degraded to hypoxanthine and further to xanthine and uric acid, a process catalyzed by xanthine oxidase (XO). Unlike majority of animals, humans are not able to degrade uric acid further to allantoin and the entire elimination occurs in the kidneys and gut. The kidneys eliminate approximately 70 % of the UA load and the remaining 30 % is eliminated by gastrointestinal tract. The handling of UA by kidneys is complex and consists of nearly free filtration by the glomeruli, followed by reabsorption, secretion and postsecretory reabsorption predominantly in the proximal tubuli [129, 130].

Uric acid is an important antioxidant but at the same time, it is linked to endothelial dysfunction, oxidative stress, decreased NO bioavailability, increased inflammation and cell apoptosis [131]. Elevated SUA is a consequence of either increased production or decreased elimination. There are several factors that influence SUA metabolism such as gender, age, race, medication, food intake, comorbidities and genetic variations [132]. In heart failure, elevated SUA may result from both increased production and decreased elimination. Increased tissue turnover, tissue hypoxia, catabolism and insulin resistance lead to accumulation of purine precursors and increased SUA production, in addition to direct XO activation by inflammatory cytokines and free oxygen radicals [7, 133]. CKD that occurs in almost half of HF patients [18] accounts for decreased renal elimination of SUA [134].

High SUA has been found to be associated with incident HF [135-138], but also with disease severity and poor prognosis in chronic HF [139-142], acute and decompensated HF [143-145]. Furthermore, association between SUA and functional measures of HF (such as LVEF, left ventricular stroke volume and cardiac output, cardiac remodeling, endothelium dysfunction and BNP levels) has also been recognized [146]. Yet the role of SUA as an independent causative factor or only a surrogate marker for established HF is still being discussed.

Gender differences in CV diseases and outcomes are well-documented [147]. In HF patients, women and men differ with concern to etiology, LVEF and prognosis of HF. Women with HF are more likely

to have a history of hypertension, preserved LVEF and better prognosis than men with HF [102, 148-150]. There are gender differences also with respect to SUA – premenopausal women have lower level of SUA compared to men, but with increasing age, the SUA level is rising [151, 152].

Despite that gender and renal function influence the SUA level, their role in the relationship between SUA and survival of HF patients is not yet clearly determined.

1.5 Errors in epidemiological studies

In the hierarchy of the research design, randomized controlled trials are considered to provide the highest level of scientific clinical evidence. Study design of RCTs grants inclusion of individuals with balanced baseline variables and breaks the link between clinician's choice and patient's outcome [153]. However, in many cases, RCTs are impossible, inappropriate, inadequate or unnecessary [154]. The complexity of heart-kidney interactions and diversity of cardiorenal patients make it difficult to design a RCT that would reflect all the relationships and that would be representative of real-world patients. In such settings, carefully designed observational studies can grant valuable information which is not possible to obtain in RCTs.

A goal of each epidemiologic study is to obtain an accurate result that reflects a true effect of an exposure on outcome. However, the result can be afflicted by errors – random and systematic [155]. Observational studies are particularly susceptible to errors that need to be considered and prevented.

1.5.1 Random error

Random error is an error by chance, unpredictable and not possible to replicate. It affects reproducibility of a study. It is always present in a measurement but it can be reduced by increasing the study size and theoretically completely erased in an infinitely large study population [155].

1.5.2 Systematic errors

Systematic error, also called a bias, is a constant error that occurs in the study design or in the conduction of the study [156]. It consistently leads to an overestimation or underestimation of the result and affects validity of a study. Systematic error is not affected by sample size. There are three main types of systematic errors – selection bias, information bias and confounding.

Selection bias

Selection bias occurs when there are systematic differences between characteristics of individuals selected for the study and those who are not. They result from factors affecting choice of subjects in the study population or study participation and may be introduced by study participants self or by investigator. Selection bias leads to differences between the comparison groups. For instance, individuals in prospective cohort groups lost to follow-up may differ from those remaining in the study if they do not have the same probability of outcome [156].

Information bias

Information bias occurs during data collection. It arises when data are misclassified and study individuals are placed into a wrong category, called a *misclassification bias*. Misclassification can be nondifferential, affecting the cases and controls identically, or differential, when those with and without disease differ in the occurrence of the exposure [156]. For instance, diseased study participants may have a different recall of an exposure than healthy controls, introducing a *recall bias*. Information bias can also be introduced by interviewer by clarifying or emphasizing certain words differently to cases and controls (*interviewer bias*) or by observer whose assessment of the outcome is influenced by knowledge about the exposure (*observer bias*).

Confounding

Confounding, confusion of the effects, occurs when effect of the exposure (risk factor) is mixed with the effect of another variable, leading to a bias [155]. Confounding variable is defined as a variable associated with the exposure (but not being an effect of the exposure) and causally related to the outcome (Figure 3) [157].

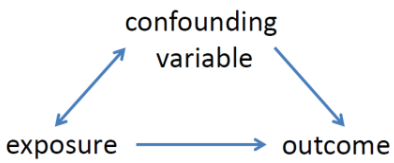


Figure 3. Relationship between risk factor, confounding variable and outcome, modified from Katz [157]

Confounding can be addressed at two stages – when deciding the study design and during data analysis.

During study design, confounding can be prevented, or at least reduced, by randomization, restriction or matching (Figure 4) [155, 158, 159]. Randomization is used in RCTs. Here, a random assignment to an experimental group or to control group also randomly spreads the known and unknown confounders between the exposed and unexposed group. The likelihood that the observed relationship between exposure and outcome is biased by the presence of confounding factors is thus reduced. Another method in preventing confounding during study design is restriction. Using this method, only individuals with the same value of the confounding variable would be selected. Such method is effective, but generalizability of the results and recruitment would be challenging. The third method to prevent confounding is matching on the presence of confounding variables. Exposed subjects with confounding variables are matched to the unexposed ones with same confounding factors. This method, however, has the same limitations as restriction.

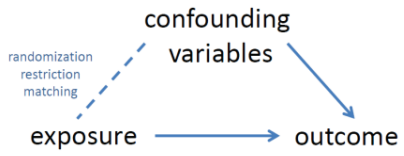


Figure 4. Reducing confounding during study design, modified from Katz [157]

During data analysis, confounding can be addressed by stratification or regression (Figure 5). Using stratification, the study population is divided into strata according to levels of the confounding variable in which the variable does not vary or varies only a little. The effect of the exposure on outcome is then measured in each stratum. Stratification is an effective method to adjust for confounding but it is not practical in the presence of multiple confounding variables. Multivariate regression analysis is a preferable method in such case as it can deal simultaneously with many confounding variables.

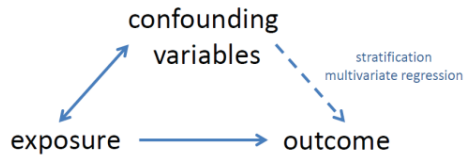


Figure 5. Reducing confounding during study analysis, modified from Winkelmayer [160]

Unlike RCTs, risk factors in observational studies are usually distributed unequally between the compared groups. Direct comparison of outcome in the groups is not possible as factors potentially related to the study outcome can be distributed unequally and the real effect of an exposure can be blurred. In observational studies, confounding has been traditionally addressed by multivariable regression analysis, but in 1983, a novel model to control for confounding was introduced by Rosenbaum and Rubin, called propensity score [161]. Propensity score is defined as the probability of receiving a certain treatment (exposure) based on measured covariates [162]. The purpose of propensity score is to improve the balance of potential confounders between the exposed and unexposed group so that the groups have the same distribution and are thus comparable. While multivariable analyses control for the association between confounding variable and outcome, propensity score model controls for the association between confounding variable and exposure (Figure 6). [163].

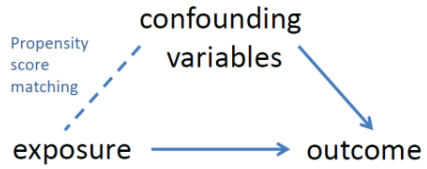


Figure 6. Reducing confounding by propensity score matching, modified from Barnieh [163]

Both methods share the ability to control confounding, but propensity score may have some advantages. The major advantage is that methods based on propensity score allow the investigator to clearly separate the design stage of the study from the analysis stage as confounding is addressed already in the design phase. In multivariable regression models, confounding is addressed during data analysis, in the same stage as estimation of the effect [164]. Also, conventional regression models require sufficient number of outcome events (approximately 10 outcome events per covariate) to avoid over-fitting. If the outcome is rare or the sample size small, this would require selection of only a limited number of covariates [165]. Propensity score summarizes a large number of measured covariates into one score and thus the methods using propensity score omit over-fitting.

2. Aims of the study

The overall aim of the study was to investigate the independent effect of factors involved in the heart-kidney interplay on survival in a Norwegian cohort of outpatients with chronic heart failure using propensity score matching to correct for confounding. The specific research aims were:

1. To investigate the independent effect of spironolactone on all-cause mortality in chronic HF patients with reduced renal function.
2. To investigate the independent effect of prevalent diabetes mellitus on all-cause mortality in Norwegian HF outpatients.
    - To assess if the effect of diabetes on all-cause mortality is modified by renal function, left ventricle function or the ischemic etiology of HF.
    - To evaluate if HF treatment differed in diabetic versus non-diabetic patients and if this could explain the differences in mortality.
3. To investigate the independent effect of high uric acid on all-cause mortality in Norwegian HF outpatients.
    - To assess if the effect of uric acid on all-cause mortality is modified by renal function or gender.

3. Materials and methods

3.1 Study design and population

The current study was a prospective, longitudinal cohort study. The studied population was a cohort of patients from the Norwegian Heart Failure Registry.

3.1.1 The Norwegian Heart Failure Registry

The Norwegian Heart Failure Registry was established in 2000 with the objective to monitor treatment of patients with chronic heart failure [19]. All patients attending heart failure clinics at Norwegian hospitals were recruited to the Registry. The HF clinics were run by cardiologists and specialized nurses after being diagnosed with chronic heart failure of any etiology following the guidelines of the ESC [10, 11]. There were three visits recorded in the Registry. At the first visit (baseline), the medical personnel recorded the relevant medical history, physical examination, echocardiography, NYHA functional class, laboratory results, and the medical management of HF. The last adjustment visit (visit 2) was recorded at stable follow-up, after the treatment had been optimized and the patient had participated in an educational program. The third visit was arranged six months after the last adjustment visit and patient's health condition, medication and laboratory results were reassessed. In April 2012 the Registry gained a status of national registry and was incorporated into the Norwegian Cardiovascular Disease Registry. Our study included 6702 patients recruited by 25 heart failure clinics between October 2000 and February 2012 (Figure 7). The reporting clinics were well distributed in all regions of Norway with a catchment area about half of Norway's population. The participants provided written consent prior to inclusion in the Registry. Mortality data are retrieved yearly from Statistics Norway.

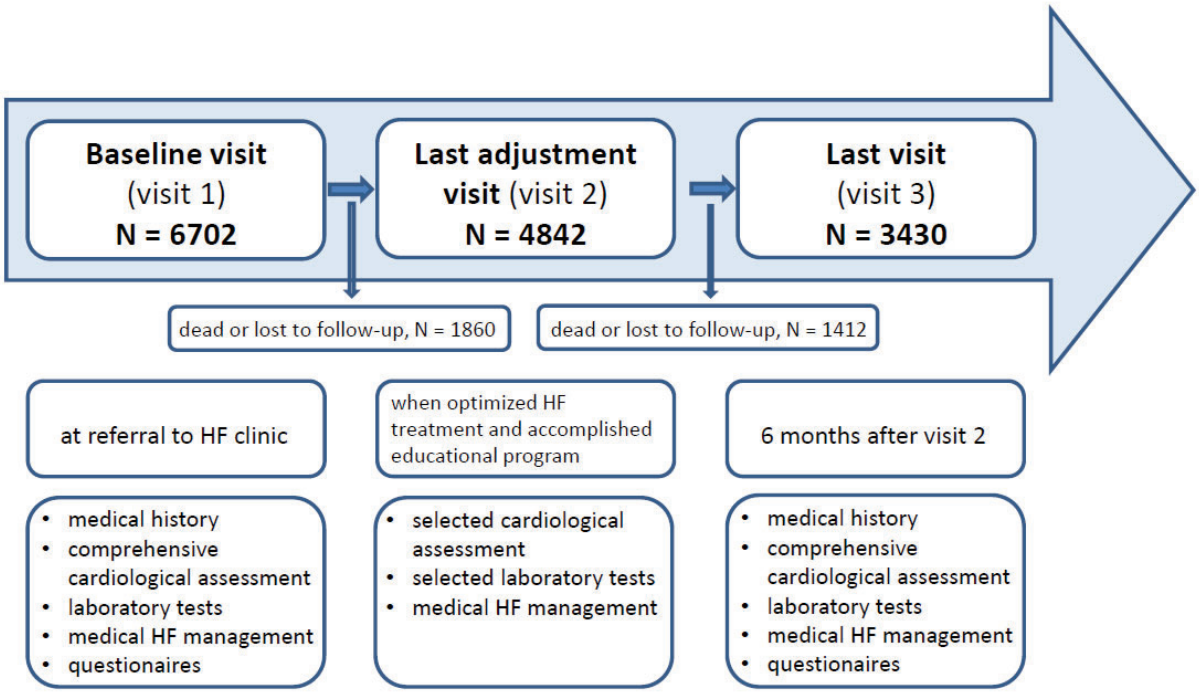


Figure 7. Norwegian Heart Failure Registry, outpatient visits October 2000 - February 2012

3.1.2 Study population in papers 1-3

Paper 1

Patients with eGFR < 60 ml/min/m^2 were eligible for the study of the effect of spironolactone treatment on survival of heart failure outpatients with reduced renal function. Patients who did not use spironolactone at the first visit and attended more than one visit to HF clinic were included in the study if data on spironolactone treatment at the last attended visit were available. Patients that were started on spironolactone at HF clinic were propensity score matched 1:1 with patients not started on spironolactone based on 16 baseline variables. Propensity score matching identified 170 well-matched pairs (Figure 8).

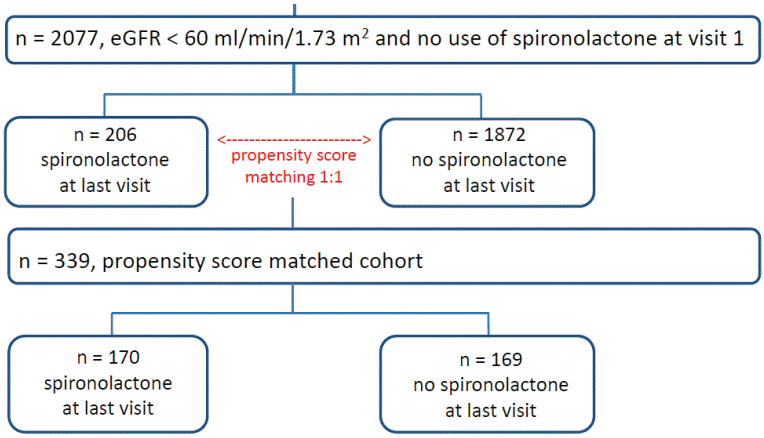


Figure 8. Flow diagram of inclusion into spironolactone study

Paper 2

In the study of the effect of diabetes mellitus on all-cause mortality of heart failure outpatients we included the individuals with available data on diagnosis of diabetes mellitus at the time of the first, baseline visit. The diagnosis was recorded on the basis of previous medical records or self-reported health condition. Patients with diabetes mellitus were then propensity score matched 1:1 with patients without diabetes based on 21 measured baseline variables. A total of 724 well-matched pairs were identified and available for survival analyses (Figure 9). To answer the study question concerning the differences in optimized HF treatment in diabetic and non-diabetic patients, we included the individuals from the propensity matched cohort with at least 2 registered visits (optimized HF treatment).

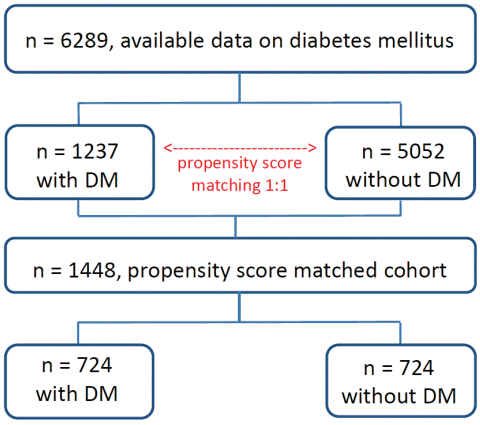


Figure 9. Flow diagram of inclusion into diabetes study

Paper 3

Individuals with valid information on SUA at baseline visit were eligible for this study of the effect of SUA on all-cause mortality of HF outpatients. We grouped the individuals into gender-specific quartiles by hospital as the participating hospitals used different assays for SUA analysis. After excluding the individuals from hospitals with small number of reported individuals, we merged patients in each SUA quartile across the gender and hospitals, achieving four groups with about 1180 patients in each quartile. Consequently, patients in the highest SUA quartile were propensity score matched 1:1 with patients in the lowest three quartiles based on 16 baseline variables. Individuals in SUA in quartile 1-3 were all selected as potential controls as their survival curves were nearly superimposable. The final, propensity score matched cohort consisted of 1856 individuals (Figure 10).

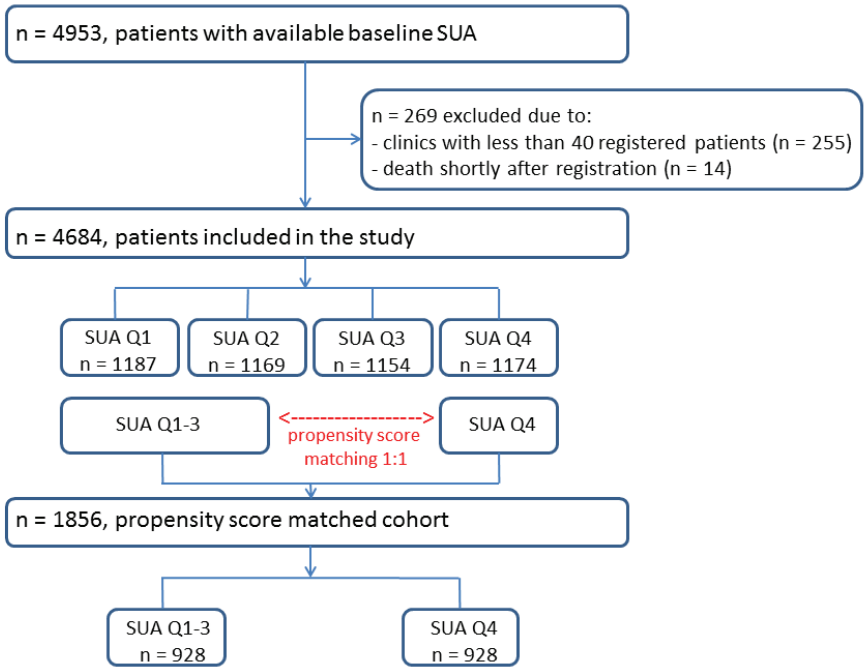


Figure 10. Flow diagram of inclusion into uric acid study

3.2 Definitions

3.2.1 Renal function

Renal function was expressed as estimated glomerular filtration rate (eGFR) and calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [166]:

eGFR = 141 × min(Scr/κ,1) α × max(Scr/κ,1) –1.209 × 0.993 Age × (1.018, if female) × (1.159, if black),

where Scr is serum creatinine (mg/dl), κ is 0.7 for females and 0.9 for males and α is –0.329 for females and –0.411 for males.

Reduced renal function was defined as eGFR< 60 ml/min/1.73m^2.

3.2.2 Heart failure severity

The Norwegian Heart Failure Registry used NYHA functional classification to categorize HF severity. HF symptoms were graded into 4 classes based on symptoms and exercise capacity. NYHA class I was characterized by presence of cardiac disease but without limitation of physical activity. NYHA class II was defined as slight limitation of physical activity: comfortable at rest but ordinary physical activity resulted in fatigue, palpitation or dyspnea. NYHA class III was described as marked limitation of physical activity: comfortable at rest but less than ordinary activity resulted in symptoms. Patients with NYHA class IV were unable to carry out any physical activity without discomfort and had symptoms of heart failure were present even at rest.

3.2.3 Left ventricular ejection fraction

In paper 1 and 2, LVEF was defined as reduced at ≤ 35% and as preserved at ≥ 50%, based on 2012 ESC Guidelines on HF [11]. In paper 3, we used 2016 ESC Guidelines on HF [8] and defined LVEF as reduced at < 40% and as preserved at ≥50%.

3.2.4 Daily drug doses

Daily doses of ACEi were converted to enalapril equivalent doses (enalapril 20 mg = lisinopril 20 mg = ramipril 10 mg = captopril 100 mg), and then expressed as percent of enalapril target dose. Target dose of enalapril was defined as 20 mg per day.

Daily doses of loop diuretics were converted to furosemide equivalent doses (furosemide 40 mg = bumetanide 1 mg).

Daily doses of β-blockers were converted to metoprolol equivalent doses (metoprolol 200 mg = bisoprolol 10 mg = carvedilol 50 mg= atenolol 100 mg).

3.2.5 Other definitions

The diagnosis of diabetes mellitus was recorded on the basis of medical records and the self-reported health status at baseline visit.

Diagnosis of hypertension was based on information on antihypertensive treatment at baseline visit.

3.3 Statistical methods

All analyses were performed using IBM SPSS statistical software (IBM SPSS Statistics, New York, N.Y., USA, versions 20, 22 and 25). Propensity score matching in paper 2 was performed using the IBM software SPSS R plug-in v2.12.1, while propensity score matching in papers 1 and 3 was performed using IBM SPSS statistical software versions 22 and 25. Kaplan Meier survival curves were obtained using STATA/SE (StataCorp LP, Texas, USA).

3.3.1 General statistics

Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies (percentage). Normality of distribution was assessed by visual inspection of the histogram, Q-Q plots and by Kolmogorov-Smirnov test of normality.

Student t-test was used when comparing continuous variables in two patient groups and analysis of variance (ANOVA) when comparing continuous variables in several groups of patients (paper 3).

Similarly, χ^2 test was used when comparing the categorical variables, irrespective of number of groups to be compared.

In paper 2 we analyzed changes in HF treatment and in paper 1 the changes in eGFR and serum potassium from the first to the last visit. Paired Student t-test was used when comparing the changes in continuous variables and McNemar test was used when comparing the changes in the categorical variables within each group. To compare the changes between the two groups we used Student t-test for continuous variables and the χ^2 test for categorical variables.

Kaplan-Meier survival curves and log rank statistics were used to investigate differences in survival between the various categories of HF outpatients.

Univariate Cox regression model was utilized to calculate hazard ratio (HR) for the studied condition (e.g. diabetes mellitus, spironolactone treatment and SUA in the highest quartile) on all-cause mortality in HF outpatients in the propensity score matched cohort. In paper 3, multivariate Cox regression model was utilized to calculate HR for SUA in the highest quartile in the gender stratified analyses. Death from any cause was defined as the endpoint. Observational time was the time from the first visit until death or until the end of the study (2-year follow-up in paper 1 and 5-year follow-up in papers 2 and 3).

The two-tailed significance level test was set to p-value < 0.05.

3.3.2 Propensity score matching

Propensity score matching is an alternative way to deal with confounding, imitating some characteristics of randomized control trials. Using a multivariate logistic regression model, an individual propensity score is calculated for each individual, identifying a likelihood of being in the group of interest.

In our study, baseline variables found to be associated with the studied condition (p-value < 0.20) as well as variables expected to confound the relationship between the studied condition and all-cause mortality were entered as independent variables in the multivariate logistic model.

In paper 1, propensity score of being treated with spironolactone was acquired on the basis of 16 baseline variables. In paper 2, propensity score of having diabetes mellitus was based on 21

baseline variables and in paper 3, propensity score for SUA in the highest quartile was obtained on the basis of 16 baseline variables.

Based on the propensity score, individuals in the group of interest (presence of diabetes mellitus, initiation of spironolactone treatment, SUA in the highest quartile) were matched 1:1 with patients in the control group (no diabetes, no spironolactone treatment, SUA in the quartile 1-3) providing the final study cohort. The matching was performed in the randomized case order with priority to exact match.

4. Summary of results

4.1 Paper I: Spironolactone Treatment and Effect on Survival in Chronic Heart Failure Patients with Reduced Renal Function: A Propensity-Matched Study.

The current study investigated the effect of spironolactone on all-cause mortality in chronic HF patients with reduced renal function, using propensity score matching to reduce the effect of confounding. A total of 206 patients, about 10 % of the HF outpatients with reduced renal function (mean eGFR 43.7 ± 11.6 mL/min/1.73 m^2) and no prior use of spironolactone, were prescribed spironolactone at HF clinic. Propensity score of being started on spironolactone was calculated on the basis of 16 predefined baseline variables and then used to match 170 patients started on spironolactone at HF clinic with 169 individuals not started on spironolactone. The baseline characteristics were well-balanced between the two propensity matched groups and no statistically significant differences were revealed between the two groups.

Use of spironolactone was independently associated with improved 2-year survival (hazard ratio (HR) 0.59, 95% confidence interval (CI) 0.37–0.92, p-value 0.020). Initiation of spironolactone was associated with statistically significant deterioration of eGFR by –4.12 ± 12.2 ml/min/1.73 m^2 and increase in serum potassium by 0.31 ± 0.55 mmol/L compared to no significant change in the other group.

We found that HF outpatients with moderately reduced renal function had a beneficial effect of spironolactone on 2-year survival despite reduction in eGFR and increase of serum potassium after initiation of the treatment.

4.2 Paper II: Prevalent Diabetes Mellitus: Mortality and Management in Norwegian Heart Failure Outpatients.

In this study of diabetes mellitus in HF outpatients, 1237 patients out of 6289 patients (about 20 % eligible patients) were identified to have diabetes. The final study population comprised 724 pairs of diabetic and non-diabetic HF patients matched 1:1 by propensity score for having diabetes. The propensity score was estimated based on 21 measured baseline variables and the final cohort was well-balanced.

We did not find prevalent diabetes mellitus to be an independent predictor of 5-year all-cause mortality in a cohort of chronic HF patients followed by cardiologists at HF clinics (HR 1.04, 95% CI 0.88–1.24, p-value 0.650). Etiology of HF, kidney function or systolic function was not found to interact the effect of diabetes on all-cause mortality.

In the analysis of differences between optimized HF treatment in patients with and without diabetes, we included only patients with at least two registered visits to HF clinic. The HF treatment at baseline was well-balanced between the two groups. After the HF treatment was optimized, all patients experienced increase in doses of ACEi and β-blockers (both p-value < 0.001) and in use of statins (p-value 0.003). However, patients with diabetes were prescribed higher doses of β-blockers (p-value 0.012) and loop diuretics (p-value 0.003) compared to non-diabetics and the rate of statin use increased more in diabetic than non-diabetic patients (p-value 0.030). There was no statistical difference between the groups in alteration of ACEi doses and rate of spironolactone use (Table 5).

Table 5. Optimized heart failure medication in diabetic and non-diabetic HF outpatients

Medication	No diabetes			Diabetes			p-value for delta change in diabetes vs. non-diabetes
	Visit 1	Last visit	p-value	Visit 1	Last visit	p-value	
ACEi/ARB use	90%	90.1%	1.000	89.2%	89.2%	1.000	0.615
ACEi dose/day,%	48.1 (±40.7)	57,1 (±45.5)	<0.001	47.8 (±42.9)	55.7 (±46.0)	<0.001	0.684
B-blocker, mg/day	82.9 (±60.9)	111.5 (±73.2)	<0.001	80.6 (±64.9)	121.3 (±74.4)	<.0.001	0.012
Loop diuretics, mg/day	66.1 (±66.5)	57.7 (±69.0)	0.001	69.1 (±65.0)	73.5 (±100.9)	0.207	0.003
Spironolactone use	30.0%	34.2%	0.053	30.8%	30.7%	1.000	0.233
Statin use	64.3%	65.5%	0.497	66.3%	71.7%	0.002	0.030

Values are expressed as percentage or mean ± SD. ARB = Angiotensin receptor blocker. ACEi dose/day expressed as percent of daily enalapril equivalent target dose. β-Blocker expressed as mg/day of daily metoprolol equivalent dose.

4.3 Paper III: Gender differences in association between uric acid and all-cause mortality in patients with chronic heart failure

In paper 3, we investigated the independent effect of high SUA on all-cause mortality in Norwegian HF outpatients and we also explored if the effect was modified by gender or renal function. Out of 4684 HF outpatients with valid registration of uric acid at baseline, 984 individuals with SUA in the highest quartile were propensity score matched 1:1 with 984 individuals with SUA in the lowest three quartiles. Patients with SUA in the lowest three quartiles were chosen as a control group based on the Kaplan-Meyer survival curves which showed that their survival curves were superimposed. In the well-matched study cohort, we found SUA in the highest quartile to be an

independent predictor of all-cause mortality in HF outpatients (HR 1.19, 95% CI 1.03–1.37, p-value 0.021). Only gender, but not renal function was found to modify the effect of high SUA on all-cause mortality (p-value for interaction 0.007, resp. 0.539). Women with SUA in the highest quartile had an inferior 5-year survival compared to women with SUA in the lowest three quartiles (HR 1.65, 95% CI 1.24–2.20, p-value 0.001). In men, high SUA was not an independent predictor of all-cause mortality (HR 1.06, 95% CI 0.89–1.25, p-value 0.527).

5. Discussion

5.1 Methodological considerations

5.1.1 Study design

The current study is an observational, longitudinal, prospective, open cohort study.

In the hierarchy of the research design, RCT are considered to provide the highest level of scientific clinical evidence, while observational studies are on the intermediate level [153]. RCTs avoid or at least restrict confounding by including only patients with balanced baseline characteristics but there are some important limitations. Study populations in RCTs are highly selected and some patient groups are underrepresented due to practical or ethical restrictions [154]. Applying inclusion criteria from major HF clinical trials, only 13–25% of heart failure patients from observational studies were estimated to be eligible for the RCTs [167].

As the exposure variables in papers 2 and 3 were diabetes and high SUA, RCT would not be a suitable study design because the study participants cannot be randomized to diabetes or high SUA. However, paper 1 investigated treatment efficacy and an RCT could thus be an alternative method to an observational study. In trials of MRAs in chronic HF, patients with creatinine more than 220 µmol/L were excluded from the Randomized Aldactone Evaluation Study (RALES) and patients with GFR less than 30 ml/min/1.73 m^2 were excluded from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). The generalizability of the findings from RCTs may thus be impaired and the implementation challenging. Carefully designed observational studies can grant information which can be difficult to obtain by RCTs [168, 169].

A cohort study consists of individuals free of the outcome of interest and the study aims to determine which exposure variables/factors are associated with the outcome. Advantage of this study design is the possibility to investigate multiple outcomes and multiple exposures [170]. However, if the studied outcome is rare, it might take a long time until it occurs and such study could be rather expensive. This was not the case in our study as the outcome of interest was all-cause mortality. A major weakness of a cohort study is introduction of a selection bias, which will be discussed in chapter 5.1.3.

The longitudinal design of the current study grants collection of the information at several points: for the first time at baseline in the beginning of follow-up, next when treatment was considered optimized and at last, 6 months after visit 2. The advantage of this design was that we could observe changes in medical treatment and laboratory findings over time, evaluate efficacy of initiated treatment and associations between exposures of interest and outcomes. However, the data were not collected after the last visit and we only assumed that by the time of outcome, the patients were using the same medication as at the time of the last visit. Furthermore, the last visit was recorded only in about half of patients as they either died or were lost to follow-up.

The prospective nature of this study is characterized by recording the information on exposure (diagnosis of diabetes, initiation of spironolactone treatment, SUA in the highest quartile) in the beginning of the follow-up. In paper 1, however, we assigned the patients to either spironolactone or no spironolactone group based on data from the last registered visit, while the follow-up started at baseline visit. The decision to start follow-up from the time of baseline visit was made due to the lack of information on exact date for spironolactone initiation, which could have happened any time between the baseline visit and the visit stating that the treatment was optimal. This might have led to an inaccurate record of the follow-up time period as the patients probably used spironolactone shorter than 2 years. However, starting the follow-up from the last visit would underestimate the total follow-up time since the patients used spironolactone for at least six months at the time of the last visit.

The dynamic nature of open study design secured a large number of included individuals. Patients were included consecutively during the period 2000-2012 when being diagnosed with chronic heart failure and they were followed until death of any case, end of study or loss to follow-up.

5.1.2 Study population and data collection

The current study comprised patients from a clinical registry, the Norwegian Heart Failure Registry. The registry was established in 2000 with purpose to improve the quality of health care for people with heart failure. Clinical registries are initiated to collect data from consecutive patients over time and observational studies from such registries provide valuable information unavailable from or supplementary to RCTs.

The study cohort was assumed to be representative of Norwegian patients with chronic heart failure as the 25 recruiting HF clinics were located in all regions of Norway, both urban and rural, and the catchment area of the recruiting clinics covered about half of Norway's population.

The major advantage of registries is that they represent real world patients and record real world management. Still, the current registry is not entirely unselected and some bias might have been introduced. This topic will be discussed in the next chapter.

The variables to be collected were decided at the establishment of the Registry but they were later expanded as the Registry found it necessary to collect a broader variety of data. Glycosylated heamoglobin (HbA1c) was not collected until 2008 leading to a large amount of missing data. Not all variables of our interest were collected, such as albuminuria, diabetes medication, doses of spironolactone, doses of ARB, hormone replacement therapy, use of SUA lowering drugs, alcohol consumption, thyroid function, and triglycerides level. Availability of such data would have added valuable information.

5.1.3 Bias and confounding

Internal and external factors may affect quality of epidemiologic study if the researcher is not aware of them and does not address them correctly. Despite careful planning, the errors can still arise. Random error remains after elimination of systematic error and occurs by chance, as variability in data. Studies with small study population are more prone to this type of error and the error can be reduced by increasing the sample size [155]. Sample size in the current study is large and should ensure suppression of this type of error. However, some systematic errors might have been introduced to the current study.

Selection bias

Selection bias results from an error in selecting the study participants and from factors affecting the study participation [155]. Some selection bias might have been introduced to the current study.

Patients enrolled in the Norwegian Heart Failure Registry were recruited from HF clinics and some degree of selection bias might have been introduced already at the time of referral to the HF clinic. The patients were referred to HF clinic from outpatient cardiology clinic or inpatient medical or

cardiology department. Those with either very mild or very severe symptoms might not have been referred and thus underrepresented in the HF Registry. The ones with less severe HF symptoms might not have been diagnosed with HF and therefore not referred to cardiologist. Also, the physician's decision to refer a patient with established diagnosis to HF clinic might have been influenced by patient's health condition. Some HF patients might have been regarded not to profit from treatment at HF clinics and thus not to be referred. As only 10 % of patients in our study had eGFR < 30 mL/min/1.73 m^2 it is reasonable to assume that these patients were rather treated by nephrologists and not cardiologists. It has been shown that typical HF patient seen by cardiologists is different from the one seen by general practitioner. HF patients in general practice are rather older, they are more frequently women and more likely to have a history of longstanding hypertension than of ischemic heart disease [171]. In contrast to this, the patients in our study were most likely to be men, to have a history of ischemic heart disease and to have HFrEF.

Selection bias could have been introduced also when estimating propensity score as it will be discussed in chapter 5.1.6.

Loss-to follow-up bias is also a type of selection bias [156] and addresses a situation when individuals lost to follow-up do not have the same probability of having the outcome of interest as individuals remaining in the study. It is reasonable to assume that subjects who did not attend all three visits in the Registry differed from the ones who completed all of them. As a consequence, reliability of the analyses that required data beyond the first visit to the Registry might have been reduced.

Information bias

Accuracy of collected data is of major importance. In the current study, user manual on data definitions and documentation was issued and updated by the Norwegian Heart Failure Registry. However, some data might have been gathered erroneously due to misinterpretation of definitions by reporting hospitals or doctors, and some values might have been entered incorrectly when transferring original data into surveys.

Misclassification occurs during data collection and can lead to placing a patient into incorrect category [155]. In our study, misclassification might have occurred as a result of imperfect diagnosis

detection when assigning patients into categories of having or not having CKD and diabetes mellitus, as well as a result of inaccurate or non-uniform instrumentation.

Albuminuria has been shown to be independent predictor of prognosis in HF patients and to be prevalent also without reduced kidney function [172]. However, cardiovascular registries often lack data on structural abnormalities and CKD is mostly defined based on functional abnormalities (eGFR less than 60 ml/min/1.73m^2). CKD patients in our study population were defined by baseline eGFR as data on albuminuria were not available. Thus, patients with kidney damage but eGFR ≥ 60 ml/min/1.73 m^2 were not defined as having CKD and some degree of information bias might have been introduced. In addition, CKD is defined as abnormalities of kidney structure or kidney function present for greater than 3 months [50]. As we defined CKD patients based on eGFR at baseline, patients with only transiently decreased eGFR may have been incorrectly registered as having CKD.

The diagnosis of diabetes was recorded based on self-reported health status or medical records. Data on glucose-lowering treatment were not collected and HbA1c was not recorded until 2008. We can assume that some patients with undiagnosed diabetes were misclassified as not having diabetes. However, the number of misclassified patients was probably small and should not have had an impact on the outcome.

It is likely that different HF clinics used different instruments and did not have uniform procedures to perform measurements such as blood pressure, weight, and height, potentially also causing some information bias.

Reducing confounding by propensity score matching

Unlike RCTs, risk factors in observational studies are usually distributed unequally in the compared groups. Direct comparison of outcome in the groups is not possible as also factors potentially related to the study outcome can be distributed unequally. Effect of the studied exposure can be mixed with effect of another, confounding variable, and the real effect of an exposure can be blurred. Confounding occurs when a researcher tries to determine the effect of an exposure on the outcome, but instead measures the effect of another factor, the confounding variable [159]. Confounding is also viewed as systematic error and needs to be prevented.

In observational studies, multivariate Cox regression model has been the most commonly used technique for regression analysis of survival data. This model enables one to provide an effect estimate by quantifying the difference in survival between patient groups and simultaneously adjust for confounding variables [173]. However, propensity score methods have been increasingly used during the past decade as an alternative to multivariate Cox regression models. Both methods share the ability to control confounding, but propensity score may have some advantages. The major advantage is that methods based on propensity score allow the investigator to clearly separate the design stage of the study from the analysis stage as confounding is addressed already in the design step. Propensity score methods improve the balance of measured confounders between the exposed and unexposed group so that the groups have the same distribution and are thus comparable. Multivariable adjustment helps the researcher to separate the effect of multiple confounding variables on the outcome, but number of variables entered in the model is not unlimited. Propensity score summarizes a large number of measured covariates into one score and thus the methods using propensity score omit over-fitting.

Once propensity score is obtained, there are several ways how to use it to estimate the effect – matching, treatment weighting, stratification and also use as a covariate in a multivariable model [174]. Matching on propensity score is the most common method due to its transparency and also we chose this method. Matching was performed 1:1 to nearest neighbor, without replacement. As complete data sets were required for the procedure, we excluded the variables with most missing values to assure high number of matched pairs. In all three papers, the baseline variables were well-balanced after matching.

After assessing the balance of baseline variables between the two propensity score matched groups, we used univariate Cox regression model for survival analysis. In the Cox regression analyses, several assumptions need to be fulfilled for the model to be valid. The proportional hazards assumption means that the hazards in the compared groups are proportional to each other and constant over the follow-up period [173]. Another assumption to be met is the assumption of censoring, meaning that the censored patients have similar survival prospects as patients remaining in the study and that the reasons for drop-out are unrelated to the study. A high number of covariates in multivariate Cox regression model makes the model more complex, in contrast to using propensity score in a univariate Cox regression model.

It is underscored that the matching methods should not be viewed in conflict with regression models, but rather to view them as complimentary and use them in combination [175]. In the gender-stratified model in paper 3 we used multivariate regression model when analyzing the effect of the exposure to high SUA on all-cause mortality due to limited number of female patients and concern that propensity score matching might not succeed to identify sufficient number of pairs.

However, one has to be aware that both multivariate Cox regression model and propensity score matching model can only adjust for the measured confounders. Residual confounding can persist and the results can be affected by confounders that are not measured or by unknown confounders.

5.1.4 Selection of covariates in regression analyses

Regression analyses estimate relationship between a dependent variable (outcome variable) and independent variables and are used to predict an outcome or to infer causal relationship between the independent variables and the outcome. In the current study, we used logistic regression analysis to estimate the propensity score and proportional hazard analysis to estimate the risk of death.

The propensity score is usually estimated by logistic regression model entering exposure as dependent variable and measured confounders as independent variables. The covariate selection is often based on prior knowledge on relationship between exposure and outcome and on statistical tests on association between the covariates and the outcome [165, 175]. We included baseline characteristics associated with exposure (exposure variables were diabetes, spironolactone treatment and SUA in the highest quartile) and potential confounders known to be associated with outcome (HF mortality) as independent variables. Before entering variables in the model, we carefully evaluated that they all could be viewed as confounders and none of them was on a causal pathway between exposure and the outcome. Furthermore, we did not enter variables with lot of missing data as well as variables closely related to each other to avoid multicollinearity. Multicollinearity arises when two variables are so closely related that the multivariate analysis of any type (in our case logistic regression analysis) cannot separate the impact of the two variables on outcome [176].

5.1.5 Interactions

An interaction, also called an effect modification, occurs when effect of one variable on the outcome is changed by value of a third variable [176]. An interaction may be uncovered by stratification, but this method cannot simultaneously adjust for other predictor variables. On the other hand, multivariate analyses can assess interaction by entering a product term of two independent variables while adjusting for other. Multiple interactions can be tested and revealed but it may be difficult to interpret the clinical significance. We restricted testing for interactions to those based on clinical grounds, predefined in study protocol. In paper I, we aimed also to check if the effect of diabetes on survival was modified by other risk factors – LVEF category, CKD and etiology of HF. In paper III, we checked if gender or CKD modified the effect of SUA on survival. While none of the assessed risk factors modified the effect of diabetes, effect of high SUA was modified by gender. The cohort was subsequently split by gender and the prognostic effect of SUA on survival was assessed separately in women and men

5.1.6 Missing data

Missing data are an inevitable problem in every study and if possible, one should omit variables with many missing data. Provided that the data are not missing not at random, there are several ways how to deal with them.

In our study, we used the complete case method, which involves excluding individuals with missing values from the statistical analysis. Multivariate logistic regression analysis, used to estimate propensity score, demands valid values of all independent variables entered in the model. In a complete case method, subjects with missing values are excluded from the analysis even though they miss only one observation of many. As a result, power of the study can be decreased due to many dropped cases and a selection bias can be introduced as patients with missing values can be systematically different from those with missing values [176]. For example, in paper 2, only 2.7 % of values were missing, but 38.4 % cases were affected and could not be included in the analysis. To avoid many dropped cases, we reduced the number of independent variables of not great importance entered in the model but we kept the variables with missing data considered to be important.

Other possible strategies on dealing with missing values include replacing the missing value with the average of the known values of the given variable (substitution by mean), replacing with the last observation before the missing value (last observation carried forward) and multiple imputation [177]. In multiple imputation, the missing value is predicted based on other data in the same subjects.

Also, creating a multiple dichotomous variable where missing value is one of categories, is also a possible way to deal with missing data. This method allows to investigate if the patients with missing values.

5.1.7 Other statistical considerations

Although some variables did not have a normal distribution, we performed only parametric tests when comparing characteristics of the examined groups. One of the assumptions for performing the parametric tests is that the data are normally distributed and in case of skewed data a non-parametric test might be chosen. However, the test is robust and with a large enough sample size (more than 30) the violation of this assumption does not cause any major problems (ref. - SPSS survival manual, p.214). Since the number of participants in our study was large, we used parametric statistics despite skewed distribution.

5.2 Discussion of main findings

5.2.1 Effect of spironolactone on all-cause mortality in chronic HF patients with reduced renal function (Paper I)

In paper I, we found initiation of spironolactone in Norwegian HF outpatients with moderately reduced kidney function to be associated with improved 2-year survival. The treatment with spironolactone was beneficial despite statistically significant deterioration of kidney function and increase in serum potassium.

Our study has contributed in evaluation of clinical efficacy and safety of HF treatment in patients underrepresented in randomized control trials. Strict inclusion criteria in clinical trials may lead to exclusion of important patient groups and the results may hence be applicable only to a minority of

patients. Despite the high prevalence of kidney dysfunction in CVD patients and the high risk of CV death in kidney patients, kidney patients have been underrepresented in clinical trials of CVD. Although the focus on kidney patients has increased the last years, analyses of CVD trials from the last decades show that kidney patients were excluded in 46-56 % of cardiovascular RTCs and are still underrepresented [97, 178, 179].

RALES, a landmark study for use of spironolactone in patients with severe HF and LVEF ≤ 35 %, found that spironolactone reduced the risk of death in HF patients by 30% [37]. Patients with s-creatinine ≥2.5 mg/dL (≥221 µmol/L) were excluded. A study by Masoudi et al. comparing RALES patients and Medicare patients found that only 25 % of "real-world" patients in US would meet the inclusion criteria of RALES [180]. They also found that after RALES, 17.3% of Medicare patients discharged after HF hospitalization were prescribed spironolactone even though they had severe kidney dysfunction (eGFR < 30 ml/min/1.73 m^2) and 14.1 % had s-creatinine > 2.5 mg/dL [181]. A later study by Vardeny showed that patients in RALES with eGFR < 60 ml/min/1.73 m^2 had mean eGFR of 47.1 ± 8.9 ml/min/1.73 m^2 [95], which is comparable to renal function in patients in our study (mean eGFR 46.2 ± 10.2 ml/min/1.73 m^2).

MRAs are associated with risk of hyperkalemia and WRF, and WRF is associated with increased mortality in HF patients [72, 182]. Patients in our study experienced both deterioration of kidney function and increase in s-potassium after initiation of spironolactone. As no uniform definition of WRF exists [183], we referred to the change in eGFR between the baseline visit and the last visit at HF clinic that was scheduled 6 months after treatment was considered to be optimal. We found the change in renal function to be significant both within the treatment group and in between the treated and not treated group. Despite deterioration of renal function, treatment with spironolactone was associated with better survival compared to well-matched patients that continued their HF treatment without spironolactone. Similar results were found in the secondary analysis of RALES [95]. In a meta-analysis of RAAS inhibitor clinical trials in HFrEF, reduction in all-cause mortality induced by RAAS inhibition was significantly greater in patients who experienced WRF than those without WRF [88]. Moreover, WRF in the placebo group was associated with increased all-cause mortality compared to no WRF in the same group. HF patients can develop WRF both spontaneously and induced by RAAS inhibition. There is now evidence that WRF in HF represents heterogeneous causes and that WRF occurring during treatment with RAAS inhibitors is

not prognostically equivalent to that unprovoked by treatment. The spontaneous WRF can represent severity of HF while WRF during initiation of RAAS inhibition can reflect the hemodynamic changes induced by treatment [88, 93, 184]. A very recent meta-analysis of MRA in patients with HF and kidney dysfunction concluded that the survival benefit of MRA was preserved in patients with eGFR between 30 amd 60 ml/min/1.73 m [185].

Earlier guidelines for HF treatment recommended use of spironolactone and eplerenone only in patients with adequate renal function and normal s-potassium [11]. However, the latest 2016 ESC guidelines encourage to caution in kidney patients and those with s-potassium > 5 mmol/L [8].

Our study has contributed with the evidence that worsened renal function after initiation of spironolactone in HF outpatients with moderate renal dysfunction did not have an adverse effect on survival even in the presence of deteriorated renal function. Caution is necessary in patients with kidney disease but at the same time a fear for adverse effects should not lead practitioners to withhold potentially life-saving therapy.

5.2.2 Prevalent Diabetes Mellitus: Mortality and Management in Norwegian Heart Failure Outpatients (Paper II)

In this propensity score matched study of chronic HF patients attending Norwegian HF clinics we report no excess risk of death associated with concomitant diabetes. Neither systolic function, renal function nor ischemic etiology of HF modified the effect of diabetes on all-cause mortality. This finding may be rather surprising as many other studies did indeed find diabetes to be an independent predictor of mortality in HF patients. However, there are some important issues that need to be underscored.

Similarly to other studies, crude data confirmed that diabetic HF outpatients suffer from worse prognosis compared to those without diabetes (crude HR 1.47; 95% CI 1.329–1.625). Nevertheless, the predictive effect of diabetes was suppressed after adjusting for confounding variables by means of propensity score matching. More diabetic than non-diabetic patients suffered from concomitant conditions that are well-recognized predictors of outcome in HF [74, 186-188]. Compared to non-diabetics, the diabetic patients had more comorbidity (ischemic heart disease, hypertension, peripheral artery disease, CKD, anemia, hyponatremia), more HF symptoms, and they used more

and higher doses of HF medications. Propensity score for having diabetes obtained based on 21 measured baseline characteristics of diabetic HF outpatients was used to find matching non-diabetics to correct for the case-mix differences. Individuals in the final cohort had well-balanced baseline characteristics and non-diabetics differed from diabetics only by the absence of the disease.

In addition to used statistical methods, the current study may differ from other studies also in the cohort features – RCT vs. observational study, hospitalized vs. ambulatory patients, and treatment conducted by cardiologists vs. other specialties. The included individuals were generally unselected chronic HF patients attending HF outpatient clinics. In contrast to observational studies, study populations in RCTs are usually highly selected, causing a mismatch between HF patients in clinical trials and patients seen in daily practice [167]. However, study populations also differ in various observational studies. Some studies include outpatients [103, 114], some include patients hospitalized for acute decompensated HF [189] and some include both [190]. Such diversity in study populations can make it difficult to interpret and compare the results. Diabetes prevalence in hospitalized HF patients and prevalence of comorbid conditions in hospitalized diabetic HF patients has been reported to be higher than in the current study [189], and hospitalized HF patients experience worse prognosis than ambulatory patients [191]. Furthermore, lack of information on how HF treatment was conducted can also contribute to different results. Several studies have reported ambulatory care by cardiologists to be associated with improved uptake of guidelines-directed medical treatment, target doses of ACEi and β-blockers, and better outcomes compared to non-cardiologists [171, 192, 193].

Previous study of Norwegian HF outpatients reported that about 90 % of patients received RAS-blocking agents and nearly 80 % received β-blockers already at baseline [18], which is comparable to other HF registries [194]. Still, the treatment had been further intensified by cardiologists at HF clinics [19]. The baseline HF treatment in our study was well-balanced between the two propensity score matched groups. We confirmed that the optimized treatment was intensified in the whole cohort but we found distinct differences in the magnitude of treatment changes between diabetics and non-diabetics. The alterations in optimized doses of β-blockers and loop-diuretics were greater in patients with diabetes than in non-diabetic HF patients and there was a greater alteration in the rate of statin use. In contrast to non-diabetic HF patients whose loop-diuretic doses were reduced,

the doses of diabetic patients were increased. There were no differences between the groups in the optimized doses of ACEi and rate of MRAs use.

The current HF guidelines do not recommend specific HF treatment in diabetic patients [8, 12] and the evidence comes mainly from subgroup analyses of RCTs. β-blockers are the cornerstone of HF treatment together with ACEi as they have been shown to reduce mortality and hospitalization rates in HFrEF [41, 44, 195]. A meta-analysis confirmed these results to be valid also in diabetic patients [196]. However, a fear for less clear symptoms of hypoglycemia may lead to restrictions in use of β-blockers in diabetic patients. Loop diuretics are widely used in HF patients as they relieve signs and clinical symptoms of congestion, but their effect on mortality has not been established [197]. Moreover, they can lead to activation of neurohormonal system [198], electrolyte disturbances and worsened renal function [199] and higher doses were reported to be associated with worse outcomes in HFrEF [199-201].

Extensive use of β-blockers already at baseline and further increase of doses during follow-up at HF clinics might have played an important role in diminishing the predictive role of diabetes in HF outpatients in our study. The prognostic effect of increased doses of diuretics and increased rate of statin use in our study remains less clear.

We did not find any interaction between the ischemic etiology, left ventricular function or CKD and the effect of diabetes on all-cause mortality. Previous studies have explored the effect modifying role of the mentioned factors with conflicting results. While some have found increased risk in diabetics to be limited to ischemic etiology of HF [113, 115], others did not [109].

We did not have information on glucose-lowering treatment and glycemic control. Earlier studies have failed to prove intensive glycemic control to reduce the risk of HF-related outcomes [202] and neither did it improve or prevent progression of cardiac dysfunction [203]. Importantly, a recent study from Swedish National Diabetes Register showed that diabetic patients with risk factors within target ranges (HbA1c level, low-density lipoprotein cholesterol level, albuminuria, smoking, and blood pressure) had no excess risk of death compared to controls without diabetes [204]. A Norwegian RCT has also proved that addressing global risk factors prevented deterioration in cardiac function in diabetic patients [205]. A novel glucose-lowering therapy with sodium-glucose cotransporter 2 inhibitors has consistently demonstrated plausible effects on lowering

cardiovascular risk including HF prevention and hospitalization for HF, advocating for a paradigm shift in diabetes management due to effects beyond glycemic control [206-208].

Our study may imply that focus on individualized HF treatment and interdisciplinary approach to HF patients may counteract the detrimental effect of diabetes on prognosis.

5.2.3 Gender differences in association between uric acid and all-cause mortality in patients with chronic heart failure (Paper III)

In paper III, we found SUA in the highest quartile to be an independent predictor of 5-year all-cause mortality in Norwegian HF outpatients (HR 1.19, 95% CI 1.03–1.37, p-value 0.021). This is in accordance with other studies that found high SUA to be a strong predictor of impaired prognosis in chronic HF [140, 141]. To our knowledge, this is the first observational study of chronic HF patients using propensity score matching to show this.

HF patients need a tailored treatment to achieve optimal outcome. Ours and others findings suggest that UA could be a treatment target in the management of hyperuricaemic HF patients. Several studies found XO inhibitor allopurinol to improve endothelial function [209, 210] and other pathophysiological features in HF [211-214], nevertheless the survival benefit has not yet been determined [215-217]. Studies aiming at direct UA lowering without XO inhibition have also failed to achieve improvement other than lowering the UA [210, 218].

An important finding in our study is that the predictive value of high SUA was gender specific. We found SUA in the highest quartile to be an independent predictor of 5-year all-cause mortality only in women but not in men. This is a novel finding, extending previous work by demonstrating the detrimental effects of high SUA in women to apply also for chronic HF. Earlier studies reported high SUA in women to be associated with CV events in acute coronary syndrome [219], hypertensive patients with left ventricular hypertrophy [220] as well as in post-menopausal women with no prior CV events [221]. The current study expands the evidence of harmful effects of UA in women.

There were some important differences between women and men in our study cohort before propensity score matching. Compared to men, women were older, they were more likely to have a history of hypertension and CKD, higher LVEF but also higher NYHA class and less likely to smoke, to have a history of IHD, intervention on coronary arteries, to use RAAS-blocking agents, statins,

acetylsalicylic acid and they used lower doses of β-blockers. The baseline characteristics of women and men in the propensity score matched model were well-balanced and the interaction term between gender and SUA in quartile 4 was examined in the propensity matched cohort.

Previously, a superior survival of women with HF has been documented [149, 222]. The survival benefit may be attributed to the action of sex hormones, differences in the underlying cause of HF, as well as differences in cardiac physiology. Sex hormones affect cardiac fibrosis, myocardial calcium handling, and metabolism of nitric oxide, glucose and fatty acids [150]. Moreover, estrogens affect also the handling of UA in kidney tubuli. The diminishing uricosuric effect of estrogens may thus account for SUA increase after the menopause [152, 223]. Women in our study cohort had a mean age of 72.1 ± 12.1 years and it is reasonable to imply that they were postmenopausal even though we did not have data on the menopausal status. Women with highest SUA were older and they had more often a history of diabetes, hypertension, IHD and CKD as well as more severe HF symptoms. Despite more prevalent IHD, women with high SUA tended to use less acetylsalicylic acid, statins and fewer of them used RAAS-blocking agents.

We report a 65% increase in risk of death in HF women with highest SUA compared to women with SUA in the three lowest quartiles. It has been suggested that the complexity of HF pathophysiology should stimulate to tailor treatment to specific characteristics of patient subgroups [7]. We postulate that SUA might be a beneficial treatment target selectively in women with chronic HF.

We did not find the kidney function to modify the effect of high SUA on all-cause mortality of HF outpatients (p-value for interaction 0.539). This is in accordance with findings of Anker et al. [140] but in contrast to the propensity score matched study of Fillipatos et al., who found hyperuricaemia to be associated with increased mortality only in patients with CKD but not without CKD [134]. The different results may be due to some substantial differences between the two studies: our study was observational, the patients were about 12 years older, SUA in quartile 4 was higher than SUA in the other study, the HF symptoms were less severe and LVEF better.

5.3 Ethical considerations

The four ethical principles in clinical research are non-maleficence, justice, autonomy and beneficence [224].

Non-maleficence is the principle not to cause a physical, moral, economic, psychological or other damage due to investigation. The current study was observational and did not pose any additional risk for the included subjects as all laboratory analyses and various examinations were performed as a part of routinely scheduled visits to HF clinics, with purpose of treatment evaluation and optimization.

The principle of justice serves to ensure equal distribution of study participants and to avoid exploitation of vulnerable groups only because they are more accessible or submissive. The only criterion of inclusion in the registry was that the patients were diagnosed with HF and followed at HF outpatient clinics. It is reasonable to assume that some patients from vulnerable groups were not referred to HF clinics and thus not included in the registry as they might have been considered not to profit from treatment at HF clinics. However, this would lead to underrepresentation and not overrepresentation of subjects from vulnerable groups.

Autonomy ensures deliberation about personal gears and aims to preserve intimacy, privacy and confidentiality. All participants gave a written informed consent prior to inclusion in the registry and only unidentifiable data were entered.

The last principle of beneficence addresses an idea of treating patients with ethics, respecting their decisions and protecting them from unintended purposes. The observational nature of the current study ensures no active intervention in patients' treatment for the purpose of the study. Still, beneficence is also an important ethical principle in clinical practice and we are confident that it was applied as a natural part of treatment at HF clinics.

The study was approved by Regional Ethics Committee South-East (2014/1449).

6. Conclusions, implications and future perspectives

In the current study of heart-kidney interactions in Norwegian heart failure outpatients, we proved propensity score matching to be a reliable method to reduce confounding in effect estimates and to bring a new knowledge about factors involved in the heart-kidney interplay.

Using propensity score matching method, we estimated treatment effect of spironolactone in real world HF patients with reduced kidney function, patients that is underrepresented in clinical trials of cardiovascular interventions. We found initiation of spironolactone treatment to be associated with improved 2-year survival compared to HF patients with reduced kidney function whose HF treatment remained without spironolactone. The favorable effect of spironolactone was observed despite increase in se-potassium and decrease in kidney function

We examined the independent prognostic effect of diabetes and high uric acid on survival of HF patients and explored if kidney function and other factors had a modifying effect on this relationship.

We did not find diabetes mellitus to be an independent predictor of 5-year all-cause mortality in chronic HF patients. Neither kidney function, etiology of HF nor LVEF was found to modify the predictive effect of diabetes. However, the optimized HF treatment of diabetic patients was more intensive, attributing to higher doses of β-blockers and loop diuretics as well as more extensive use of statins in diabetic compared to non-diabetic patients.

SUA in the highest quartile was associated with inferior 5-year survival of chronic HF patients compared to patients with SUA in the lowest three quartiles. Only gender and not kidney function modified the effect of high SUA. The predictive effect of high SUA on all-cause mortality was gender specific and only present in women. Women with high SUA had inferior 5-year survival compared to women with low SUA.

The complexity of HF should stimulate to treatment tailored for characteristics of subgroups. We advocate for a holistic, multidisciplinary approach to diabetic HF patients with focus on identification and management of modifiable factors and comorbidities as well as optimizing the medical and non-medical treatment in order to improve prognosis of these high-risk patients. In context of our study we postulate that SUA might be a beneficial treatment target selectively in

women with chronic HF. We have documented improved survival in HF patients with kidney dysfunction treated with spironolactone. This may contribute to reduce fear for adverse effects of spironolactone that prevents therapists from prescribing this possibly lifesaving treatment to HF patients with kidney dysfunction.

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Errata list

Thesis, page 17:
Original text: “Table 3. Prevalence of kidney disease in general population and HF outpatients in Norway [3, 4]”
Corrected text: “Table 3. Prevalence of kidney disease in general population and HF outpatients in Norway”

Thesis, page 19, last paragraph:
Original text: “CRS type 3, acute cardiorenal syndrome, is characterized by acute kidney injury precipitating acute cardiac injury [80].”
Corrected text: “CRS type 3, acute renocardiac syndrome, is characterized by acute kidney injury precipitating acute cardiac injury [80].”

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Original Paper

Spironolactone Treatment and Effect on Survival in Chronic Heart Failure Patients with Reduced Renal Function: A Propensity-Matched Study

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Heart failure · Reduced renal function · Spironolactone · Prognosis

Abstract
Background/Aims: Spironolactone may be hazardous in heart failure (HF) patients with renal dysfunction due to risk of hyperkalemia and worsened renal function. We aimed to evaluate the effect of spironolactone on all-cause mortality in HF outpatients with renal dysfunction in a propensity-score-matched study. ***Methods:*** A total of 2,077 patients from the Norwegian Heart Failure Registry with renal dysfunction (eGFR <60 mL/min/1.73 m^2) not treated with spironolactone at the first visit at the HF clinic were eligible for the study. Patients started on spironolactone at the outpatient HF clinics (n = 206) were propensity-score-matched 1:1 with patients not started on spironolactone, based on 16 measured baseline characteristics. Kaplan-Meier and Cox regression analyses were used to investigate the independent effect of spironolactone on 2-year all-cause mortality. ***Results:*** Propensity score matching identified 170 pairs of patients, one group receiving spironolactone and the other not. The two groups were well matched (mean age 76.7 ± 8.1 years, 66.4% males, and eGFR 46.2 ± 10.2 mL/min/1.73 m^2). Treatment with spironolactone was associated with increased potassium (delta potassium 0.31 ± 0.55 vs. 0.05 ± 0.41 mmol/L, p < 0.001) and decreased eGFR (delta eGFR –4.12 ± 12.2 vs. –0.98 ± 7.88 mL/min/1.73 m^2, p = 0.006) compared to the non-spironolactone group. After 2 years, 84% of patients were alive in the spironolactone group and 73% of patients in the non-spironolactone group (HR 0.59, 95% CI 0.37–0.92, p = 0.020). ***Conclusion:*** In HF outpatients with renal dysfunction, treatment with spironolactone was associated with

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improved 2-year survival compared to well-matched patients not treated with spironolactone. Favorable survival was observed despite worsened renal function and increased potassium in the spironolactone group.

Introduction

Reduced renal function is common in outpatients with chronic heart failure (HF) and an independent predictor of all-cause mortality [1–3]. While the prevalence in the general population is about 4.7% [4], nearly 50% of patients with chronic HF have glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 [1, 2]. Still, patients with kidney disease are underrepresented in randomized controlled trials (RCTs) of cardiovascular interventions [5]. Although RCTs are considered as gold standard when evaluating the effectiveness of therapeutic agents, well-designed observational studies may provide important information in subgroups not addressed in RCTs [6].

The use of spironolactone in addition to ACE inhibitor (ACEi) and β-blocker is recommended in symptomatic patients with reduced left ventricular ejection fraction (LVEF) [7, 8]. Caution is necessary in patients with renal dysfunction, as use of spironolactone may cause hyperkalemia and worsening renal function [9, 10]. Worsening renal function is a strong predictor of increased mortality in HF patients, and the safety of spironolactone in patients with reduced renal function is still a matter of uncertainty [11–14]. Yet, spironolactone is used extensively in HF outpatients with renal dysfunction [2].

The aim of our study was to evaluate the effect of spironolactone on all-cause mortality in chronic HF patients with reduced renal function using a propensity-score-matched model on Norwegian HF outpatients.

Material and Methods

The Norwegian Heart Failure Registry

Since the year 2000, the Norwegian Heart Failure Registry has collected data on outpatients referred to HF clinics in Norwegian hospitals. In 2012, recruitment of patients occurred in 25 HF clinics in the different Norwegian regions with a catchment area representing about half of Norway's population. The recruiting HF clinics are run by cardiologists and specialized nurses. The patients were enrolled successively after being diagnosed with chronic HF of any etiology according to the guidelines of the European Society of Cardiology (ESC) [7, 15], and three visits were recorded. At the first visit (baseline), medical history, physical examination, echocardiography, New York Heart Association (NYHA) functional class, laboratory results, and the medical management of HF were registered. The second visit was registered after the cardiologists had optimized the medical treatment and the patient had participated in an educational program. The third visit, arranged 6 months after visit 2, served as an assessment of the patient's health condition, medication, and laboratory results after intervention at the HF clinic. Mortality data are retrieved yearly from Statistics Norway. A total of 6,779 patients were included by February 2012. HF outpatients with reduced renal function (estimated GFR [eGFR] <60 mL/min/1.73 m^2) not using spironolactone at the first visit were enrolled in the study (n = 2,077).

Definitions

Renal function was expressed as eGFR and calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16].

$$eGFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if black)}.$$

Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males and α is –0.329 for females and –0.411 for males. Renal dysfunction was defined as eGFR <60 mL/min/1.73 m^2.

Based on ESC guidelines on HF [7], LVEF was defined as reduced at ≤35% and as preserved at ≥50%.

Table 1. Baseline characteristics of 2,077 heart failure outpatients with renal dysfunction and no previous use of spironolactone

	Patients with valid data	Total (n = 2,077)	Started on spironolactone (n = 206)	Not started on spironolactone (n = 1,871)	p value
Age, years	2,077 (100)	76.1±8.8	76.1±8.2	76.1±8.9	0.982
Male gender	2,077 (100)	1,356 (65.3)	139 (67.5)	1,217 (65.0)	0.487
Body mass index	1,765 (85.0)	25.8±4.8	27.2±5.3	25.7±4.7	<0.001
Smoking	2,068 (99.6)	225 (10.9)	14 (6.8)	211 (11.3)	0.050
Medical history					
Ischemic heart disease	2,000 (96.3)	1,277 (63.9)	126 (63.3)	1,151 (63.9)	0.869
Hypertension	1,938 (93.3)	750 (38.7)	80 (40.4)	670 (38.5)	0.603
Claudication and/or previous stroke	1,938 (93.3)	386 (19.9)	36 (18.2)	350 (20.1)	0.519
PCI/CABG	1,931 (93.0)	692 (35.8)	67 (34.0)	625 (36.0)	0.573
Physical findings					
Heart rate, beats/min	2,073 (99.8)	71.2±14.9	71.7±14.7	71.1±15.0	0.595
SBP, mm Hg	2,076 (100)	128.0±22.9	128.0±23.6	128.0±22.9	0.979
LVEF groups					0.078
LVEF ≤35%		1,152 (65.5)	102 (58.6)	1,050 (66.3)	
35% < LVEF < 50%		408 (23.2)	45 (25.9)	363 (22.9)	
LVEF ≥50%		198 (11.3)	27 (15.5)	171 (10.8)	
NYHA class III/IV	2,037 (98.1)	1,199 (58.9)	144 (70.9)	1,055 (57.5)	<0.001
Medication					
RAS blockade	2,074 (99.9)	1,780 (85.8)	171 (83.0)	1,609 (86.1)	0.222
ACEi dose/day, % of target dose	2,065 (99.4)	40.0±38.8	47.9±44.0	39.1±38.1	0.002
β-Blocker dose/day, mg	2,044 (98.4)	70.0±66.3	69.2±67.1	70.1±66.2	0.859
Loop diuretics dose/day, mg	2,076 (100)	69.4±65.3	70.7±47.8	69.2±67.0	0.750
RAS + β-blocker use	2,070 (99.7)	1,476 (71.3)	136 (66.3)	1,340 (71.8)	0.098
Acetylsalicylic acid use	2,076 (100)	991 (47.7)	78 (37.9)	913 (48.8)	0.003
Statin use	2,077 (100)	1,108 (53.3)	102 (49.5)	1,006 (53.8)	0.245
Laboratory values					
eGFR, mL/min/1.73 m^2	2,077 (100)	43.7±11.6	45.7±9.9	43.5±11.8	0.010
Serum potassium, mmol/L	2,071 (99.7)	4.39±0.50	4.25±0.48	4.40±0.49	<0.001
Serum sodium, mmol/L	2,075 (99.9)	140.3±3.3	140.1±4.0	140.3±3.3	0.387

Values are expressed as n (%) or mean ± SD. ACEi dose/day, percent of daily enalapril equivalent target dose; β-blocker dose/day, daily metoprolol equivalent dose; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI/CABG, percutaneous coronary intervention and/or coronary artery bypass graft; SBP, systolic blood pressure.

Daily doses of ACEi were converted to enalapril equivalent doses (enalapril 20 mg = lisinopril 20 mg = ramipril 10 mg = captopril 100 mg), and then expressed as percent of enalapril target dose. Target dose of enalapril was defined as 20 mg per day. Daily doses of loop diuretics were converted to furosemide equivalent doses (furosemide 40 mg = bumetanide 1 mg). Daily doses of β-blockers were converted to metoprolol equivalent doses (metoprolol 200 mg = bisoprolol 10 mg = carvedilol 50 mg = atenolol 100 mg).

The follow-up time was set to 2 years as data on persistent use of spironolactone after the last registered visit were not available.

Statistical Analysis

Baseline characteristics were presented as mean ± standard deviation for continuous variables and as frequency (percentage) for categorical data. Student t test was used when comparing continuous variables. Similarly, χ^2 test was used when comparing categorical variables.

A multivariate logistic regression model was built to calculate the individual propensity score for being started on spironolactone at the outpatient HF clinic. Spironolactone use at the last visit at the outpatient HF

Table 2. Characteristics of 170 pairs of propensity-matched heart failure outpatients with renal dysfunction and no previous use of spironolactone

	Total (n = 339)	Started on spironolactone (n = 170)	Not started on spironolactone (n = 169)	p value
Age, years	76.7±8.1	76.4±8.0	77.1±8.1	0.445
Male gender	225 (66.4)	113 (66.5)	112 (66.3)	0.969
Body mass index	26.8±5.0	27.0±5.1	26.7±4.9	0.510
Smoking	27 (8.0)	12 (7.1)	15 (8.9)	0.537
Medical history				
Ischemic heart disease	220 (64.9)	107 (62.9)	113 (66.9)	0.449
Hypertension	143 (42.2)	68 (40.0)	75 (44.4)	0.414
Claudication and/or previous stroke	71 (20.9)	35 (20.6)	36 (21.3)	0.872
PCI/CABG	115 (33.9)	58 (34.1)	57 (33.7)	0.940
Physical findings				
Heart rate, beats/min	71.8±15.1	71.4±13.7	72.3±16.4	0.610
SBP, mm Hg	130.4±22.4	129.6±22.7	131.2±22.1	0.502
LVEF groups				0.084
LVEF ≤35%	183 (60.6)	82 (55.0)	101 (66.0)	
35% < LVEF < 50%	76 (25.2)	40 (26.8)	36 (23.5)	
LVEF ≥50%	43 (14.2)	27 (18.1)	16 (10.5)	
NYHA class III/IV	231 (68.1)	118 (69.4)	113 (66.9)	0.615
Medication first visit				
RAS blockade	284 (83.8)	141 (82.9)	143 (84.6)	0.676
ACEi dose/day, % of target dose	46.9±42.6	47.5±44.0	46.3±41.3	0.791
β-Blocker dose/day, mg	69.1±65.0	67.5±65.1	70.7±65.1	0.657
RAS + β-blocker use	224 (66.3)	109 (64.5)	115 (68.0)	0.490
Loop diuretics dose/day, mg	68.1±54.7	71.8±49.1	64.4±60.0	0.215
Acetylsalicylic acid use	142 (41.9)	66 (38.8)	76 (45.0)	0.251
Statin use	173 (51.0)	89 (52.4)	84 (49.7)	0.626
Medication last visit				
RAS blockade	287 (82.5)	137 (78.7)	150 (86.2)	0.067
ACEi dose/day, % of target dose	48.8±44.0	47.8±44.3	49.8±43.9	0.661
β-Blocker dose/day, mg	93.9±75.4	96.4±79.4	91.4±71.3	0.526
RAS + β-blocker use	241 (69.1)	114 (65.1)	127 (73.0)	0.113
Loop diuretics dose/day, mg	65.1±56.1	66.1±53.9	64.0±58.3	0.715
Acetylsalicylic acid use	146 (40.3)	67 (37.0)	79 (43.6)	0.199
Statin use	193 (53.3)	92 (50.8)	101 (55.8)	0.343
Laboratory values				
eGFR, mL/min/1.73 m^2	46.2±10.2	45.6±10.2	46.8±10.2	0.282
Serum potassium, mmol/L	4.27±0.46	4.23±0.47	4.30±0.45	0.164
Serum sodium, mmol/L	140.2±3.7	140.1±4.0	140.3±3.4	0.713

Values are expressed as n (%) or mean ± SD. ACEi dose/day, percent of daily enalapril equivalent target dose; β-blocker dose/day, daily metoprolol equivalent dose; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI/CABG, percutaneous coronary intervention and/or coronary artery bypass graft; SBP, systolic blood pressure.

clinic was entered as the dependent variable in the model. Baseline variables associated with spironolactone treatment ($p < 0.20$) were entered as independent variables, together with important potential confounding variables associated with mortality in HF patients. As complete data sets are required for the propensity score matching procedure, variables with many missing values (serum cholesterol and LVEF) were excluded from the analyses. The independent variables in the propensity matching procedure were then: age, gender,

BMI, ischemic heart disease, claudication and/or previous stroke, percutaneous coronary intervention and/or coronary artery bypass graft, systolic blood pressure, NYHA functional class 3 and 4, use of RAS-blocking agents, percent of ACEi daily target dose, diuretics dose, use of acetylsalicylic acid, use of statin, eGFR, serum potassium, and serum sodium.

Patients whose optimized HF treatment at the last visit included spironolactone were propensity-score-matched 1:1 with patients not using spironolactone in a randomized case order with match tolerance 0.1 and a priority to exact match.

Kaplan-Meier statistics was used to investigate differences in survival between HF outpatients with reduced renal function that were prescribed spironolactone during HF treatment optimization at HF clinics and patients not on spironolactone. Univariate Cox regression model was utilized to calculate hazard ratio (HR) for spironolactone use on all-cause mortality in HF outpatients with reduced renal function.

Student *t* test was used to assess changes in eGFR and serum potassium from the first to the last visit between the two treatment groups, and paired *t* test was used to assess changes within each treatment group.

Statistical analyses were carried out using SPSS for Windows version 22 (IBM SPSS Statistics, New York, NY, USA). Level of significance was set as p value ≤0.05.

Results

Baseline characteristics of 2,077 HF outpatients with reduced renal function and no prior use of spironolactone at the first visit to HF clinics are presented in Table 1. The mean age was 76.1 ± 8.8 years, 65.3% were males, and the mean eGFR was 43.7 ± 11.6 mL/min/1.73 m^2. Ten percent (n = 206) were registered as using spironolactone at the last visit. Compared to HF outpatients whose optimized medical treatment remained without spironolactone, the future spironolactone users had higher BMI and NYHA class, higher eGFR, and lower serum potassium, and they used higher doses of ACEi (Table 1).

Of a total of 1,814 HF outpatients with no prior use of spironolactone and complete datasets, 170 patients treated with spironolactone at the last visit were propensity-score-matched 1:1 with 169 HF outpatients not treated with spironolactone. Baseline characteristics were well balanced in the two examined groups (Table 2). Two-year mortality rate was 22%. After 48 months, 84% patients were alive in the spironolactone group and 73% patients in the non-spironolactone group. The use of spironolactone was an independent predictor of improved survival in HF outpatients with reduced eGFR (2-year mortality HR 0.59, 95% CI 0.37–0.92, p = 0.020; Fig. 1).

During a mean time of 8.0 ± 6.3 months from the first visit to the last visit, there was a significant change in both eGFR and serum potassium in the spironolactone group compared to the non-spironolactone group (Table 3). Patients treated with spironolactone experienced an increase in serum potassium from 4.24 ± 0.47 to 4.52 ± 0.51 mmol/L (p < 0.001) and a decrease in eGFR from 45.5 ± 10.2 to 41.4 ± 14.6 mL/min/1.73 m^2 (p < 0.001), while there was no significant change in neither serum potassium nor eGFR in patients not using spironolactone.

Discussion

In the present study of Norwegian HF outpatients with renal dysfunction, patients treated with spironolactone had improved 2-year survival compared to the propensity-matched patients not treated with spironolactone. The survival benefit was observed despite decrease in renal function and increase in serum potassium levels in patients treated with spironolactone.

Table 3. Change in eGFR and serum potassium in heart failure outpatients with renal dysfunction during follow-up at the heart failure clinic (no spironolactone use at baseline)

	Patients with valid data	Total (n = 339)	Started on spironolactone (n = 170)	Not started on spironolactone (n = 169)	p value
eGFR change	330 (97.3)	–2.57±10.4	–4.12±12.2	–0.98±7.9	0.006
Serum potassium change	327 (96.5)	0.18±0.51	0.31±0.55	0.05±0.41	<0.001

Values are expressed as n (%) or mean ± SD. eGFR, estimated glomerular filtration rate.

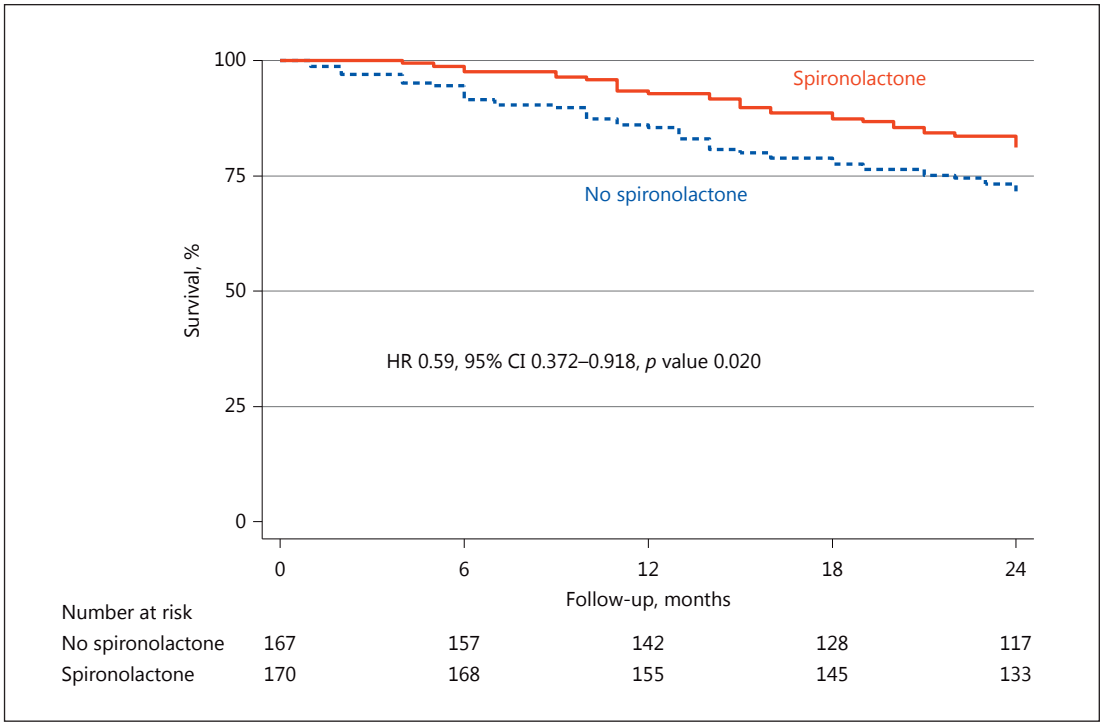

Fig. 1. Kaplan-Meier survival plot of heart failure outpatients with renal dysfunction propensity-matched by spironolactone treatment at the last visit at the heart failure clinic.

Mineralocorticoid receptor antagonists have been shown to improve survival in patients with advanced HF with reduced ejection fraction [17–19]. A recent study from the Swedish Heart Failure Registry reported an interaction between spironolactone use and renal function concerning all-cause mortality, indicating a relatively more favorable effect of spironolactone in patients with reduced renal function compared to patients with preserved GFR [20]. In a subgroup analysis of RALES (Randomized Aldactone Evaluation Study), individuals with reduced eGFR had similar reduction in relative risk of all-cause mortality as individuals with eGFR >60 mL/min/1.73 m^2 [21]. However, study populations in RCTs are highly selected and patients with reduced renal function are underrepresented. Coca et al. [5] found that individuals with renal disease were excluded in 56% of cardiovascular RCTs. Furthermore, only 13–25% of individuals from observational studies were estimated to be eligible for HF RCTs [22]. Patients included in our study were unselected patients treated in Norwegian outpatient

HF clinics. Compared to the subgroup of RALES patients with reduced kidney function [21], patients in the present study were older and had lower eGFR and higher serum potassium.

The use of mineralocorticoid receptor antagonists in HF patients with reduced renal function has been debated due to safety concerns. Extended use of spironolactone after publication of RALES resulted in increased rate of hospitalization for hyperkalemia [7–9]. In our study, the beneficial effect of spironolactone on survival was observed despite decrease in renal function and increase in serum potassium during follow-up at the outpatient HF clinics. It is well accepted that worsening renal function has a negative impact on survival in HF patients [11, 12, 23]. However, the prognostic effect of worsening renal function might depend on the HF medication used. A meta-analysis showed that improved survival associated with use of RAAS inhibitors was greatest in patients with worsening renal function [11]. Likewise, Vardeny et al. [21] demonstrated a favorable effect of spironolactone on survival in HF patients with reduced eGFR despite worsening renal function. On the other hand, worsening renal function following the use of high-dose loop diuretics was associated with increased mortality [24]. Given the beneficial effect of spironolactone on survival in HF patients despite decreased eGFR, one could hypothesize that some reduction in renal function with spironolactone should be accepted and should not lead to discontinuation of treatment. However, the degree of worsening renal function and hyperkalemia that should be tolerated needs to be further investigated.

We used propensity-score-matched analysis to correct for differences between baseline characteristics of patients treated and not treated with spironolactone. Propensity score matching makes it possible to design an observational study so that it mimics some of the characteristics of RCTs by balancing the baseline differences between the study and control group. It is an increasingly used method that might be superior to multivariate Cox regression when correcting for confounding variables in observational studies [25]. Based on 16 predefined measured variables in the present study, patients prescribed spironolactone were matched 1:1 with patients not prescribed spironolactone. However, neither propensity score matching nor multivariate Cox regression can correct for unmeasured confounding variables. Yet, the large number of variables used for the estimation of propensity score may back the reliability of our findings.

There are some important limitations. Although the study population consists of unselected outpatients attending HF clinics, some degree of selection might be present. The patients that were prescribed spironolactone were not selected at random, but rather after careful evaluation by the cardiologist. Therefore, we cannot conclude that spironolactone use would be beneficial for all patients with reduced kidney function. Furthermore, the majority of the included individuals had moderately reduced kidney function with eGFR 30–59 mL/min/1.73 m^2 and only 10% had eGFR <30 mL/min/1.73 m^2. It is likely to assume that patients with severely reduced kidney function would most probably be treated by nephrologists rather than cardiologists, and therefore would not be included in the Heart Failure Registry.

Only mortality data were available after the last registered visit at the outpatient HF clinic. Data on doses of spironolactone and other medication, hospital admissions for decompensated HF, or adverse events would have strengthened the study. Such data were not available. The follow-up time was restricted to 2 years because of lack of data on persistent use of spironolactone.

In conclusion, spironolactone improved the 2-year survival in HF outpatients with reduced renal function compared to propensity-score-matched patients not treated with spironolactone. Favorable survival was observed despite the fact that patients treated with spironolactone experienced a decrease in renal function and an increase in serum potassium. Reluctance to prescribe spironolactone owing to fear for adverse renal events may deprive HF patients with reduced renal function of possibly lifesaving treatment.

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Statement of Ethics

All enrolled patients had given written informed consent prior to inclusion in the database. The study was approved by the National Data Inspectorate and the Regional Committee of Medical Research Ethics.

Disclosure Statement

B.W.-G. reports personal fees from Novartis Pharma, outside the submitted work. M.G. reports personal fees from Novartis Pharma and Vifor Pharma, outside the submitted work. D.A. reports personal fees from Novartis Pharma, St. Jude Medical, and Vifor Pharma, outside the submitted work. The other authors have no conflict of interest related to the work to disclose.

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Prevalent Diabetes Mellitus: Mortality and Management in Norwegian Heart Failure Outpatients

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For editorial comment see p. 411

Key Words
Diabetes mellitus · Chronic heart failure · Survival analysis · Propensity score matching

Abstract
Objectives: Heart failure (HF) patients with diabetes mellitus experience poor prognosis. We assessed the independent predictive effect of prevalent diabetes mellitus on all-cause mortality in HF outpatients. Furthermore, we investigated if optimized HF medication differed in diabetic versus nondiabetic patients. ***Methods:*** From 6,289 patients included in the Norwegian HF registry during 2000–2012, 724 diabetic HF outpatients were propensity-score-matched with nondiabetic HF outpatients (1:1), based on 21 measured baseline variables. Baseline characteristics, measured comorbidities and medication were balanced in the matched sample. ***Results:*** Diabetes was not an independent predictor of all-cause mortality in the propensity-matched analyses (hazard ratio 1.041; 95% confidence interval 0.875–1.240). No interactions were found between the prognostic impact of diabetes and the strata renal function, systolic function or etiology of chronic HF. Diabetic HF outpatients were independently prescribed higher doses of β-blockers and loop diuretics (both $p < 0.001$) and were more prone to receive statins ($p = 0.003$) than nondiabetics. ***Conclusions:*** Prevalent diabetes mellitus was not an independent predictor of all-cause mortality in HF outpatients. Explanations other than tight glycemic control should be assessed to improve the prognosis of diabetic HF outpatients. The more intensive, optimized HF medication for diabetic HF outpatients may, to a certain degree, explain our results.

Introduction

Chronic heart failure (HF) and diabetes mellitus are major public health problems and both have increasing prevalence worldwide [1–4]. The Framingham Study demonstrated the association between diabetes mellitus and congestive HF more than 30 years ago; compared to the general population, men and women with diabetes mellitus have a 2- and 5-fold greater relative risk to develop HF, respectively [5]. Hypertension, coronary artery disease and renal dysfunction, all major risk factors for HF [6, 7], are prevalent in diabetic patients and may contribute to the risk of HF [8–11]. Other less-understood mechanisms could also contribute to the increased risk of chronic HF in diabetic patients [12].

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Despite the novel principles of HF treatment having improved the prognosis, chronic HF is still a leading cause of hospitalization in patients >65 years of age and the mortality rate remains high [2, 13–16]. Diabetes is a major factor for poor outcome in patients with cardiovascular disease [17, 18]. In patients with established HF, the prognostic effect of diabetes mellitus is less clear. A subgroup analysis in the SOLVD (Studies of Left Ventricular Dysfunction) treatment trial was the first to suggest that diabetes was an independent predictor of all-cause mortality in chronic HF patients with a reduced ejection fraction (HF-REF) and ischemic etiology [19]. Diabetes was later found to be a predictor of all-cause mortality in other selected study populations with HF-REF [11, 20, 21]. However, such populations do not necessarily represent real-life patients because important subgroups are sometimes not included. Patients in clinical trials are often younger and have less comorbidity [22] than regular patients. Furthermore, there are less robust data with regard to the prognostic value of diabetes in HF patients with preserved ejection fraction, and the interaction between diabetes and ischemic etiology of HF remains under debate.

Propensity-matched analyses make it possible to design an observational study so that it mimics some of the characteristics of a randomized controlled trial [23]. Propensity matching creates pairs of patients that have the same likelihood of having diabetes with respect to the measured confounding variables. Thus, one can directly compare the outcomes of diabetic and nondiabetic patients. Most frequently, observational studies utilize multivariate Cox regression analyses to adjust for confounding variables [24–26]. Cox regression models must be modelled correctly concerning the association between the covariables and the outcome [27]. Propensity-matched analyses could be superior to Cox regression analyses and give further insight into the independent prognostic effect of diabetes in chronic HF patients [23].

Given this background, our primary aim was to utilize propensity-matched analyses to investigate the independent effect of prevalent diabetes mellitus on all-cause mortality in Norwegian outpatients with chronic HF. Furthermore, we aimed to assess the potential interactions between systolic and renal function, the ischemic etiology of HF and diabetes with respect to all-cause mortality. Finally, we wanted to evaluate if the HF medication optimized at Norwegian outpatient HF clinics for diabetic versus nondiabetic patients differs, and, if so, whether this could explain the differences in mortality.

Materials and Methods

The Norwegian Heart Failure Registry

The Norwegian Heart Failure Registry was established in October 2000. Outpatients referred to participating HF clinics in Norway were enrolled consecutively when they were diagnosed with HF according to the guidelines of the European Society of Cardiology [28, 29]. Intentionally, three visits to the outpatient HF clinics should have been recorded for each patient. At visit 1, a medical history, physical examination, echocardiography, laboratory results and the medical management of HF were registered. Visit 2 was registered when the medical treatment was optimized and the patient had participated in a patient education program. The last visit (visit 3) was scheduled for 6 months after visit 2. Mortality data were retrieved from the Norwegian National Registry. All enrolled patients gave their written informed consent prior to inclusion in the database. By February 2012, 6,746 patients from 25 HF clinics, with a catchment area of about half of the population of Norway, were included. The presence or absence of diabetes mellitus at visit 1 was registered in 6,289 patients who were then included in the study of the independent effects of diabetes mellitus on all-cause mortality. For the analysis of optimized HF medication in diabetic and nondiabetic patients, the participants needed to have registered at least 2 visits. The study was approved by the National Data Inspectorate and the Regional Committee of Medical and Health Research Ethics.

Definitions

The diagnosis of diabetes mellitus was recorded on the basis of medical records and the self-reported health status at visit 1.

Renal function, expressed as the estimated glomerular filtration rate (eGFR), was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [30]:

$$eGFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times (1.018, \text{if female}) \times (1.159, \text{if black}),$$

where Scr is serum creatinine (mg/dl), κ is 0.7 for females and 0.9 for males and α is –0.329 for females and –0.411 for males.

Based on eGFR, renal function was classified into stages 1–5 according to the KDOQI (Kidney Disease Outcome Quality Initiative) clinical practice guidelines [31]. An eGFR <60 ml/min/m^2 was defined as reduced renal function.

Left-ventricular ejection fraction (LVEF) was classified as preserved or reduced, based on the European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF [29]. Preserved LVEF was defined as ≥50% and reduced LVEF as ≤35%. LVEF between 35 and 50% was defined as a grey zone.

The New York Heart Association (NYHA) functional classification was used to grade the HF into classes I–IV based on the symptoms [29].

Daily doses of angiotensin-converting enzyme inhibitor (ACEi) were converted to enalapril-equivalent doses (enalapril 1 mg = lisinopril 1 mg = ramipril 0.5 mg = captopril 5 mg) and then expressed as a percent of the enalapril target dose, defined as 20 mg per day. Daily doses of loop diuretics were converted to furosemide-equivalent doses (furosemide 40 mg = bumetanide 1 mg). Daily doses of β-blockers were converted to metoprolol-equivalent doses (metoprolol 20 mg = bisoprolol 1 mg = carvedilol 5 mg = atenolol 10 mg).

Composite variable claudication and/or previous stroke were defined as a measure of noncoronary atherosclerotic disease.

Table 1. Baseline characteristics of 6,289 patients attending outpatient HF clinics

	Patients with valid data	Total (n = 6,289)	No diabetes (n = 5,052)	Diabetes (n = 1,237)	p value
Age, years	6,283 (99.9)	69.5±12.1	69.5±12.4	69.8±10.8	0.419
Male gender	6,288 (100)	4,476 (71.2)	3,576 (70.8)	900 (72.8)	0.173
BMI	5,541 (88.1)	26.3±5.0	25.9±4.8	28.0±5.7	<0.001
Current smoker	6,257 (99.5)	980 (15.7)	829 (16.5)	151 (12.3)	<0.001
NYHA class	6,182 (98.3)				<0.001
I		305 (4.9)	273 (5.5)	32 (2.6)	
II		2,691 (43.5)	2,232 (44.9)	459 (37.9)	
III		3,080 (49.8)	2,384 (48.0)	696 (57.5)	
IV		106 (1.7)	82 (1.6)	24 (2.0)	
Heart rate, beats/min	6,280 (99.9)	72.6±15.1	72.4±15.2	73.6±14.8	0.015
SBP, mm Hg	6,286 (100)	126.1±22.4	125.4±22.3	129.3±22.9	<0.001
LVEF, %	5,558 (88.4)	32.4±11.4	32.4±11.5	32.6±11.0	0.473
LVEF ≤35%		3,869 (69.6)	3,131 (70.0)	738 (68.1)	
35% < LVEF < 50%		1,184 (21.3)	942 (21.1)	242 (22.3)	
LVEF ≥50%		505 (9.1)	401 (9.0)	104 (9.6)	
Cause of HF					
IHD	5,994 (95.3)	3,399 (56.7)	2,628 (54.5)	771 (65.6)	<0.001
Comorbidities					
Hypertension	6,261 (99.6)	2,009 (32.1)	1,440 (28.6)	569 (46.3)	<0.001
Claudication and/or previous stroke	6,268 (99.7)	954 (15.2)	696 (13.8)	258 (20.9)	<0.001
PCI/CABG	6,249 (99.4)	2,296 (36.7)	1,765 (35.2)	531 (43.2)	<0.001
COPD	5,960 (94.8)	1,010 (16.9)	783 (16.4)	227 (19.3)	0.016
Medication					
ACEi dose/day, % of target dose	6,258 (99.5)	45.4±40.0	44.9±38.6	47.7±45.1	0.045
β-Blocker, mg/day	6,200 (98.6)	71.3±64.4	70.0±63.3	80.9±68.1	<0.001
Loop diuretics, mg/day	6,287 (100)	57.3±58.7	51.7±51.9	80.4±76.5	<0.001
Spironolactone use	6,279 (99.8)	1,496 (23.8)	1,122 (22.2)	374 (30.3)	<0.001
CCB use	6,211 (98.8)	497 (8.0)	352 (7.1)	145 (11.8)	<0.001
ASA use	6,285 (99.9)	2,947 (46.9)	2,312 (45.8)	635 (51.4)	<0.001
Statin use	6,280 (99.9)	3,407 (54.3)	2,601 (51.6)	806 (65.2)	<0.001
GFR stage	6,250 (99.4)				<0.001
1: eGFR ≥90		879 (14.1)	720 (14.3)	159 (12.9)	
2: eGFR 60–89		2,623 (42.0)	2,179 (43.4)	444 (36.1)	
3: eGFR 30–59		2,359 (37.7)	1,850 (36.9)	509 (41.4)	
4+5: eGFR <30		389 (6.2)	271 (5.4)	118 (9.6)	
eGFR <60	6,250 (99.4)	2,747 (44.0)	2,120 (42.2)	627 (51.0)	<0.001
Laboratory values					
eGFR, ml/min/1.73 m^2	6,250 (99.4)	64.2±22.4	65.1±22.2	60.1±23.2	<0.001
Hemoglobin, g/100 ml	5,998 (95.4)	13.8±1.7	13.9±1.7	13.5±1.7	<0.001
Serum uric acid, mmol/l	5,014 (79.7)	458.3±132.1	453.7±130.4	477.3±137.3	<0.001
Serum creatinine, μmol/l	6,256 (99.5)	106.3±44.2	104.3±42.4	114.3±50.0	<0.001
Serum potassium, mmol/l	6,250 (99.4)	4.4±0.47	4.4±0.46	4.4±0.50	0.104
Serum sodium, mmol/l	6,251 (99.4)	139.9±3.3	140.0±3.2	139.5±3.4	<0.001
Serum cholesterol, mmol/l	5,304 (84.3)	4.7±1.3	4.8±1.3	4.3±1.2	<0.001

Values are expressed as n (%) or mean ± SD. CCB = Calcium channel blocker; COPD = chronic obstructive pulmonary disease; IHD = ischemic heart disease; PCI/CABG = percutaneous coronary intervention and/or coronary artery bypass graft; SBP = systolic blood pressure.

Table 2. Baseline characteristics of Norwegian HF outpatients after propensity score matching

	No diabetes (n = 724)	Diabetes (n = 724)	p value
Age, years	69.9±11.5	69.1±10.6	0.206
Male gender	523 (72.2)	527 (72.8)	0.814
BMI	27.6±5.6	27.8±5.6	0.568
Current smoker	108 (14.9)	104 (14.4)	0.766
NYHA class III/IV	449 (62.0)	435 (60.1)	0.451
Heart rate, beats/min	73.2±16.3	73.7±14.5	0.590
SBP, mm Hg	129.5±23.5	129.8±22.6	0.805
LVEF %	33.3±12.0	33.3±11.1	0.938
LVEF group			0.776
LVEF ≥50%	72 (9.9)	73 (10.1)	
LVEF 35–50%	167 (23.1)	178 (24.6)	
LVEF ≤35%	485 (67.0)	473 (65.3)	
IHD	483 (66.7)	480 (66.3)	0.867
Comorbidities			
Hypertension	357 (49.3)	354 (48.9)	0.875
Claudication and/or previous stroke	143 (19.8)	157 (21.7)	0.364
Medication			
ACEi dose/day, % of target dose	48.2±42.1	47.0±45.7	0.602
β-blocker dose/day, mg	80.3±63.0	80.0±65.0	0.928
Loop diuretics dose/day, mg	70.5±73.4	76.0±79.4	0.173
Spironolactone use	217 (30.0)	216 (29.8)	0.954
Statin use	467 (64.5)	480 (66.3)	0.473
CCB use	71 (9.8)	81 (11.2)	0.391
Laboratory values			
eGFR, ml/min/1.73 m^2	62.1±23.5	61.8±23.0	0.835
Hemoglobin, g/100 ml	13.5±1.7	13.5±1.7	0.772
Serum sodium, mmol/l	139.5±3.3	139.5±3.5	0.894
Serum cholesterol, mmol/l	4.4±1.2	4.4±1.2	0.957

Values are expressed as n (%) or mean ± SD. CCB = Calcium channel blocker; IHD = ischemic heart disease; SBP = systolic blood pressure.

Statistical Analysis

Baseline characteristics were presented as mean ± standard deviation (SD) for continuous variables and as percentages for categorical data. To compare continuous variables in diabetic and nondiabetic patients, the Student t test was used. The χ^2 test was used when comparing categorical variables between the groups.

In the total study population, 25 baseline variables were significantly different between the diabetic and nondiabetic patients. These variables as well as age and gender were entered into a logistic regression model with diabetes mellitus as a dependent variable to calculate an individual propensity score of having diabetes. To increase the number of included cases, the 4 variables that contributed least to the propensity score, i.e. serum uric acid level, the use of aspirin, previous percutaneous coronary intervention or coronary artery bypass grafting and inhospital days during the past 6 months, were excluded, and a new propensity score was estimated. The removal of the 4 variables did not change the individual propensity score (R^2 linear = 0.983). In the propensity-matched model, we corrected for the following independent variables: gender, age, hypertension, claudication and/or previous stroke, ischemic heart disease, current smoking, BMI, systolic blood pressure, heart rate, LVEF, eGFR, levels of hemoglobin, serum sodium and serum cholesterol, the percentages of the ACEi daily target dose, diuretics dose and β-blocker dose, the use of spironolactone, statins and calcium-channel blockers and NYHA functional classes 3 and 4. Propensity score matching of 1:1 identified 724 pairs of patients with complete data sets. Kaplan-Meier statistics and univariate Cox regression analyses were used to assess hazard ratios (HR) of diabetes mellitus on all-cause mortality in the propensity-score-matched dataset.

Stratified analyses were performed to investigate whether the effect of having diabetes mellitus on all-cause mortality was different in the strata of ejection fraction, the etiology of chronic HF and renal function. Interactions were checked by entering product terms into the Cox models.

Only 2.7% of the values in the registry were missing, but led to 38.4% missing cases in the regression analyses. The variables serum cholesterol, BMI and LVEF accounted for the majority of missing values.

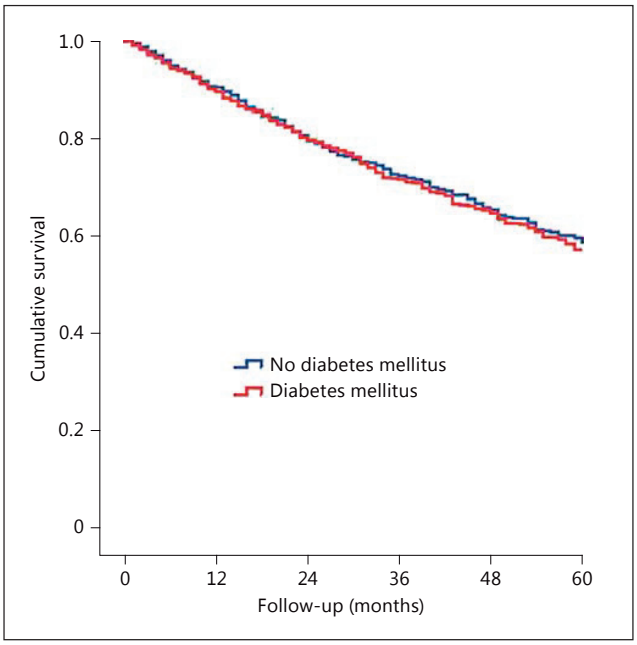

Fig. 1. Kaplan-Meier survival plot of propensity-matched HF outpatients with and without diabetes mellitus.

Alterations in medical treatment during the follow-up were investigated. In the propensity-matched model, baseline medication was balanced in patients with and without diabetes. In patients with >1 registered visit to the HF clinics, we examined how the medication changed by the last visit. The paired Student t test was used when investigating alterations in doses of ACEi, β-blockers and loop diuretics. The McNemar test was used when investigating the change in the number of patients treated with renin-angiotensin system (RAS) blockers, spironolactone and statins. Any alteration of drug doses for diabetic versus nondiabetic patients was explored with the Student t test, and the χ^2 test was used to compare the proportion of patients treated by RAS blockers, spironolactone and statins in the 2 groups.

Assumptions for the multivariate models were checked and found to be adequately met.

The analyses were performed using IBM SPSS statistical software v20.0 (IBM SPSS Statistics, New York, N.Y., USA). Propensity score matching was performed using the IBM software SPSS R plug-in v2.12.1 [32]. The level of significance was set to $p < 0.05$.

Results

The baseline characteristics of 6,289 Norwegian outpatients with chronic HF are presented in table 1. Mean age was 69.5 ± 12.1 years, 71% were men and 20% had diabetes mellitus. Patients with diabetes mellitus had more comorbidity, a higher NYHA class, used more medication and higher doses, had a higher blood pressure, heart rate and BMI and lower hemoglobin, serum cholesterol and serum sodium levels. There were fewer diabetic patients than nondiabetic patients who were current smokers (table 1). Median follow-up time was 45 (range 0–142) months. The 5-year mortality rate was 0.38. The median survival time of diabetic patients was 64 [95% confidence interval (CI) 58.4–69.6] months compared to 94 (95% CI 88.0–100.0) months in nondiabetic patients (HR 1.47; 95% CI 1.329–1.625; $p < 0.001$).

The propensity-matching procedure identified 724 pairs of patients (diabetes vs. nondiabetes) with an equal risk profile. After matching, the initial case-mix differences between patients with and without diabetes were balanced concerning all measured variables (table 2). The 5-year mortality rate in the propensity-matched cohort was 0.39. Diabetes mellitus was not an independent predictor of all-cause mortality in patients with chronic HF (HR 1.041; 95% CI 0.875–1.240; $p = 0.650$; fig. 1). The prognostic impact of prevalent diabetes mellitus was not different between groups for the strata renal function, systolic function or HF etiology (table 3). Interactions with age and gender were also checked and found to be negative.

Baseline medication was equal in the patients with and without a diagnosis of diabetes mellitus in the propensity-matched sample. After the therapy was optimized by cardiologists at the HF clinics, daily doses of β-blocker and ACEi (both $p < 0.001$) and the use of statins were increased ($p = 0.003$) compared to the first visit (table 4). HF patients with diabetes mellitus were more prone to receive higher doses of β-blockers ($p = 0.012$) and loop diuretics ($p = 0.003$), in addition to more extensive use of statins ($p = 0.030$) compared to nondiabetics. There were no differences in prescribing RAS-inhibiting agents or mineralocorticoid receptor antagonists (MRAs) between patients with and without diabetes mellitus (table 4).

Discussion

In this propensity-matched study of Norwegian HF outpatients, diabetes mellitus was not an independent predictor of all-cause mortality. This finding was consistent for the strata systolic function, renal function and ischemic versus nonischemic etiology of chronic HF. No interaction with age or gender was found.

Our results are in conflict with previous studies which found diabetes mellitus to be a strong independent predictor of mortality in chronic HF patients. Diabetes mel-

Table 3. HR of prevalent diabetes mellitus in a propensity-score-matched study of Norwegian HF outpatients

	Patients, n	HR	95% CI	p value for interaction
All	1,448	1.036	0.087–1.234	
IHD	963	1.067	0.867–1.314	n.s.
Non-IHD	485	0.970	0.704–1.338	
LVEF ≤35%	958	1.100	0.884–1.369	
35% < LVEF < 50%	345	0.912	0.641–1.299	n.s.
LVEF ≥50%	145	0.953	0.577–1.574	
eGFR <60 ml/min/1.73 m^2	704	0.913	0.738–1.130	n.s.
eGFR ≥60 ml/min/1.73 m^2	744	1.253	0.925–1.698	

Stratified analyses were performed in different strata of HF origin, LVEF and renal function. IHD = Ischemic heart disease; n.s. = not significant.

Table 4. Medication in Norwegian HF outpatients in a propensity-matched model

Medication	Total		No diabetes		Diabetes		p value interaction
	visit 1	last visit	visit 1	last visit	visit 1	last visit	
ACEi/ARB use	89.6	89.7	90	90.1	89.2	89.2	0.615
ACEi dose/day, %	47.9±41.8	56.4±45.7	48.1±40.7	57.1±45.5	47.8±42.9	55.7±46.0	0.684
β-Blocker, mg/day	81.6±62.7	116.3±73.9	82.9±60.9	111.5±73.2	80.6±64.9	121.3±74.4	0.012
Loop diuretics, mg/day	67.6±65.7	65.5±86.4	66.1±66.5	57.7±69.0	69.1±65.0	73.5±100.9	0.003
Spironolactone use	30.6	32.3	30.0	34.2	30.8	30.7	0.233
Statin use	65.3	68.5	64.3	65.5	66.3	71.7	0.030

Values are expressed as percentages or mean ± SD. ARB = Angiotensin receptor blocker. ACEi dose/day expressed as percent of daily enalapril equivalent target dose. β-Blocker expressed as mg/day of daily metoprolol equivalent dose.

litus was first identified to independently predict mortality in patients with HF-REF [11] and later in patients with HF with preserved ejection fraction [20, 33]. An interaction with HF etiology was proposed, as diabetes mellitus was found to be a predictor of mortality in HF-REF patients with the ischemic etiology but not with the non-ischemic etiology of HF [19, 21, 26]. None of these conclusions are supported by our study. The reason for the conflicting results might be due to differences in the study populations and statistical methods. Randomized controlled trials include highly selected patients and also systematically exclude important subgroups of patients who are frequently seen in the daily practice [22]. It has been estimated that only 13–25% of HF patients from epidemiologic studies would be eligible for clinical HF trials [34, 35]. The generalization of results from clinical trials to a real-life population would then be questionable. Our cohort was a real-life population treated at outpatient HF clinics. They were HF patients with a mean age of 70 years, about 70% being men and about 20% having diabetes mellitus at baseline, comparable to HF populations in other observational studies [24, 26, 36].

Multivariate Cox regression is the most commonly used method to correct for confounding factors and assess the independent effect on survival of a specific variable. Cox regression models must be modelled correctly concerning the association between covariables and the outcome [27]. Propensity score matching is an alternative method that is increasingly utilized in observational studies. Based on predefined measured variables, the group of interest will be matched with unaffected individuals with comparable characteristics decided by the propensity score. None of the methods is able to correct for unmeasured confounding variables. However, propensity score matching will mimic some particular characteristics of a randomized controlled trial and could be superior to multivariate Cox regression when correcting for confounding factors in observational studies [23]. The large number of measured variables used to compute the propensity score in our study should ensure reliability of our results.

In our study, patients with diabetes mellitus were on higher doses of diuretics and β-blockers and a larger proportion of them were on MRAs, calcium-channel blockers and statins compared to the nondiabetics when first visiting the outpatient HF clinics. It is recommended that patients with HF-REF and diabetes mellitus are treated with ACEi/angiotensin receptor blocker and β-blockers, supplemented with MRAs if symptoms persist [21, 37–43]. Outpatients with stable HF have a similar response to established HF treatment, irrespective of whether they have diabetes mellitus or not [44]. However, recent trials with novel therapies suggest that HF patients with diabetes might be more prone to developing adverse effects and that drugs may have different effects on HF patients with and without diabetes mellitus [45, 46].

The HF treatment at inclusion was well-matched in our propensity-matched patients with and without diabetes mellitus. After HF medication was optimized at the outpatient HF clinics, diabetic patients were prescribed higher doses of β-blockers and loop diuretics and more statins. Previous studies have shown that diabetic HF patients treated with β-blockers have a reduced HR for hospitalization and mortality [21, 47]. Thus, the intensified β-blocker treatment of Norwegian HF patients with diabetes mellitus might have contributed to our finding that the survival of diabetic HF patients had not deteriorated. The prognostic impact of the more extensive use of statins and diuretics in HF patients with diabetes mellitus in our study is less clear. Increasing doses of diuretics have been associated with both improved and worsened survival in observational studies, but the prognostic impact has never been evaluated in clinical trials [29, 48]. Statins did not prove to be beneficial in HF patients when prescribed in the absence of other indications [49, 50].

The study data originated from Norwegian Heart Failure Registry. We were unable to interfere with the collection of data, and the analyses were hence restricted to the existing data in the registry. The cases included in the propensity-matched analyses had to have complete data registration of the selected independent variables. After excluding the cases with incomplete data sets, 724 pairs of chronic HF patients were included in these analyses. We cannot eliminate that the propensity-matching procedure introduced a selection bias to our material as complete datasets were necessary to calculate a propensity score. The high number of independent variables included in the models should ensure the reliability of our results, but could have introduced a selection bias to our study because more patients did not have complete data sets and thus were not eligible for propensity score matching.

The diagnosis of diabetes mellitus at baseline was based on the medical records and the self-reported comorbidities. As glycosylated hemoglobin (HbA1c) was not recorded until 2008, only a minority of study patients had registered HbA1c values. No specific diabetes medication was registered. Thus, we were restricted to information from medical records and a self-reported diagnosis of diabetes mellitus at baseline. Some patients with undiagnosed diabetes mellitus may have been reported as not having diabetes. Furthermore, we could not examine the impact of glycemic control on the outcome. Previous studies on patients with diabetes mellitus at a high cardiovascular risk failed to show a positive effect of intensive glucose control on the outcomes of macrovascular disease or mortality [51]. Patients with advanced HF and diabetes mellitus and low HbA1c levels had a significantly increased HR for death compared to those with higher HbA1c levels [52–54]. This finding is not consistent in all studies, however [55]. As our study found diabetes mellitus to not be an independent predictor of mortality in patients with chronic HF, tight glycemic control should probably not be a major treatment goal in chronic HF patients.

Despite our finding that diabetes mellitus is not an independent predictor of all-cause mortality, diabetic HF patients experienced a high crude HR of mortality. They had more prevalent ischemic heart disease, hypertension and peripheral artery disease and lower hemoglobin and sodium levels, all well-recognized predictors of worse outcome in patients with HF [56–62]. They are also at a high risk of concomitant chronic kidney disease. Kidney disease is now acknowledged as a major cardiovascular risk factor [63–66] and independently predicts the outcome in chronic HF [67].

In summary, prevalent diabetes mellitus was not an independent predictor of all-cause mortality in Norwegian outpatients with chronic HF. Our findings support explanations other than tight glycemic control require assessment, in order to improve the prognosis of chronic HF patients with diabetes mellitus. One should focus on multidisciplinary cooperation to identify and manage comorbidities as well as on an increased effort to optimize the medical and nonmedical HF treatment so as to improve the prognosis of these high-risk patients.

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RESEARCH ARTICLE Open Access

Gender differences in association between uric acid and all-cause mortality in patients with chronic heart failure

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Abstract

Background: Elevated serum uric acid (SUA) is associated with poor prognosis in patients with cardiovascular disease, yet it is still not decided whether the role of SUA is causal or only reflects an underlying disease. The purpose of the study was to investigate if SUA was an independent predictor of 5-year all-cause mortality in a propensity score matched cohort of chronic heart failure (HF) outpatients. Furthermore, to assess whether gender or renal function modified the effect of SUA.

Methods: Patients ($n = 4684$) from the Norwegian Heart Failure Registry with baseline SUA were included in the study. Individuals in the highest gender-specific SUA quartile were propensity score matched 1:1 with patients in the lowest three SUA quartiles. The propensity score matching procedure created 928 pairs of patients (73.4% males, mean age 71.4 ± 11.5 years) with comparable baseline characteristics. Kaplan Meier and Cox regression analyses were used to investigate the independent effect of SUA on all-cause mortality.

Results: SUA in the highest quartile was an independent predictor of all-cause mortality in HF outpatients (hazard ratio (HR) 1.19, 95% confidence interval (CI) 1.03–1.37, *p*-value 0.021). Gender was found to interact the relationship between SUA and all-cause mortality (*p*-value for interaction 0.007). High SUA was an independent predictor of all-cause mortality in women (HR 1.65, 95% CI 1.24–2.20, *p*-value 0.001), but not in men (HR 1.06, 95% CI 0.89–1.25, *p*-value 0.527). Renal function did not influence the relationship between SUA and all-cause mortality (*p*-value for interaction 0.539).

Conclusions: High SUA was independently associated with inferior 5-year survival in Norwegian HF outpatients. The finding was modified by gender and high SUA was only an independent predictor of 5-year all-cause mortality in women, not in men.

Keywords: Uric acid, Heart failure, Gender, Kidney disease, All-cause mortality, Propensity score, Epidemiology

Background

The relationship between elevated serum uric acid (SUA) and cardiovascular (CV) disease and mortality is well recognized [1, 2], yet it is still undecided whether the association reflects a causal inference or whether SUA is a risk marker reflecting the burden of the underlying disease.

SUA, the end product of purine metabolism in humans, is catalysed by xanthine oxidase (XO) and predominantly eliminated by the kidneys [3]. Renal function, gender, race, and medication may all influence SUA level [2]. In addition, genetic studies have uncovered variants in urate reabsorption and excretion transporters that are responsible for some variation in SUA level [4].

High SUA in heart failure (HF) may result from impaired oxidative metabolism causing accumulation of uric acid precursors and increased XO activation [5] as well as from decreased renal elimination as chronic kidney disease (CKD) is highly prevalent [6].

High SUA levels have been found to be related to incident HF [7–10] and to be associated with poor outcomes in HF patients [11–14]. An association between SUA and incident, prevalent and progressive CKD has also been

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detected [15–17] but the results concerning effect of SUA on mortality in CKD patients are inconsistent [18–21].

Cardiovascular risk factors and outcomes differ between men and women [22]. Gender differences are also apparent in HF patients, both with regard to aetiology, left ventricle ejection fraction (LVEF) and prognosis [23–26]. The association between SUA and CV disease outcomes appears to be more pronounced in women than in men [7, 27, 28] but the role of gender in the relationship between SUA and survival of HF patients is not yet clearly determined.

Reducing the effect of confounding is crucial when estimating associations in observational studies. Propensity score matching is a statistical method that accounts for confounding variables in a different manner than traditional multivariate Cox proportional hazards model and might be a superior method [29].

The aim of the current study was to examine whether SUA is an independent predictor of all-cause mortality in a propensity score matched cohort of Norwegian HF outpatients. Furthermore, we aimed to analyse if the effect of SUA on all-cause mortality is modified by gender or renal function.

Methods

The Norwegian heart failure registry

The Norwegian Heart Failure Registry has collected data on outpatients referred to HF clinics in Norwegian hospitals since 2000. By February 2012, a total of 6675 patients were enrolled by 25 HF clinics in different Norwegian regions that cover about half of Norway's population. The participating HF clinics were run by cardiologists and specialized nurses. Patients were registered after they had been diagnosed with chronic HF of any aetiology following the guidelines of the European Society of Cardiology (ESC) [30, 31]. Three visits were recorded. At the time of the first visit (baseline), medical history, physical examination, echocardiography, New York Heart Association (NYHA) functional class, laboratory results, and the medical management of HF were recorded. The last adjustment visit was recorded at stable follow-up, after the multidisciplinary team had optimized the treatment and the patient had participated in an educational program. At the time of the third visit, arranged 6 months after the last adjustment visit, patient's health condition was reassessed, as well as medication and laboratory results. Mortality data are retrieved yearly from Statistics Norway.

Study population

A total of 4953 (74.2%) patients in the Norwegian Heart Failure Registry had available baseline measurements of SUA and were eligible for the study. The patients in each reporting hospital were grouped into gender specific SUA quartiles, as the participating hospitals used different laboratory assays for SUA analyses and the recommended reference range of SUA differs for women and men (women 18–49 years: 155–350 μmol/l, women over 50 years: 155–400 μmol/l, men: 230–480 μmol/l) [32]. Subjects from hospitals with less than 40 registered subjects were excluded to achieve proper stratification. Consequently, 4684 patients from 19 hospitals were stratified and included in the analyses. Finally, patients in each SUA quartile were merged together across hospitals and gender, comprising about 1180 subjects in each group.

Definitions

Renal function was expressed as estimated glomerular filtration rate (eGFR) and calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [33]. Reduced renal function was defined as eGFR< 60 ml/min/1.73 m^2.

Based on 2016 ESC Guidelines on HF [34], LVEF was defined as reduced at < 40% and as preserved at ≥50%.

Diagnosis of hypertension was based on information on antihypertensive treatment.

Daily doses of angiotensin-converting enzyme inhibitors (ACEi) were converted to enalapril equivalent doses (enalapril 20 mg = lisinopril 20 mg = ramipril 10 mg = captopril 100 mg), and then expressed as percent of enalapril target dose. Target dose of enalapril was defined as 20 mg per day. Daily doses of loop diuretics were converted to furosemide equivalent doses (furosemide 40 mg = bumetanide 1 mg). Daily doses of β-blockers were converted to metoprolol equivalent doses (metoprolol 200 mg = bisoprolol 10 mg = carvedilol 50 mg = atenolol 100 mg).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies (percentage). Differences in continuous variables were compared by one-way analysis of variance and Student t-test as required. Similarly, differences in categorical variables were compared by χ^2 test. The two-tailed significance level test was set to $p < 0.05$.

An individual propensity score, the likelihood of SUA being in the highest quartile, was obtained for each patient using a multivariate logistic regression model. Baseline variables found to be associated with SUA in the highest quartile (p-value < 0.10) and variables that could potentially confound the relationship between SUA and mortality were chosen as independent variables when calculating the propensity score. The following 16 covariates were entered in the model: gender, age, body mass index (BMI), smoking, diabetes mellitus, claudication and/or previous stroke, systolic blood pressure, NYHA functional class, use of renin-angiotensin-system (RAS)-blocking agents, β-blocker dose, diuretic dose, use of statin, eGFR, haemoglobin, serum sodium and serum potassium. Patients with SUA in the fourth quartile were then matched 1:1 to patients

Table 1 Baseline characteristics of HF outpatients before and after propensity score matching, by SUA quartiles

	Quartiles of SUA in 4684 HF outpatients					1856 HF Outpatients after PSM		
	1 ($n = 1187$)	2 ($n = 1169$)	3 ($n = 1154$)	4 ($n = 1174$)	*P*-value	SUA Quartile 1–3 ($n = 928$)	SUA Quartile 4 ($n = 928$)	*P*-value
Se-uric acid, μmol/L	310.6 ± 51.5	405.4 ± 35.8	490.3 ± 36.5	635.2 ± 88.2	< 0.001	427.7 ± 80.3	633.3 ± 85.3	< 0.001
Se-uric acid, mg/dL	5.22 ± 0.87	6.82 ± 0.60	8.24 ± 0.61	10.68 ± 1.48		7.19 ± 1.35	10.65 ± 1.43	
Male gender, %	73.0	73.7	74.5	71.9	0.527	73.5	73.3	0.916
Age, years	68.0 ± 12.8	68.8 ± 11.9	69.5 ± 12.1	71.9 ± 11.1	< 0.001	71.3 ± 11.3	71.4 ± 11.7	0.770
Body mass index, kg/m^2	25.3 ± 4.7	26.2 ± 5.0	27.0 ± 5.3	26.9 ± 5.3	< 0.001	26.5 ± 5.2	26.6 ± 5.1	0.683
Smoking, %	18.5	15.9	13.8	13.0	0.001	14.3	13.8	0.738
Medical history								
Diabetes mellitus, %	15.9	18.7	19.8	24.0	< 0.001	20.8	21.6	0.691
Ischaemic heart disease, %	55.1	54.5	56.1	58.1	0.334	57.8	57.5	0.919
Hypertension, %	22.9	32.8	33.7	38.8	< 0.001	36.8	38.7	0.395
Claudication/stroke, %	13.6	14.8	15.2	17.2	0.106	17.6	17.1	0.806
PCI/CABG, %	37.2	39.8	37.7	37.7	0.575	38.7	38.6	0.968
Reduced renal function, %	21.6	31.9	47.4	71.9	< 0.001	67.1	68.5	0.518
Physical findings								
Heart rate, beats/min	71.8 ± 14.3	71.9 ± 14.4	73.0 ± 15.5	73.6 ± 15.5	0.008	74.5 ± 16.1	73.7 ± 15.3	0.265
SBP, mmHg	127.9 ± 22.2	128.1 ± 22.7	127.0 ± 21.7	123.4 ± 22.5	< 0.001	125.3 ± 22.0	124.4 ± 22.4	0.398
LVEF, %	33.4 ± 11.1	32.7 ± 11.2	32.4 ± 11.6	32.4 ± 12.5	0.131	32.3 ± 11.7	32.2 ± 12.7	0.956
LVEF groups					0.171			0.557
LVEF< 40%	72.2	74.6	73.2	74.9		74.3	75.6	
40% ≤ LVEF< 50%	18.6	16.3	18.1	14.6		16.0	14.1	
LVEF≥50%	9.2	9.1	8.7	10.6		9.8	10.3	
NYHA Class					< 0.001			0.548
I + II, %	58.4	52.2	47.8	37.6		39.8	36.9	
III + IV, %	41.7	47.9	52.3	62.4		60.3	63.0	
Medication								
RAS-blocking agent use, %	89.0	90.8	90.1	87.2	0.027	88.8	88.1	0.663
ACEi dose/day, % of target dose	48.1 ± 36.4	53.1 ± 37.8	54.9 ± 38.0	52.9 ± 41.8	0.001	51.6 ± 38.3	53.1 ± 42.2	0.486
ARB use, %	14.2	14.7	16.8	17.4	0.089	16.6	17.0	0.804
β-blocker dose/day, mg	61.1 ± 58.2	74.2 ± 67.4	72.3 ± 61.8	77.7 ± 66.7	< 0.001	76.8 ± 66.1	75.2 ± 65.6	0.605
Loop diuretics dose/day, mg	34.4 ± 43.9	47.6 ± 53.6	62.9 ± 48.5	87.5 ± 72.5	< 0.001	72.2 ± 70.5	83.4 ± 70.4	0.001
Calcium channel blocker use, %	7.4	8.2	8.3	8.4	0.785	8.9	7.3	0.225
Acetylsalicylic acid use, %	51.3	47.9	45.5	43.4	0.001	44.5	43.4	0.644
Statin use, %	56.0	56.1	54.3	51.8	0.124	51.9	51.6	0.889
Laboratory values								
eGFR, ml/min/1.73 m^2	75.3 ± 20.4	69.2 ± 20.5	62.6 ± 21.0	50.9 ± 20.7	< 0.001	54.1 ± 19.8	52.9 ± 20.8	0.205
Haemoglobin, g/100 mL	13.79 ± 1.57	14.00 ± 1.65	13.89 ± 1.72	13.70 ± 1.89	< 0.001	13.78 ± 1.78	13.75 ± 1.85	0.700
Se-potassium, mmol/L	4.38 ± 0.41	4.41 ± 0.43	4.38 ± 0.49	4.41 ± 0.52	0.136	4.43 ± 0.50	4.40 ± 0.50	0.280
Se-sodium, mmol/L	139.7 ± 3.3	140.0 ± 3.1	140.0 ± 3.2	139.7 ± 3.4	0.024	139.8 ± 3.3	139.7 ± 3.3	0.530
Se-cholesterol, mmol/L	4.65 ± 1.23	4.71 ± 1.22	4.79 ± 1.31	4.72 ± 1.33	0.097	4.73 ± 1.29	4.75 ± 1.31	0.745

Values are expressed as mean ± SD or percent. ACEi dose/day, percent of daily enalapril equivalent target dose; ARB, angiotensin receptor blocker; β-blocker dose/day, daily metoprolol equivalent dose; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI/CABG, percutaneous coronary intervention and/or coronary artery bypass graft; PSM, propensity score matching; RAS-blocking agent, renin-angiotensin system blocking agent; SBP, systolic blood pressure; SUA, serum uric acid

with SUA in quartiles 1–3 on the propensity score, using match tolerance of 0.05 with no replacement and preference to exact match.

Five-year survival curves were presented using Kaplan-Meier statistics. Univariate Cox proportional hazards model was used in the propensity score matched cohort and presented as hazard ratio (HR) and 95% confidential interval (95% CI). Due to the limited number of female patients, multivariable Cox proportional hazards model was used when evaluating the effect of SUA on all-cause mortality in the gender-stratified model. Baseline variables found to be associated with SUA in the highest quartile in women (p-value< 0.10) were included in the multivariate model: age, BMI, smoking, ischaemic heart disease, diabetes mellitus, hypertension, NYHA functional class, systolic blood pressure, LVEF, use of RAS-blocking agents, β-blocker dose, diuretic dose, eGFR, and serum sodium.

All statistical analyses were performed using IBM SPSS Statistics version 25 (IBM SPSS Statistics, New York, USA). Kaplan Meier survival curves were obtained using STATA/SE version 14.1 (StataCorp LP, Texas, USA).

Results

Baseline characteristics and propensity score matching

Baseline characteristics of the 4684 included HF outpatients are presented by SUA quartiles in Table 1. The mean age was 69.6 ± 12.2 years and 73.3% were males. Patients in higher SUA quartiles were more prone to be older, to have a history of diabetes and hypertension, more severe HF symptoms, higher BMI and worse renal function compared to patients in the lower SUA quartiles. They used higher doses of diuretics and β-blockers and were less likely to use RAS-blocking agents and acetylsalicylic acid. The median follow-up was 50 (interquartile range (IQR) 27, 78) months.

Kaplan-Meier survival curves for SUA in quartiles 1–3 were almost superimposable and all-cause mortality for individuals with SUA in quartile 4 was significantly greater than for those with SUA in quartiles 1–3 (log-rank < 0.001, Fig. 1). Individuals with SUA in the lowest three quartiles were therefore all selected to be potential controls in the propensity matched model. A total of 928 subjects with SUA in quartile 4 were matched 1:1 by propensity score to subjects with SUA in quartiles 1–3. Baseline characteristics of the 1856 propensity score matched subjects were well-balanced (Table 1).

Survival analyses and outcomes based on SUA level

SUA in the highest quartile was an independent predictor of all-cause mortality in HF outpatients (HR 1.19, 95% CI 1.03–1.37, p-value 0.021, Fig. 2).

Gender was found to interact the relationship between SUA and all-cause mortality in the propensity matched model (p-value for interaction 0.007). Differences in the survival of HF outpatients depending on gender and SUA quartile are depicted in Kaplan-Meier survival curves in Fig. 3. High SUA was an independent predictor of all-cause mortality in women (HR 1.65, 95% CI 1.24–2.20, p-value 0.001) but not in men (HR 1.06, 95% CI 0.89–1.25, p-value 0.527). Renal function did not interact the relationship between SUA and all-cause mortality (p-value for interaction 0.539).

Women and men with SUA in the highest quartile differed both in age, comorbidity, medication, and physical and laboratory findings from those with lower SUA (Table 2). The number of female patients was limited and a gender-stratified propensity matched model was not possible. Subsequently, gender specific multivariate Cox proportional hazard model analyses in the subgroups of 1251 female and 3433 male HF outpatients were performed

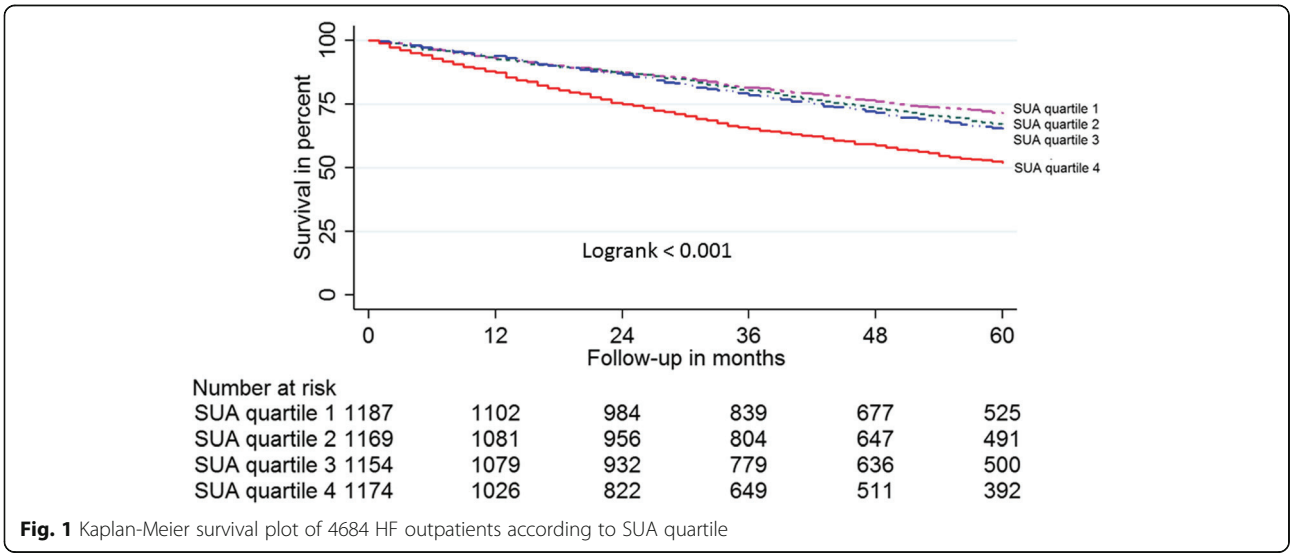

Fig. 1 Kaplan-Meier survival plot of 4684 HF outpatients according to SUA quartile

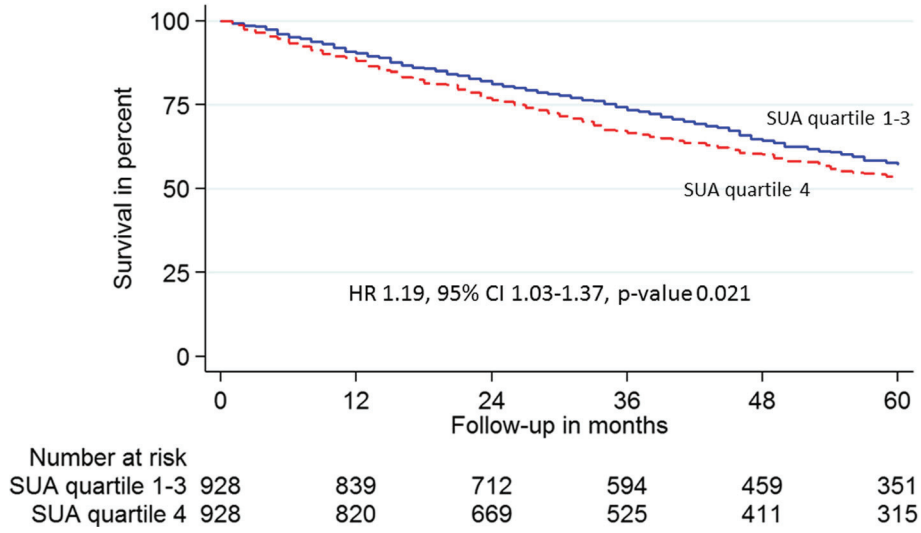

Fig. 2 Kaplan-Meier survival plot of 1856 HF outpatients propensity score matched by SUA in quartile 4

to further explore gender differences in the prognostic value of SUA on survival. In the subgroup of female HF outpatients, SUA in the highest quartile was confirmed to be an independent predictor of all-cause mortality (HR 1.51, 95% CI 1.13–2.02, *p*-value 0.005). On the contrary, SUA did not independently predict all-cause mortality in the subgroup of male HF outpatients (HR 1.10, 95% CI 0.94–1.30, *p*-value 0.249).

Discussion

The current study demonstrates that high level of SUA was an independent predictor of 5-year all-cause mortality in patients with chronic HF. The finding was gender specific and only found in women. To our knowledge, this is the first propensity score matched study to report the gender modifying effect on the relationship between SUA and all-cause mortality in chronic HF. The predictive value of SUA on mortality was not modified by renal function.

Other studies have found an association between high levels of SUA and poor outcome in chronic HF patients [13, 21, 35–37], still the causal relationship is considered undecided. We report SUA in the fourth quartile to be an independent predictor of all-cause mortality selectively in women, both in the propensity score matched model and multivariate Cox regression model.

Gender differences in the effect of SUA on outcomes have been reported previously in patients with CV disease. In hypertensive patients with left ventricular hypertrophy, the association between SUA and CV events was reported to be stronger in women than in men [28]. A study of patients with acute coronary syndrome showed that SUA was predictive of CV events in women but not in men [38]. Similarly, in a population based survey, SUA was found to be an independent predictor of mortality in women only [27]. Our results now expand the evidence for gender differences in the effect of SUA also to be valid in HF outpatients.

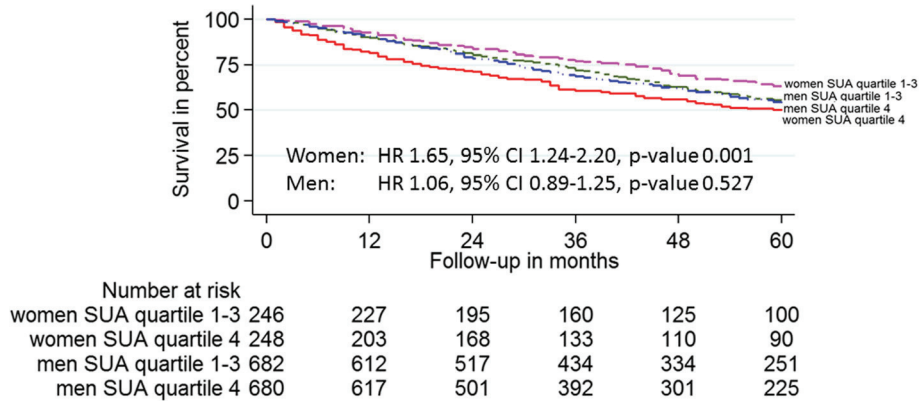

Fig. 3 Kaplan-Meier survival plot of propensity score matched HF outpatients according to gender and SUA quartile

Table 2 Gender-specific baseline characteristics of HF outpatients, by SUA quartiles

	All ($n = 4684$)			Women ($n = 1251$)			Men ($n = 3443$)		
	Women ($n = 1251$)	Men ($n = 3433$)	*P*-value	SUA Quartile 1–3 ($n = 921$)	SUA Quartile 4 ($n = 330$)	*P*-value	SUA Quartile 1–3 ($n = 2589$)	SUA Quartile 4 ($n = 844$)	*P*-value
Se-uric acid, μmol/L	435.2 ± 143.9	468.9 ± 127.1	< 0.001	367.4 ± 86.1	624.1 ± 96.6	< 0.001	413.3 ± 80.7	639.6 ± 84.3	< 0.001
Se-uric acid, mg/dL	7.32 ± 2.42	7.88 ± 2.14		6.18 ± 1.45	10.49 ± 1.62		6.95 ± 1.36	10.75 ± 1.42	
Age, years	72.1 ± 12.1	68.6 ± 12.1	< 0.001	70.7 ± 12.3	76.2 ± 10.4	< 0.001	68.1 ± 12.2	70.3 ± 11.6	< 0.001
Body mass index, kg/m^2	25.6 ± 5.6	26.6 ± 4.9	< 0.001	25.4 ± 5.6	26.1 ± 5.4	0.054	26.4 ± 4.9	27.1 ± 5.2	0.001
Smoking, %	12.6	16.3	0.002	14.3	7.9	0.002	16.8	15.1	0.247
Medical history									
Diabetes mellitus, %	18.7	19.9	0.352	16.6	24.6	0.001	18.7	23.7	0.001
Ischaemic heart disease, %	46.0	59.6	< 0.001	44.2	50.8	0.045	59.1	61.1	0.323
Hypertension, %	37.1	30.2	< 0.001	33.5	47.1	< 0.001	28.4	35.6	< 0.001
Claudication/stroke, %	13.6	15.8	0.071	13.4	14.1	0.777	14.9	18.4	0.016
PCI/CABG, %	26.1	42.5	< 0.001	25.9	26.7	0.774	42.6	42.0	0.746
Reduced renal function, %	51.3	40.1	< 0.001	39.7	83.6	< 0.001	31.3	67.3	< 0.001
Physical findings									
Heart rate, beats/min	73.5 ± 14.3	72.2 ± 15.2	0.008	73.1 ± 14.5	74.6 ± 13.7	0.105	71.9 ± 14.8	73.1 ± 16.1	0.044
SBP, mmHg	128.2 ± 23.1	126.0 ± 22.0	0.004	128.9 ± 23.2	126.3 ± 22.8	0.079	127.2 ± 21.8	122.3 ± 22.4	< 0.001
LVEF, %	35.8 ± 13.3	31.7 ± 10.8	< 0.001	35.3 ± 12.5	37.1 ± 15.3	0.092	32.0 ± 10.7	30.8 ± 10.9	0.007
LVEF groups			< 0.001			0.023			0.031
LVEF< 40%	64.6	76.8		66.1	59.8		75.8	80.0	
40%≤LVEF<50%	19.5	16.0		19.7	18.9		17.0	13.1	
LVEF≥50%	15.9	7.2		14.1	21.2		7.2	6.9	
NYHA Class			0.001			< 0.001			< 0.001
I + II, %	44.1	50.8		50.0	27.5		53.8	41.5	
III + IV, %	55.9	49.2		50.0	72.5		46.2	58.4	
Medication									
RAS-blocking agent use, %	87.3	90.0	0.008	88.7	83.3	0.012	90.4	88.7	0.159
ACEi dose/day, % of target dose	49.3 ± 40.0	53.2 ± 38.0	0.005	49.3 ± 36.9	49.4 ± 47.8	0.975	52.9 ± 37.7	54.2 ± 39.2	0.452
ARB use, %	17.4	15.2	0.060	16.8	19.1	0.353	14.7	16.7	0.144
β-blocker dose/day, mg	67.6 ± 62.2	72.6 ± 64.5	0.017	65.6 ± 60.0	73.1 ± 14.5	0.059	70.4 ± 63.7	79–4 ± 66.2	< 0.001
Loop diuretics dose/day, mg	86.7	85.1	0.149	44.2 ± 45.6	90.4 ± 83.1	< 0.001	49.2 ± 51.5	86.4 ± 67.9	< 0.001
Calcium channel blocker use, %	9.2	7.6	0.080	8.6	10.9	0.205	7.7	7.4	0.727

Table 2 Gender-specific baseline characteristics of HF outpatients, by SUA quartiles *(Continued)*

	All ($n = 4684$)			Women ($n = 1251$)			Men ($n = 3443$)		
	Women ($n = 1251$)	Men ($n = 3433$)	*P*-value	SUA Quartile 1–3 ($n = 921$)	SUA Quartile 4 ($n = 330$)	*P*-value	SUA Quartile 1–3 ($n = 2589$)	SUA Quartile 4 ($n = 844$)	*P*-value
Acetylsalicylic acid use, %	44.4	48.0	0.027	45.3	41.8	0.278	49.3	44.0	0.007
Statin use, %	46.7	57.4	< 0.001	47.7	43.9	0.245	58.2	54.9	0.086
Laboratory values									
eGFR, ml/min/1.73 m^2	60.3 ± 22.7	66.1 ± 22.3	< 0.001	66.0 ± 21.5	44.6 ± 18.1	< 0.001	70.2 ± 21.1	53.4 ± 21.1	< 0.001
Haemoglobin, g/100 mL	13.31 ± 1.53	14.04 ± 1.74	< 0.001	13.32 ± 1.43	13.21 ± 1.77	0.202	14.09 ± 1.68	13.90 ± 1.90	0.010
Se-potassium, mmol/L	4.32 ± 0.48	4.42 ± 0.46	< 0.001	4.32 ± 0.45	4.32 ± 0.53	0.950	4.41 ± 0.44	4.45 ± 0.51	0.055
Se-sodium, mmol/L	139.4 ± 3.1	140.0 ± 3.1	< 0.001	139.6 ± 3.5	139.1 ± 3.5	0.047	140.0 ± 3.1	139.9 ± 3.1	0.331
Se-cholesterol, mmol/L	5.08 ± 1.34	4.58 ± 1.22	< 0.001	5.06 ± 1.33	5.11 ± 1.38	0.588	4.59 ± 1.20	4.56 ± 1.28	0.561

Values are expressed as mean ± SD or percent. ACEi dose/day, percent of daily enalapril equivalent target dose; ARB, angiotensin receptor blocker; β-blocker dose/day, daily metoprolol equivalent dose; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI/CABG, percutaneous coronary intervention and/or coronary artery bypass graft; RAS-blocking agent, renin-angiotensin system blocking agent; SBP, systolic blood pressure; SUA serum uric acid

In most previous studies assessing differences in survival between men and women with HF, women have been reported to have better survival than men [25, 39–44]. Sex hormones affect myocardial calcium handling, nitric oxide, glucose and fatty metabolism as well as cardiac fibrosis, and may participate in the mechanisms for differences between female and male failing hearts [26]. SUA is a potent antioxidant but at the same time, SUA and XO lead to reduced nitric oxide bioavailability, ensuing endothelial dysfunction, inflammation and vasoconstriction [45]. Menopause has been found to be associated with increasing SUA, possibly due to altered effect of oestrogen on renal tubular handling of uric acid [46]. We did not have information on menopausal status in female HF outpatients in the current study, but the mean age of 72.1 ± 12.1 years implies that the great majority were postmenopausal. Our study revealed distinct differences between women and men with SUA in quartile 4 with regard to age, type, symptoms and treatment of HF, as well as comorbidity and renal function. Still, both the propensity score matched model and multivariate Cox regression model identified SUA in the highest quartile to be a predictor of all-cause mortality in women independently of the above mentioned confounding variables. The mechanisms for the deteriorating effect of high SUA on survival selectively in postmenopausal women need to be further explored, yet our findings may imply SUA being a future treatment target in female HF patients. Urate-lowering therapy is currently not recommended in asymptomatic hyperuricemia due to limited benefit-risk data in non-gout diseases [47]. Nevertheless, XO-inhibiting therapy has been shown to have beneficial effects in some patient groups [48]. In HF patients with hyperuricemia, XO-inhibition did not improve survival, but it is noteworthy that the study was not gender stratified and only of 24-week duration [49].

Renal function did not modify the effect of SUA on all-cause mortality in the present study. This corroborates the observation by Anker et al. [13] who also found SUA to be a predictor of poor outcome in HF independent of renal function, while Filippatos et al. [21] found SUA to be associated with poor outcome only in HF patients without CKD. Studies exploring SUA impact in patients with CKD show inconsistent results [18–20].

Some limitations of our study need to be considered. Because of various laboratory assays for SUA analyses in the reporting hospitals, we grouped patients in each hospital into gender-specific SUA quartiles. Small groups may cause a systematic error and therefore we did not include patients from hospitals with less than 40 registered individuals. On the other hand, we might have introduced a selection bias by excluding some hospitals. Patients in each SUA quartile were merged together across hospitals and gender, eventually leading to some overlapping SUA values in the four quartiles.

We used both propensity score method and multivariate Cox regression method to reduce the bias by confounding. Propensity score matching is an increasingly used method that mimics some characteristics of randomized control trials (RCT) and makes it possible to directly compare outcomes in the two studied groups [29]. We used propensity score matching when assessing the impact of high SUA on survival in all HF outpatients. Propensity score for having SUA in the highest quartile was estimated based on 16 measured baseline variables. Two groups of patients were established based on propensity score, differing in the presence or absence of SUA in the fourth quartile and, similarly to RCTs, we could then directly compare survival in the groups. Distribution of baseline characteristic in the propensity matched groups was well-balanced except for daily doses of diuretics. However, the difference was minor and is unlikely to explain the disparity in survival. Furthermore, the large size of the study population and the high number of variables used for estimation of propensity score and the fact that nearly 80% of patients with SUA in the highest quartile were propensity score matched should ensure reliability of our results. In the gender stratified analyses, we used multivariate Cox proportional hazard model to correct for the confounding variables as propensity score matching would lead to small size of the examined groups and thus could possibly introduce a selection bias. Yet, neither propensity score matching nor multivariate Cox proportional hazards method can correct for unmeasured confounding variables.

The current study is observational and therefore restricted to the existing data in the Norwegian Heart Failure Registry. We could not influence selection of the collected variables. Information on alcohol consumption, losartan use, hormone replacement therapy, the use of SUA lowering drugs, thyroid function, and triglycerides level could have added valuable information. At the same time, the observational nature of this study is among its strengths as the included patients represent a relatively unselected population in contrast to highly selected subjects in RCTs.

Conclusions

SUA in the highest quartile was independently associated with inferior 5-year survival in Norwegian HF outpatients. The finding was modified by gender and high SUA was only an independent predictor of 5-year all-cause mortality in women but not in men. Our findings indicate that SUA might be a therapeutic target selectively in female HF patients. Renal function did not modify the effect of SUA on all-cause mortality.

Abbreviations

ACEi: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin II receptor blocker; BMI: Body mass index; CI: Confidence interval; CKD: Chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CV: Cardiovascular; eGFR: Estimated glomerular filtration rate; ESC: European

Society of Cardiology; HF: Heart failure; HR: Hazard ratio; IQR: Interquartile range; LVEF: Left ventricle ejection fraction; NYHA: New York Heart Association; PCI/CABG: Percutaneous coronary intervention and/or coronary artery bypass graft; RAS: Renin-angiotensin system; SUA: Serum uric acid; XO: Xanthine oxidase

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Availability of data and materials
The data that support the findings of this study are available from the Norwegian Heart Failure Registry but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Norwegian Heart Failure Registry.

Authors' contributions
VS, BWG and IO are responsible for the study design. MG provided the data on behalf of the Norwegian Heart Failure Registry. VS and BWG performed the statistical analyses and VS wrote the manuscript. VS, BWG, IO, AH, MDS, ASW, MG and DA have all participated in interpretation of the results and critically revised and approved the final version of the manuscript. All authors take public responsibility for the content.

Ethics approval and consent to participate
All patients enrolled in the Norwegian Heart Failure Registry had given written informed consent prior to inclusion in the database. The study was approved by the Regional Committee of Medical Research Ethics South East (Ref. no. 2014/1449).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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