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# RENAL DYSFUNCTION IN HEART FAILURE, INSIGHTS ON PREVALENCE AND PROGNOSIS

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*Alt for å finne det sannes mysterium,*
*- det er den ekte forskers kriterium.*

*Henrik Ibsen, Peer Gynt (1867)*

*Til min far*

# Renal dysfunction in heart failure, insights on prevalence and prognosis

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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# ABSTRACT


## Background

Kidney disease is common in heart failure (HF) and has been found to be associated with worse outcomes. The impact of different degrees of chronic kidney disease (CKD) in HF, as well as the link to, and impact of CKD in HF with reduced (HFrEF), the newly defined mid-range (HFmrEF) and preserved ejection fraction (HFpEF) have been uncertain. Studies of worsening renal function (WRF) in the various EF groups are lacking. HF treatment of HFrEF is well defined, while we lack knowledge of the effect of heart failure treatment in HFpEF, HFmrEF and in patients with HF and CKD.

## Aims

1. To examine prevalence and prognostic impact of different degrees of kidney dysfunction in unselected HF patients.

2. To perform a comprehensive comparison of CKD in HF with HFpEF, HFmrEF and HFrEF with regards to prevalence, clinical correlates and prognosis.

3. To examine the risk for and impact of WRF in HFpEF, HFmrEF and HFrEF.

4. To analyze the association between mineralocorticoid receptor antagonist (MRA) treatment and outcome in patients with myocardial infarction (MI) and HF in relation to EF groups and CKD.

## Prevalence and prognostic impact of kidney disease in heart failure

We studied 47,716 patients in the Swedish Heart Failure Registry (SwedeHF) 2000-2013. Patients were divided into five renal function strata based on estimated glomerular filtration rate (eGFR). 51% of the patients had eGFR < 60 ml/min/1.73 m2 and 11% had eGFR < 30 ml/min/1.73 m2. The mortality risk increased with decreasing eGFR and persisted after adjusting for differences in baseline characteristics, severity of heart disease and medical treatment.

## Associations with and prognostic impact of CKD in HFpEF, HFmrEF and HFrEF

Of 40,230 patients with measured EF in SwedeHF, 22% had HFpEF, 21% had HFmrEF, and 57% had HFrEF, with a CKD prevalence of 56%, 48%, and 45%, respectively. Associations between covariates and CKD were similar in all EF groups. There was higher mortality in all EF groups in patients with CKD. After adjustment, CKD was more strongly associated with death in HFrEF and HFmrEF than in HFpEF.

## WRF in different EF categories

After merging the SwedeHF registry with the laboratory data in Stockholm Creatinine Measurement (SCREAM) database, 7,154 patients in Stockholm between 2006-2010 were

studied. After discharge, the risk for WRF was higher in HFpEF than in HFmrEF and HFrEF. Variables related to more severe HF were predictive of WRF. WRF within year one after the index-HF event was strongly associated with long-term mortality, but in HFpEF only with the most severe WRF.

**Outcome in MI patients with HF with or without MRA treatment**

Patients with MI and HF registered in the Swedish national myocardial infarction registry, SWEDEHEART, between 2005-2014, were studied. Of 45,071 patients with MI and HF, 10% were treated with MRA. Patients with reduced EF < 40% were more often treated with MRA compared to mid-range EF 40-49% and normal EF $\geq$ 50%. Of patients with CKD, 9% received MRA. After adjustment, MRA use was associated with a lower mortality in patients with EF < 40% but not with EF $\geq$ 50% while the association between MRA use and outcome was similar regardless of presence or not of CKD.

**Conclusions**

In unselected HF patients, half of the patients have at least moderate renal dysfunction. There is a strong graded association between renal dysfunction and both short- and long-term outcome. CKD is slightly more common in patients with HFpEF but is associated with similar covariates regardless of EF. CKD is strongly associated with mortality regardless of EF group, although less strongly in HFpEF than in HFmrEF and HFrEF. The long-term risk of WRF is high in HF and especially in HFpEF. WRF within one year of discharge is a strong negative prognostic factor in all EF groups during long term follow-up, although in HFpEF only in those with the most severe WRF. In patients with MI and HF, MRA treatment is associated with better long-term survival in patients with reduced but not with preserved EF, while the association between MRA use and outcome seems to be similar regardless of presence or not of CKD.

# SAMMANFATTNING


## Bakgrund

Nedsatt njurfunktion är vanligt vid hjärtsvikt och har visat sig vara en negativ prognostisk faktor. Betydelsen av olika grader av sänkt njurfunktion vid hjärtsvikt samt sambandet mellan och betydelsen av njursvikt vid hjärtsvikt med sänkt (HFrEF), lätt sänkt (HFmrEF) och bevarad ejektionsfraktion (HFpEF) är okänt. Studier av försämring av njurfunktionen över tid (WRF) i de olika EF grupperna saknas. Hjärtsviktsbehandling vid HFrEF är väl studerad, medan vi saknar kunskap om hjärtsviktsbehandling vid HFpEF och HFmrEF och vid hjärtsvikt med samtidig njursvikt.

## Syfte

1. Att undersöka förekomsten och prognostisk betydelse av olika grader av nedsatt njurfunktion hos oselekterade hjärtsviktspatienter.

2. Att göra en jämförelse av njursvikt vid HFpEF, HFmrEF och HFrEF avseende förekomst, kliniska samband och prognostisk betydelse.

3. Att undersöka förekomst av och den prognostiska betydelsen av WRF vid HFpEF, HFmrEF och HFrEF.

4. Att undersöka associationen mellan behandling med mineralkortikoidreceptorantagonister (MRA) och utfall hos patienter med hjärtinfarkt och hjärtsvikt i relation till EF grupp och förekomst av njursvikt.

## Prevalens och prognostisk betydelse av njursvikt vid hjärtsvikt

Vi studerade 47 716 patients i det Svenska Hjärtsviktsregistret (Riks-Svikt) 2000-2013. Patienterna blev indelade i fem njurfunktionsgrupper baserat på estimerat glomerulär filtrationshastighet (eGFR). 51 % av patienterna hade minst måttlig njurfunktionsnedsättning (eGFR < 60 ml/min/1.73 m2) och 11 % hade minst avancerat nedsatt njurfunktion (eGFR < 30 ml/min/1.73 m2). Mortalitetsrisken ökade med sjunkande eGFR och kvarstod efter justering för skillnader i bakgrundsvariablerna, svårighetsgraden av hjärtsjukdomen och medicinsk behandling.

## Associationer med och prognostisk betydelse av njursvikt vid HFpEF, HFmrEF och HFrEF

Av 40 230 patienter i Riks-Svikt hade 22% HFpEF , 21% HFmrEF och 57% HFrEF med en prevalens av njursvikt på 56%, 48%, and 45%. Det var liknande associationer mellan bakgrundsvariablerna och njursvikt i alla EF grupperna. Det var en högre mortalitet hos patienterna med njursvikt. Efter justering var njursvikt starkare associerat med död och predicerade död starkare vid HFrEF och HFmrEF än vid HFpEF.

**Försämring av njurfunktion över tid vid olika EF kategorier**

Efter samkörning av Riks-Svikt med data från Stockholm Creatinine Measurement (SCREAM) databasen, studerades 7154 patienter i Stockholm från åren 2006-2010. Risken för WRF var högst hos patienterna med HFpEF. Faktorer relaterade till svår hjärtsvikt var också relaterade till WRF. WRF under det första året var starkt associerat med mortalitet över lång tid, dock vid HFpEF var det enbart vid svårare WRF.

**Patienter med hjärtinfarkt och hjärtsvikt med och utan behandling med MRA**

Patienter med hjärtinfarkt och hjärtsvikt registrerade i det Svenska Hjärtinfarktsregistret (SWEDEHEART), 2005-2014 studerades. Av 45 071 patienter med hjärtinfarkt och hjärtsvikt behandlades 10% med MRA. Patienter med sänkt EF < 40% hade oftare MRA behandling jämfört med patienter med EF 40-49% och bevarad EF $\geq$ 50%. Av patienterna med njursvikt fick 9% MRA behandling. Efter justering var MRA behandling associerat med lägre dödlighet hos patienter med EF < 40% och EF 40-49% men inte vid EF $\geq$ 50% medan risken för död med MRA behandling var oförändrad oberoende av förekomst av njursvikt.

**Slutsatser**

Hälften av alla oselekterade hjärtsviktspatienter har minst måttligt nedsatt njurfunktion. Sänkt njurfunktion har en graderad association med prognosen på kort och lång sikt. Njursvikt är något mera vanligt vid HFpEF, men är associerat med samma variabler oberoende av EF grupp. Njursvikt är starkt associerat med mortalitet i alla EF grupper, men har en mindre stark prognostisk betydelse vid HFpEF än vid HFmrEF och HFrEF. Det är en hög risk för försämring av njurfunktionen över tid vid hjärtsvikt, särskilt vid HFpEF. WRF under första året efter en hjärtsviktshändelse är en stark negativ prognostisk faktor, dock vid HFpEF enbart vid svårare WRF. Hos patienter med hjärtinfarkt och hjärtsvikt är MRA behandling associerat med förbättrad överlevnad vid sänkt men inte vid bevarad EF. Oberoende av förekomst av njursvikt så ser associationen mellan MRA behandling och dödlighet ut att vara oförändrad.

# LIST OF SCIENTIFIC PAPERS

I. Prevalence and prognostic impact of kidney disease on heart failure patients
*Open Heart. 2016 Jan 18;3(1):e000324*

II. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range and reduced ejection fraction
*Eur J Heart Fail*. 2017; Dec;19(12):1606-1614

III. Incidence of, associations with and prognostic impact of worsening renal function in heart failure with different ejection fraction categories
*Submitted manuscript July 2018*

IV. Association between mineralocorticoid receptor antagonist use and outcome in myocardial infarction patients with heart failure
*J Am Heart Assoc 2018 Jul 6;7(14)*

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ACEi | angiotensin converting enzyme inhibitors |
| AHF | acute heart failure |
| AKI | acute kidney injury |
| ARB | angiotensin receptor blockers |
| CHF | chronic heart failure |
| CKD | chronic kidney disease |
| CKD-EPI | the Chronic Kidney Disease Epidemiology Collaboration |
| COPD | chronic obstructive pulmonary disease |
| CRS | cardiorenal syndrome |
| CVP | central venous pressure |
| eGFR | estimated glomerular filtration rate |
| HF | heart failure |
| HFmrEF | heart failure with mid-range ejection fraction |
| HFpEF | heart failure with preserved ejection fraction |
| HFrEF | heart failure with reduced ejection fraction |
| IHD | ischemic heart disease |
| LVEF | left ventricular ejection fraction |
| MI | myocardial infarction |
| MRA | mineralocorticoid receptor antagonists |
| NYHA | New York Heart Association |
| RAAS | renin-angiotensin-aldosterone system |
| sMDRD | simplified Modification of Diet in Renal Disease |
| SCREAM | the Stockholm Creatinine Measurement |
| SWEDEHEART | the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies |
| SwedeHF | the Swedish heart failure register |
| WRF | worsening renal function |

# INTRODUCTION

## Background

Heart failure (HF) and kidney disease are common diseases that often appear concomitantly and may lead to one another (1). The prevalence of these conditions is increasing due to a population with increasing age and comorbidities and improved treatment of acute myocardial infarction (MI) (2). Both HF and kidney disease have a severe impact on the patients' prognosis and patients with severe failure in both organs have the shortest lifespan (3). It is still a challenge to understand the complexity of these syndromes and how to optimally treat these patients that historically have been excluded from clinical trials (4).

## Prevalence of kidney failure in heart failure

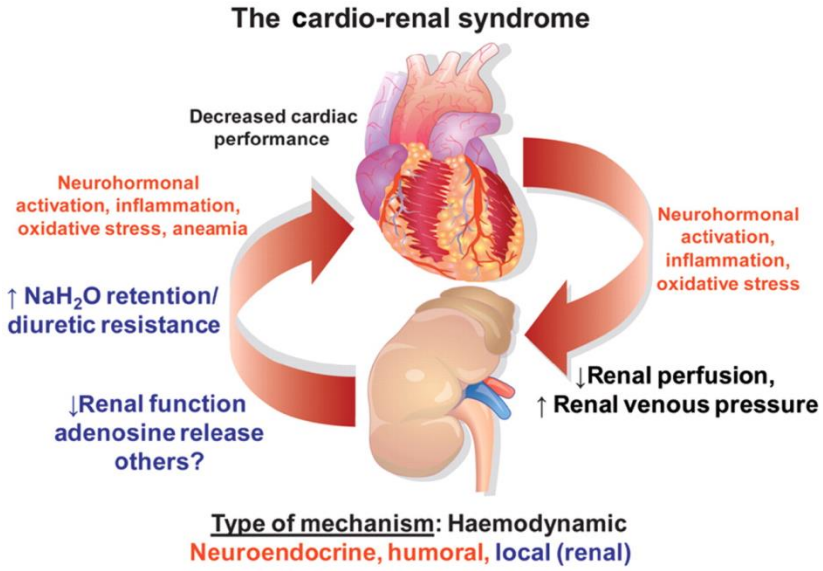
There is a high prevalence of kidney dysfunction among patients hospitalized for acute heart failure (AHF) varying from 30 % to 70 % depending on the definition of kidney disease (5-8). Patients with HF that are not hospitalized tend to have a lower prevalence of chronic kidney disease (CKD) (6). Many previous studies of kidney function in HF patients have been limited by inclusion of highly selected randomized controlled trial patients or small sample sizes (9, 10). In **studies I-III** kidney dysfunction and worsening renal function (WRF) are studied in unselected HF patients that we encounter in daily clinical practice.

## The Cardiorenal syndrome

In 1931 an article was published describing increased venous pressure and the association with impaired renal blood flow in dogs (11). During the subsequent years the heart and kidney function were reported to be connected by hemodynamic factors (12). The concomitant syndrome of HF and kidney disease was defined as the cardiorenal syndrome (CRS) in 2008 by Ronco and his colleagues as a mean for future studies (13). The cardiorenal syndrome describes how the heart and kidney are closely linked together by hemodynamics, neurohormones and the sympathetic nervous system (14) (Figure 1).

CRS type 1 was defined as acute heart failure leading to acute kidney injury ( AKI) caused by hemodynamic changes with forward and backward failure, sympathetic nervous system activation, neurohormonal activation with renin-angiotensin-aldosterone system (RAAS) activation, hypothalamic-pituitary stress reaction, inflammation and immune cell signaling, systemic endotoxemic exposure from the gut and infections and iatrogenesis (15). High central venous pressure (CVP) has since long been known to affect the kidneys (11) and renal venous congestion is believed to be the most important hemodynamic factor driving WRF in patients with HF (16). It has also been found that increased intra-abdominal pressure is common in acute decompensated HF and is associated with impaired kidney function (17).

**Figure 1**




**Metra et al. The role of the kidney in heart failure**
**Eur Heart J. 2012**
Reproduced with permission from Oxford University Press

CRS type 2 includes progressive CKD resulting from chronic heart failure (CHF), with many of the same mechanisms as in CRS 1 where multiple episodes of decompensation contribute to progress of both HF and CKD (18). The neurohormonal activation plays an important part in CRS, where Angiotensin II, a potent stimulator of the sympathetic nervous system, increases systemic vascular resistance, venous tone, sodium reabsorption and congestion and has a trophic effect on cardiomyocytes and renal tubular cells leading to cellular hypertrophy, apoptosis and fibrosis (19). Aldosterone promotes inflammation and fibrosis in the heart and kidney (20) and activation of the sympathetic system leads to HF progression as adrenergic receptors in the kidney increase sodium reabsorption and further RAAS stimulation (21). Inflammatory activation with increase of cytokines and endothelial activation in HF may also affect the kidneys (22, 23). Diuretic resistance which may lead to further deterioration of heart and kidney function by increased congestion, has recently been shown to be caused primarily by tubular resistance (24).

CRS type 3 is where an episode of AKI precipitates and contributes to the development of HF by inflammatory mediators, oxidative stress, apoptosis and activation of neuroendocrine systems combined with volume overload, metabolic acidosis, retention of uremic toxins, hyperkalemia and hypocalcemia (25). Experimental data implies that cardiac injury may be induced partly by cytokines in AKI (26).

CRS 4 is defined as primary CKD leading to a chronic impairment of cardiac function, with ventricular hypertrophy, diastolic dysfunction, and/or increased risk of adverse cardiovascular events (27). In CRS 4 comorbidities, volume overload, uremia, inflammation, malnutrition,

calcium-phosphate abnormality, neurohormonal activation, oxidative stress and endothelial dysfunction play a role in the pathogenesis.

Finally CRS type 5 is defined as concomitant cardiac and renal dysfunction in the setting of different systemic disorders. Here one small study has suggested a possible relationship between endotoxin levels and renal cell death in septic patients (28). Although the CRS types represent a thorough theoretical model, it has its limitation regarding pathophysiologic and subclinical parallel changes. The bidirectional simultaneous relationship between the heart and kidney is complex and there is still limited understanding of the pathophysiologic link between renal dysfunction and HF. The relation to CKD may even be different in HF with preserved (HFpEF) and reduced ejection fraction (HFrEF) (29). In **study III** we examine the association between different types of HF with subsequent WRF.

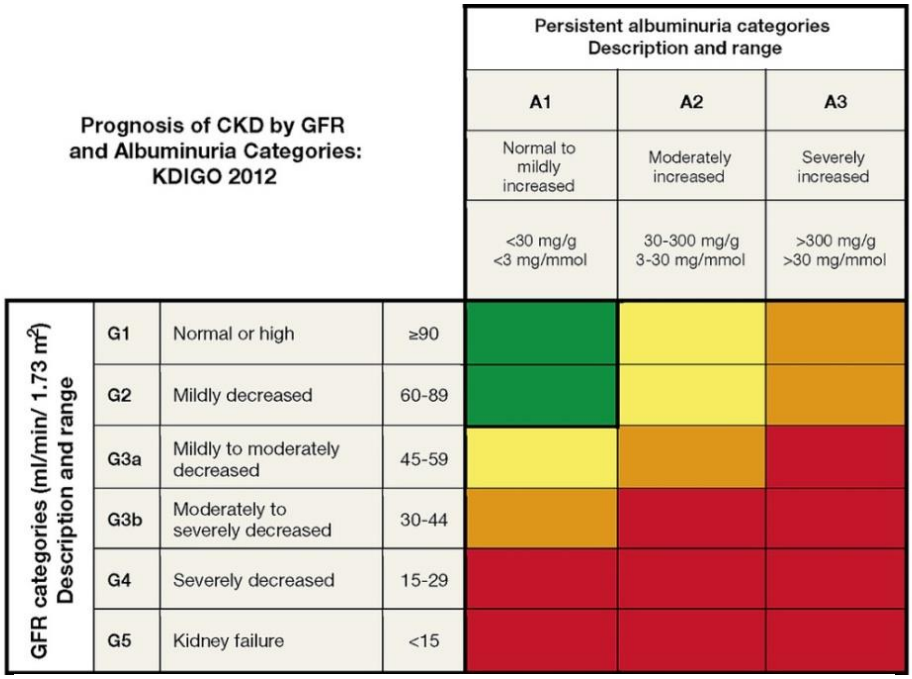
**Definition and diagnosis of kidney disease**

Measurement of creatinine is the easiest way to diagnose kidney disease. Creatinine is affected by age, muscle mass and hydration which is why estimated glomerular filtration rate (eGFR) is a more reliable measure. In earlier large studies of HF and CKD, the diagnosis of kidney disease were defined by a certain level of creatinine or were mainly based on diagnostic codes (8, 30, 31) and there were a lack of studies of non-selected contemporary HF populations looking at different eGFR groups.

Both the simplified Modification of Diet in Renal Disease (sMDRD) and The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) take into account age and sex, but CKD-EPI has been shown to be the most accurate method of estimating glomerular filtration rate in HF (32). When studying kidney dysfunction the patients can be divided in five kidney function categories by using the criteria from the National Kidney Foundation, Kidney Disease Improving Global Outcomes (KDIGO) with normal (GFR > 90 ml/min/1.73 m2), mildly decreased (GFR 60-89 ml/min/1.73 m2), moderately decreased (GFR 30 – 59 ml/min/1.73 m2), severely decreased GFR (GFR 15 – 29 ml/min/1.73 m2), and kidney failure (GFR < 15 ml/min/1.73 m2).

According to the KDIGO guidelines, CKD is defined as abnormalities present for over 3 months of kidney structure or function and the classification is also based on cause and amount of albuminuria (33) ( Figure 2). However, CKD is most often defined as eGFR < 60 ml/min/1.73m2 which has been found to be associated with increased mortality (34). In **study I** we study the prevalence of the different eGFR strata in HF and their impact on prognosis while in **study II** we study the prevalence of CKD in the different EF groups.

**Figure 2**




Green: low risk (if no other markers of kidney disease, no CKD),
yellow: moderate risk, orange: high risk, red: very high risk
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## Biomarkers for kidney dysfunction in HF

Biomarkers associated with CKD have also been found to predict prognosis in patients with HF illustrating the close relationship between the heart and kidney function.

In clinical practice Cystatine C, an endogenous cysteine proteinase inhibitor produced by nucleated cells, is well established as a biomarker for kidney dysfunction and is particularly well studied in AHF and is associated with prognosis (35, 36).

Urea increase in both CKD and HF by low eGFR, hemodynamics, cachexia and muscular atrophy and has been found to be a strong predictor of mortality (37).

Plasma levels of natriuretic peptides reflect atrial and ventricular filling pressures and increase therefore in decongested HF patients and in CKD because of fluid retention and reduced renal elimination (38, 39). NT-proBNP has been found to predict hospitalization and mortality and reduction of NT-proBNP is associated with reduced risk for hospital stay for HF worsening (40, 41).

Biomarkers predictive of renal dysfunction have also been found to be predictive of new HF. Albuminuria has in population studies been found to predict HF (42, 43). Albuminuria is also observed in patients with HF and is thought to be secondary to glomerular and tubular damage in HF, reflecting the cardio renal connection (44) and has been shown to be a strong

independent risk factor alongside eGFR in HF (45). We have sparse knowledge of the link between CKD and the development of HF in the different EF groups with their different pathogenesis and phenotypes. In one recent study of 4 large community based cohorts, biomarkers of renal dysfunction, endothelial dysfunction and inflammation were associated with incident HFrEF while only natriuretic peptides and urinary albumin to creatinine ratio were associated with HFpEF (46).

**Comorbidities in HF and CRS**

Comorbidities are frequent in HF, they may be the cause of both HF and CKD and they may also be a result of CRS as in hypertension and anemia. Anemia and impaired iron metabolism are important in CRS (47) and may have a negative impact on both hemodynamics and endothelial function (48). Arteriosclerotic disease may lead to an acceleration of CRS, being a common cause of both HF and CKD while CKD is a known risk factor for arteriosclerotic disease (49, 50).

In an analysis of the European Heart Failure Pilot survey, which included 3,226 patients, the majority had a least one comorbidity, the most prevalent being CKD, anemia, and diabetes (51). Results showed that comorbidities were independently associated with higher age, higher NYHA class, ischemic etiology of HF, higher heart rate, history of hypertension and AF and that only diabetes, CKD, and anemia were associated with a higher risk of mortality and hospitalization. In the ADHERE database the frequency of common risk factors for renal dysfunction, such as hypertension and diabetes increased when GFR decreased and clinical atherosclerosis, as manifested by coronary artery disease or peripheral vascular disease was more common with WRF (7). However there has been a lack of understanding of comorbidities over the spectrum of CKD classes and in the different EF groups. In **study I** we study the impact of renal dysfunction in relation to the various comorbidities and in **study II** we study the factors associated to CKD in different EF groups.

**CKD and EF categories**

**HF with reduced EF**

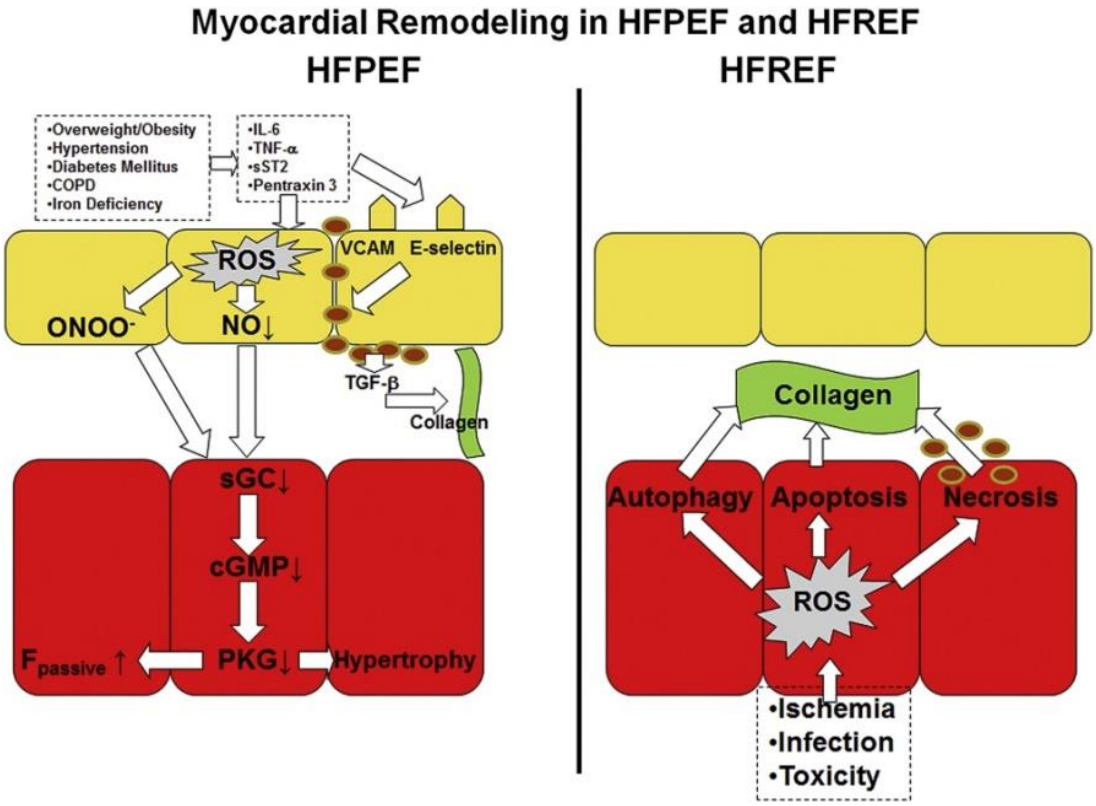
Most studies have described CKD and WRF in HFrEF (5, 52, 53). The presence of CKD has been found to be independent of EF, as in a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) where the patients with CKD had more advanced symptoms measured by NYHA class but there was no significant difference in average left ventricular ejection fraction (LVEF) between those with and without CKD (9).

**HF with preserved EF**

Earlier studies have often not differentiated between HFpEF and HFrEF (2) and have included highly selected patients where CKD has been examined only as part of a general

comorbidity burden (54). When studied, HFpEF was earlier variably defined as EF ≥ 40-55% (55, 56). HFpEF is a heterogeneous syndrome that has been poorly understood. Compared to HFrEF which has an extensive evidence based treatment algorithm, HFpEF has to date no evidence based treatment (57). Patients with HFpEF are frequently female and older and seem to have more comorbidities than patients with HFrEF (58, 59). In a Swedish-French study of 539 HFpEF patients, the comorbidities in HFpEF included hypertension (78%), atrial fibrillation/flutter (65%), anaemia (51%), renal dysfunction (46%), CAD (33%), diabetes (30%), lung disease (25%), and cancer (16%) (60). It is still unclear whether HFpEF is a separate syndrome dominated by diastolic dysfunction or primarily a manifestation of age and age-related co-morbidities, obesity, and deconditioning. A paradigm was presented in 2013, where the pathogenesis of HFpEF in contrast to HFrEF was thought to be driven by comorbidities (61) (Figure 3). The link to CKD is still uncertain, CKD in HFpEF may also be a reflection of higher age and comorbidity or it may evolve independently. HFpEF on the other hand seem to be involved in progressive kidney dysfunction by several mechanisms. HFpEF is thought to be associated with endothelial dysfunction (62) and inflammation (63) and has a high proportion of right ventricular dysfunction, all leading to CKD with a possible bidirectional effect (64) (Figure 4).

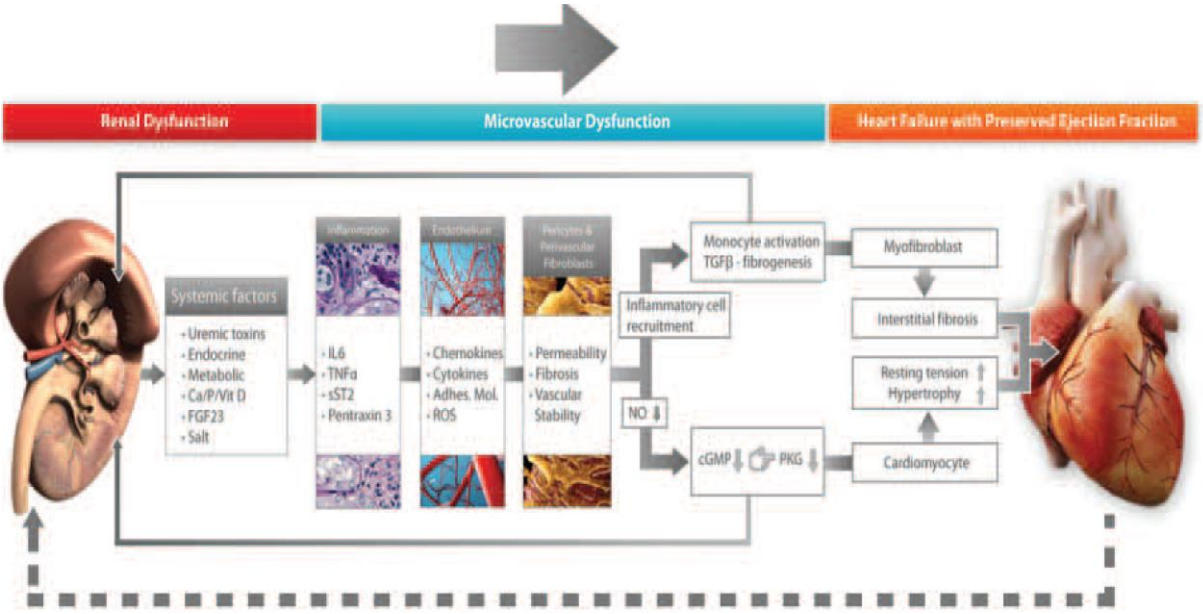
**Figure 3**




In HFPEF, myocardial dysfunction and remodeling are driven by endothelial oxidative stress. In HFREF, oxidative stress originates in the cardiomyocytes. In advanced HFREF, both mechanisms get superimposed.

**Paulus et al, A novel paradigm for preserved ejection fraction, JACC 2013.**

**Figure 4 Proposed relationship between renal dysfunction and HFpEF**




The direction of causality may prove to be in the opposite direction and most probably will be bidirectional. IL-6, interleukin-6; TNFα, tumor necrosis factor-α; sST2, soluble ST2; ROS, reactive oxygen species; NO, nitric oxide; cGMP, cyclic guanosine monophosphate; PKG, protein kinase G; TGFβ, transforming growth factor-β.
**Ter Maaten Eur J Heart Fail 2016** Reproduced with permission from Wiley.

## HF with mid-range EF

According to earlier guidelines, patients with an EF in the range 35–50% had probably primarily mild systolic dysfunction with no clear recommendations regarding treatment (65). HF with mid–range ejection fraction (HFmrEF) has increasingly been viewed as a separate category (56, 66, 67) and was defined as a distinct EF 40-49% phenotype in particular need of further study in the European Society of Cardiology Heart Failure Guidelines of 2016 (57).

We had previously very little knowledge of this middle group, if it was a separate entity or merely part of a continuum between HFrEF and HFpEF. The link with CKD was poorly understood and there were no studies comparing HFpEF, HFmrEF and HFrEF with regard to CKD.

In **study II** and **III** we examine CKD and WRF in the different EF groups.

## Worsening renal function

Decreasing GFR is frequent in HF. In the general population renal function usually declines by 0.5-1.0 ml/min/1.73m2 per year, while in chronic HF, GFR has been found to decrease 2-3

times faster (68, 69). During acute hospitalization for HF, renal function may deteriorate substantially faster which has been found to be an important risk factor (70).

The definition of WRF varies between different studies and publications, and is usually defined as either 26.5 µmol/l (0.3 mg/dl) increase in creatinine or 20-25% increase in eGFR from baseline (70). In nephrology decreasing renal function is referred to as AKI, but here both the time aspect of increase in creatinine, either within 48 hours or within 1-7 days, and the urinary production is taken into consideration (71).

WRF occurs frequently among hospitalized patients. In one study of 1,004 patients hospitalized with HF, WRF developed in 27% of the cases and several studies have shown increased mortality risk in HF patients with WRF (72, 73).

Patients hospitalized with AHF and transient WRF have been found to have similar prognosis as patients with preserved kidney function while patients with persistent WRF have a worse prognosis (74). As patients with transient WRF have signs of hemoconcentration, transient WRF seems to primarily be caused by decongestion by diuretics and may not represent kidney damage (75). On the other hand WRF in combination with congestion has sinister prognosis, as shown in the study of Metra et al. where HF patients with WRF and congestion had more than doubled risk for death compared to the patients with WRF and no congestion (76).

Prior HF, diabetes, baseline creatinine, high systolic blood pressure and anemia have earlier been found to be predictors of in-hospital WRF (72, 77). There is little knowledge of WRF and its predictors after discharge and in patients with CHF. WRF after discharge has mostly been examined in the early phase after discharge and has been found to be a stronger predictor for outcome than in-hospital WRF (77). One small study noted that WRF at 1 year after discharge was associated with increased long term mortality during a mean follow-up at 35 months (78). Another study of 1,216 patients with CHF found that 13 % of the patients developed WRF during the following 6 months, and the predictors for WRF included thiazide diuretics, vascular disease and baseline urea (79).

To date there have been no studies of WRF after discharge comparing WRF in the different EF categories in an unselected HF population. In **study III**, we analyze the risk for long-term WRF and prognostic impact of WRF in patients in HFpEF, HFmrEF and HFrEF.

**Prognosis**

Despite all modern treatment, mortality remains high (80). Most previous studies examined short-term prognosis in both HFrEF and HFpEF, whereas data on long-term follow-up has been lacking (7, 81, 82). The comorbidity burden and increasing age contribute to the poor prognosis in HF (83). There are many variables that predict both hospitalization and mortality (84, 85), and CKD has been found to be an important independent risk factor (86). In a study

of Hillege et al in 2000, it was found that patients with advanced HF and with moderate to severely decreased eGFR had almost three times the mortality risk as patients with mildly decreased eGFR (87). The high mortality risk may be due to several factors. High CVP which is common in CRS has been shown to be associated with mortality (16). In CKD there are numerous factors associated to increased cardiovascular risk including hypertension, increased filling pressures, inflammation, oxidative stress, increased lipid levels, acidosis, deranged calcium-phosphate balance and anemia (49).

Although there is a known increased mortality risk with CKD in HF, earlier studies had divergent findings concerning the importance of CKD in HFpEF compared to HFrEF (5, 88, 89). Regarding CKD and prognosis in HFmrEF, there was no data. In **study II** we study the different EF groups and analyze the impact on prognosis of CKD in the different EF categories.

**Treatment of HF patients with CKD**

**RAAS blockers and beta blockers**

Patients with low eGFR are less often treated with guidelines recommended heart failure treatment, because of fear of or proven deterioration of the kidney function. Caution is recommended when treating patients with severely depressed kidney function and these patients have systematically been excluded from randomized clinical trials (57).

However, in a cohort of 754 patients, Angiotensin converting enzyme inhibitors (ACEi) and beta blockers were associated with similar reductions in mortality in patients with and without renal insufficiency (53). In a sub-analysis of the Valsartan in Heart Failure Trial (Val-Heft), the effect of valsartan on mortality did not differ in patients with and without CKD (90). Even subgroup analyses from the Heart Outcomes Prevention Evaluation (HOPE) and the Cardiac Insufficiency Bisoprolol Study II (CIBIS II) trial confirmed that ramipril and bisoprolol were equally efficacious and safe in patients with and without mild to moderate renal insufficiency (91, 92). Treatment with RAAS blockade may lead to increase in creatinine and WRF by dilation of the efferent arteriole and reduced glomerular perfusion (93). In HFrEF, the potential negative impact of WRF has been shown to be balanced by the beneficial effect of the RAAS blockade, in contrast to HFpEF where WRF has been associated with increased risk for HF hospitalization and death without any demonstrable survival benefit from RAAS blockade (94-96).

**Mineralocortocoid receptor antagonists**

As aldosterone promotes inflammation and fibrosis, mineralocortocoid receptor antagonists (MRA) is a hypothetically appealing treatment especially in HFpEF where inflammation and hypertension is common (97).

Aldosterone regulates sodium and potassium homeostasis but can also initiate an inflammatory response causing fibrosis of the heart, vessels and kidneys (97). The aldosterone receptor antagonists spironolactone and eplerenone have been shown to reduce morbidity and mortality among patients with HFrEF and among patients with acute MI complicated by left ventricular dysfunction and HF (98, 99). Inflammation and fibrosis are believed to be part of the pathogenesis of HFpEF (61), which is why MRA may represent a possible treatment directly affecting the progress of the disease. Although the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study of aldosterone blockade in HFpEF did not show any positive effects on outcome, post-hoc regional analyses indicate beneficial effects in the American patients (100, 101). When treating patients with CKD there is a risk of WRF and hyperkalemia, although a sub-analysis of the eplerenone treatment study of patients with HF in NYHA class II showed that eplerenone still had survival benefit (102).

There has been a lack of studies of treatment with MRA in unselected patients with HF and CKD in real life and we have little knowledge of MRA treatment in patients with HFpEF and HFmrEF. In **study IV** we examine the impact of MRA treatment in patients with MI and HF, in different EF groups and with and without CKD.

# AIMS

The main aim of the thesis was to examine the prevalence of kidney dysfunction in unselected HF patients in relation to different EF categories and to examine the impact of kidney dysfunction on survival in HFpEF, HFmrEF and HFrEF.

The specific aims were

1. To determine the prevalence of different degrees of kidney dysfunction and to examine their association with short- and long-term outcome in a large unselected contemporary HF population and some of its subgroups (**Study I**).

2. To perform a comprehensive comparison of CKD in HFpEF, HFmrEF and HFrEF with regard to prevalence, clinical correlates and long-term prognostic role (**Study II**).

3. To compare the long-term incidence of, associations with and prognostic impact of WRF in HFpEF, HFmrEF and HFrEF (**Study III**).

4. To assess the use of MRA and the association between MRA treatment and outcome in patients with MI and HF in different EF groups and in the absence and presence of CKD (**Study IV**).

# PATIENTS AND METHODS

## Data sources

### Study I, II and III

The Swedish heart failure register (SwedeHF) has since 2000 included patients with HF and offers a unique possibility to study a large cohort of unselected HF patients (103). It is a web based national quality register including HF patients, with 54% coverage of all patients hospitalized with HF as the main diagnosis in Sweden according to the latest report in 2015.

The majority of the patients (91%) are registered at hospital, the remaining in the primary care. Inclusion criteria are clinician-judged HF and approximately eighty variables are recorded at discharge or during visit to a physician or health care team. Variables in the registry include baseline description of the patients, risk factors, history of heart disease, cardiac interventions, cardiac evaluation with electrocardiogram and echocardiogram, laboratory tests at discharge or at the out-patient visit and medication. Registration of hemoglobin and creatinine are mandatory. The patients are informed of their participation in the SwedeHF and are allowed to opt out, but individual patient consent is not required. The register is monitored yearly; in 2015, in 8 hospitals 30 random registrations were reviewed and compared with the patients' medical records. The database is managed by Uppsala Clinical Research Center (Uppsala, Sweden).

### Study III

In study III we merged data from SwedeHF with the Stockholm Creatinine Measurement (SCREAM) database. The SCREAM cohort 2006-2011 was a collaborative project between Karolinska Institutet and the Stockholm County Council to assess the burden of kidney disease and inappropriate drug use in the region (104). The core component of SCREAM was laboratory data related to kidney function. The laboratories extracted the requested laboratory tests for all patients who had undertaken these tests in the region. All laboratories used standardized methods of creatinine measurements traceable to dilution mass spectroscopy standards. The SCREAM database contains laboratory data of 98% of all patients with cardiovascular disease in Stockholm 2006-2011.

### Study IV

In the fourth study we analyze data from the nationwide SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry (105). SWEDEHEART includes almost all patients hospitalized for acute MI and admitted to a coronary care unit or other specialized facility with coverage of 96% of patients < 80 years old and around 80% of

elderly patients (106). The registry covers all hospitals taking care of acute cardiac patients in Sweden (n=72). In the acute coronary care part of the registry, more than 100 variables are collected prospectively including admission logistics, patient demographics, risk factors, past medical history, medical treatment before admission, electrocardiographic changes, biochemical markers, clinical investigations, medical treatment in hospital, interventions, hospital outcome, diagnoses and medication at discharge. Patients receive information about their participation in SWEDEHEART on admission and are allowed to opt out. The registry is monitored on a regular basis with visits to approximately 30 randomly selected hospitals each year, comparing data entered into SWEDEHEART with the information in the patients' health records, repeatedly showing an agreement of 95-96%.

The data in **study IV** was linked to the Swedish Prescribed Drug Registry, which contains all pharmacy-drug dispensations in the country for each unique citizen to get information of the prevalence of spironolactone and eplerenone in patients after discharge.

**In study I-IV**: Mortality data was obtained by running the registries against the Population Register in Sweden which includes the vital status of all Swedish citizens and permanent residents.

## Study populations

### Study I

A total of 47,716 unique patients from SwedeHF 2000-2013 were studied after exclusion of patients with missing data on creatinine, age and with creatinine measured with methods not traceable to isotope dilution mass spectroscopy standards (Figure 5).

### Study II

In total 40,230 unique patients from SwedeHF 2000-2013 were studied after exclusion of patients with missing data for age or creatinine, creatinine measurement by non-standardized methods, patients that died during hospitalization and exclusion of patients with missing data of EF (Figure 5).

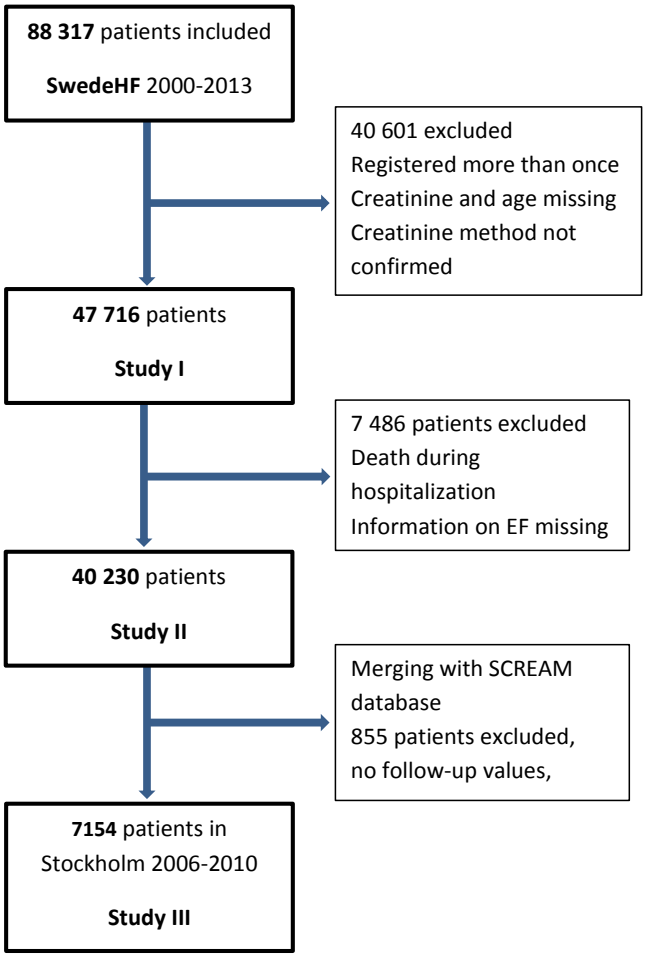
### Study III

In total 7,154 unique patients from SwedeHF in Stockholm 2006-2010 were studied after exclusion of patients with no recorded measurements of EF and no follow-up values of creatinine (Figure 5).

### Study IV

A cohort of 45,071 unique patients from SWEDEHEART 2005-2014 with acute MI and HF (previously known or diagnosed during hospitalization (defined as; Killip >1, administration of intravenous diuretics/inotropes or use of continuous positive airway pressure)) were studied after exclusion of patients with prior MRA use and patients that died during hospitalization or within 2 weeks from discharge.

**Figure 5 Study populations, study I-III**




## Methods, outcome and Statistics

Glomerular filtration rate was estimated with the CKD-EPI equation (32). LVEF was both in SwedeHF and SWEDEHEART obtained from the latest available measurement and method according to local practice (in Sweden generally echocardiography with the Simpson method). HFpEF was defined as HF with EF ≥ 50%, HFmrEF as HF with EF 40-49% and HFrEF as HF with EF < 40%.

**Study I**

The patients were divided into 5 renal function categories with normal function (eGFR ≥ 90), mild dysfunction (eGFR 60-89), moderate dysfunction (eGFR 30-59), severe dysfunction (eGFR 15-29), and end stage renal disease (eGFR < 15 ml/min/1.73 m2) based on creatinine obtained at discharge for hospitalized patients and at the closest date preceding an outpatient visit.

Outcome was all cause mortality during up to 12 years follow-up.

Crude survival was assessed and illustrated by Kaplan-Meier analyses. Uni- and multivariable Cox proportional hazard regression was used to examine the association between kidney function and outcome using three models: in the first model adjustment were made for variables possibly influencing both kidney dysfunction and outcome (age, gender, smoking, hypertension and diabetes), in the second model variables related to the etiology and severity of heart failure were added (heart failure > 6 months, ischemic heart disease (IHD), previous valvular intervention, non-sinus rhythm in the electrocardiogram, heart rate, LVEF, New York Heart Association (NYHA) class, systolic blood pressure and hemoglobin level) and in the third model we also made adjustments for given treatment (ACEi, angiotensin receptor blockers **(**ARB), beta blockers, aldosterone antagonists, statins and cardiac resynchronization therapy (CRT)).

**Study II**

CKD was defined as eGFR < 60 ml/min/1.73m2, based on creatinine obtained at discharge for hospitalized patients and at the closest date preceding an outpatient visit.

In the analyses of association between baseline variables and baseline CKD, the dependent variable was CKD. In analyses of the association between CKD and prognosis, the outcome was death from any cause.

Associations between baseline variables and baseline CKD were assessed with multivariable logistic regression using a total of 28 clinically relevant variables: age, gender, civil status, care in cardiology ward, hypertension, diabetes, smoking, IHD, atrial fibrillation, valvular heart disease, chronic obstructive lung disease (COPD) , revascularization, hospitalization at diagnosis, HF duration > 6 months, NYHA class, haemoglobin, systolic blood pressure, heart rate, RAAS blockers, beta blockers, aldosterone antagonists, digoxin, statins, nitrats, oral anticoagulants, antiplatelet treatment, specialist follow-up and heart failure team follow-up. Pre-selected variables of interest were illustrated in a Forest plot.

Crude survival was assessed and illustrated with Kaplan-Meier analyses.

Uni- and multivariate Cox proportional hazard regression analyses were used to examine the association between CKD and mortality and adjustments were made for the same 28 variables as above. Analysis of interaction between CKD and EF group was performed by creating an interaction term in a Cox regression analysis.

Prognostic value of kidney function, regardless of chosen cut-off value for eGFR, was assessed by area under the curve in ROC analyses.

Missing data of the variables in the multivariable analyses was handled by multiple imputation with 10 dataset.

**Study III**

WRF was defined as $\geq$ 25% decrease in estimated glomerular filtration rate (eGFR) when studying associations between baseline characteristics and WRF within one year and within five years follow-up.

WRF was divided in 25-49% and $\geq$ 50% decrease in eGFR when studying the association between WRF within year one and subsequent mortality up to six years follow-up. Baseline creatinine was obtained at the closest date preceding an outpatient visit or at discharge for hospitalized patients. Subsequent measurements were performed as considered indicated in the clinical routine.

The associations between EF groups and subsequent WRF and between WRF within one year and subsequent mortality were assessed with Kaplan-Meier analyses and multivariable Cox regression using a total of 31 clinically relevant variables including demography (age, gender, civil status, care at a cardiology clinic), risk factors (diabetes mellitus, hypertension), previous cardiovascular disease (IHD, atrial fibrillation, valvular heart disease), comorbidity (COPD), previous procedures (revascularization), characterization of HF (hospitalization at inclusion, HF duration over 6 month, NYHA class, use of inotropes, CRT, physical status (non-sinus rhythm, heart rate (< 70, $\geq$ 70 beats per minute), systolic blood pressure (< 100, 100-139, $\geq$ 140 mm Hg), lab (Hb < 120 , $\geq$ 120 g/dl), CKD ( < 30, 30-59, $\geq$ 60 ml/min/1.73m2 )), WRF during hospitalization (defined as a 25% decrease in eGFR and 26.5 µmol/l increase in creatinine) and medication at discharge (ACEi/ARB, beta blockers, MRA, digoxin, statins, nitrates, antiplatelets, anticoagulants, diuretics). In the analysis of the association between WRF and subsequent mortality a stepwise adjustment for baseline eGFR and then the remaining variables was made.

The multi-adjusted risk for WRF $\geq$ 25% within one year and within five years and the multi-adjusted mortality risk with WRF 25-49% and WRF $\geq$ 50% in the different EF groups were illustrated in Forest plots.

Missing data was handled by multiple imputation with 20 dataset using the same variables as in the multivariable analyses.

**Study IV**

MRA use after discharge was defined as a recorded dispensation of spironolactone or eplerenone within 2 weeks after discharge. CKD was defined as eGFR < 60 ml/min/1.73m2.

The outcome was all-cause mortality up to 3 years of follow-up.

The association between the use of MRA and mortality in the different EF groups and in the presence or not of CKD were assessed with uni- and multivariable Cox regression analyses. Adjustments were made for 28 variables; center as random effect, year of admission, age, gender, risk factors (diabetes mellitus, hypertension), previous cardiovascular disease ( MI, HF, peripheral vessel disease), previous other diseases (COPD, cancer), status at presentation (ST-elevation, Killip > 1, atrial fibrillation), intervention and treatment (PCI,CABG, iv diuretics, inotropes), medication at discharge (ACEi/ARB, beta-blockers, calcium antagonists, diuretics, digoxin, statin therapy, antiplatelet therapy and warfarin), atrial fibrillation at discharge and eGFR.

Analyses of interaction between MRA and EF groups and MRA and CKD were performed by creating an interaction term in the Cox regression analysis. For continuous variables natural cubic splines with 4 degrees of freedom (knots) were used.

Multiple imputation was used to create 30 imputed data sets. Incomplete variables were imputed using the random forest based MICE algorithm.

A sensitivity analysis of complete cases was performed to validate the robustness of the results.

Statistics in **Study I** and **II** were made in SPSS version 22, with use of STATA version 13 for figures in **study II**. In **study III** STATA version 14.1 was used, with SPSS version 24 for imputations and in **study IV** statistics were made with R.

**Ethical consideration**

The registries conform to the national laws and the declaration of Helsinki. The studies were approved by the regional ethical review boards in Linköping and Stockholm.

# RESULTS

## Study I

Kidney function and heart disease

A total of 24,225 (51%) patients had at least a moderate kidney dysfunction (eGFR < 60 ml/min/ 1.73 m2) and 5,065 (11%) at least a severe kidney dysfunction (eGFR < 30 ml/min/1.73 m2) while 813 (2%) were classified as end stage renal disease (eGFR < 15 ml/min/1.73 m2). Patients with lower kidney function were older, more often female and had more frequently had hypertension and diabetes mellitus.

Patients with poor kidney function were more likely to have IHD. Atrial fibrillation, stroke and valvular heart disease were more common in those with reduced kidney function but they were less likely to have dilated cardiomyopathy. Patients with reduced kidney function had a higher likelihood of HF with a known duration of more than 6 months and were more often hospitalized at inclusion. Mildly symptomatic heart failure was more common in those with preserved kidney function and severe HF increased with worsened kidney function. Patients with reduced eGFR had more often preserved LVEF, whereas in patients with preserved kidney function severe left ventricular systolic dysfunction (LVEF < 30%) was more common.

Physical findings

There were no major differences between the eGFR strata regarding heart rate, blood pressure and body mass index. Presence of left bundle branch block and QRS-width did not differ between eGFR-strata. The laboratory data showed that patients with low eGFR had more often low hemoglobin and a high potassium level and a markedly higher level of N–terminal pro-brain natriuretic peptide (NT-proBNP).

Treatment

Patients with reduced kidney function were less likely to be treated with ACEi, beta-blockers and aldosterone blockade. If treated, they were also less likely to receive what was considered to be guideline recommended target dose of ACEi, ARB and beta-blockers. Statins and anticoagulant treatment were used less often whereas aspirin was used more often in those with impaired kidney function.

Outcome

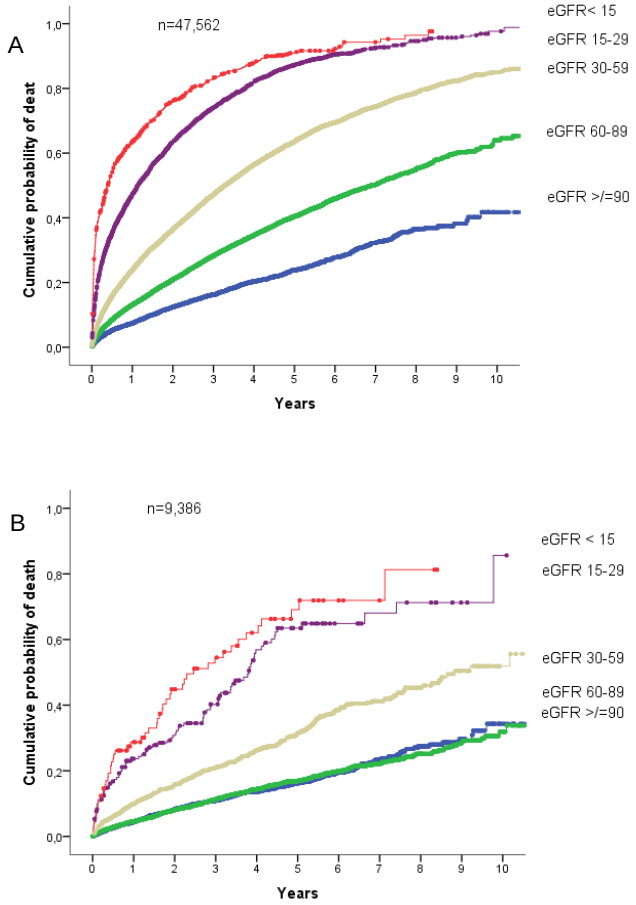
Half of all patients with eGFR < 15 ml/min/1.73 m2 had died after 6 months and after one year over 40% of those with severe kidney dysfunction and 60% of the patients with end stage renal disease had died (Table 1).

There was an increasing mortality with decreasing kidney function regardless of age, presence of diabetes or not, NYHA class, and hemoglobin levels.

Although patients with HF with a duration of more than 6 months had higher one year mortality than patients with HF with a shorter duration (25% vs. 16%), the prognosis was primarily dependent on the eGFR. One year mortality in patients with normal kidney function was 7% in HF with duration less than 6 months vs. 8% with duration more than 6 months and in patients with eGFR < 15 one year mortality was 61% vs. 63%.

During long-term follow-up, the cumulative probability of death at five years was more than 80% in patients with at least severe kidney dysfunction (eGFR < 30) and 60% in those with moderate kidney dysfunction (eGFR 30-59) ( Figure 6). Even in the age group below 65 years the prognosis was sinister with a 60% probability of death at 5 years in those with severe kidney dysfunction.

**Figure 6**




(A) Mortality in patients with heart failure and different estimated glomerular filtration rate (eGFR) strata, crude survival assessed by Kaplan-Meier analysis, log rank p<0.001.
(B) Mortality in patients under 65 years with heart failure and different GFR strata, crude survival assessed by Kaplan-Meier analysis.
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When adjusting for baseline variables possibly influencing both kidney dysfunction and outcome (age, gender, smoking, hypertension and diabetes) in model 1 the association between eGFR and mortality was attenuated (Table 1). When adding HF related variables in model 2 the association between eGFR strata and mortality was further somewhat weakened but still significant. When adjusting for differences in medical treatment in model 3 the association between eGFR strata and mortality remained unchanged.

**Table 1 Mortality and unadjusted and adjusted mortality risk in relation to eGFR**

| | eGFR≥90 n=5251 | eGFR 60-89 n=18 240 | eGFR 30-59 n=19 016 | eGFR 15-29 n=4252 | eGFR<15 n=813 |
|---|---|---|---|---|---|
| **In hospital** (%) | 1% | 2% | 3% | 10% | 28% |
| **At 6 month**s (%) | 5% | 8% | 16% | 35% | 53% |
| **At 1 year** (%) | 7% | 13% | 23% | 46% | 62% |
| **Longterm (HR)(unadjusted)** | 1 | 1.85 (1.73-1.97) | 3.57 (3.35-3.80) | 7.72 (7.20-8.28) | 11.71 (10.62-12.90) |
| **Model 1 (HR)**(n=47545) | 1 | 0.83 (0.77-0.89) | 1.13 (1.05-1.21) | 2.12 (1.96-2.29) | 4.19 (3.79-4.64) |
| **Model 2 (HR)**(n=27304) | 1 | 0.84 (0.74-0.92) | 1.10 (1.00-1.20) | 1.87 (1.68-2.08) | 3.26 (2.79-3.80) |
| **Model 3 (HR)**(n=27302) | 1 | 0.86 (0.79-0.95) | 1.13 (1.03-1.24) | 1.85 (1.67-2.07) | 2.96 (2.53-3.47) |

In model 1 adjustment for baseline variables possibly influencing both kidney dysfunction and outcome (age, gender, smoking, hypertension and diabetes). In model 2 variables related to the etiology and severity of heart failure (heart failure > 6 months, IHD, atrial fibrillation, valvular heart disease, dilated cardiomyopathy, previous revascularization, previous valvular intervention, non-sinus rhythm in the electrocardiogram, heart rate, LVEF, NYHA class, systolic blood pressure and hemoglobin level) were added. In model 3 adjustment for given treatment (ACEi, ARB, beta blockers, aldosterone antagonists, statins and CRT)

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## Study II

Patients and baselines characteristics

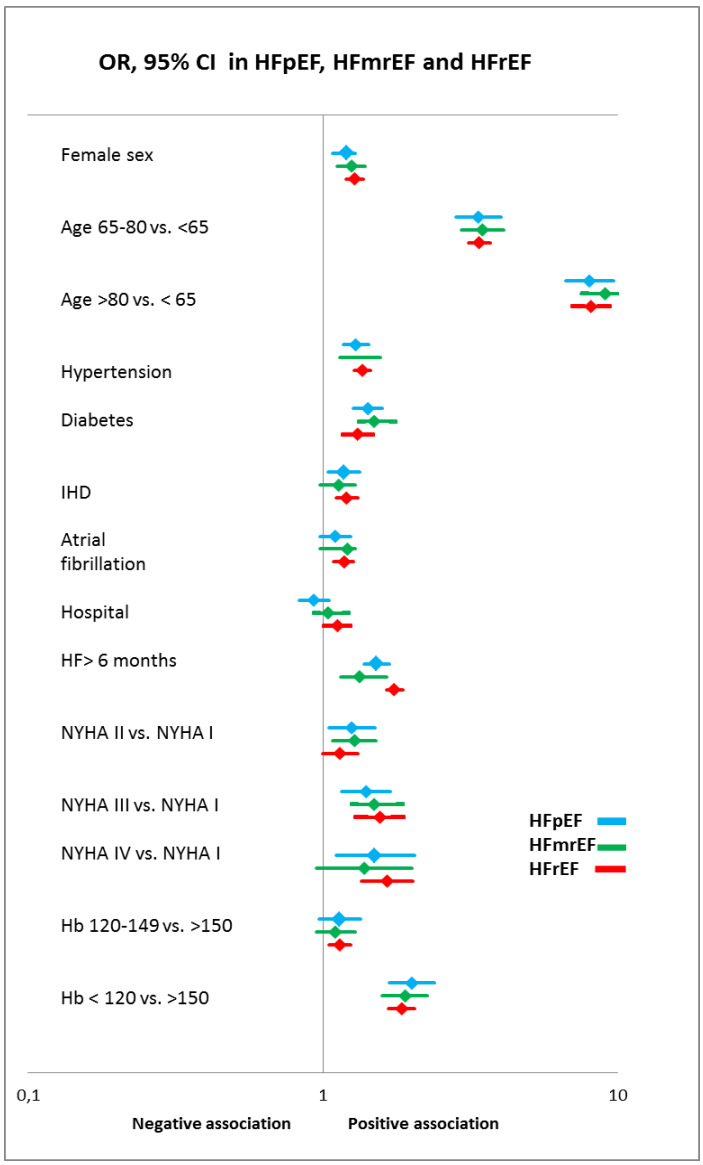
Of 88,317 registrations in SwedeHF 2000 – 2013, 40,230 unique patients were included after applying exclusion criteria mentioned earlier. 8,875 (22%) were classified as HFpEF, 8,374 (21%) as HFmrEF and 22,981 (57%) as HFrEF.

CKD was more common in HFpEF than in HFmrEF and HFrEF, 56% vs. 48% and 45% respectively. Patients with HFmrEF were younger and less often female than HFpEF but older and more often female than HFrEF.

In all EF categories the patients with CKD had higher age, more comorbidity and more severe HF. There was more hypertension, atrial fibrillation and valvular heart disease in HFpEF while there was more IHD in HFmrEF and HFrEF, and with higher prevalence in patients with CKD. There were a higher proportion of diabetes in patients with CKD, but no difference between HFpEF, HFmrEF and HFrEF.

Patients had higher systolic blood pressures in HFpEF and HFmrEF and slightly higher BMI in HFpEF, with no major differences in the presence vs. absence of CKD. In all EF groups hemoglobin level decreased with lower kidney function and was lowest in HFpEF. NT-proBNP was approximately doubled in CKD vs. non-CKD, regardless of EF and was highest in HFrEF.

**Figure 7 Multivariable logistic regression; Association with CKD**




OR= Odds ratio

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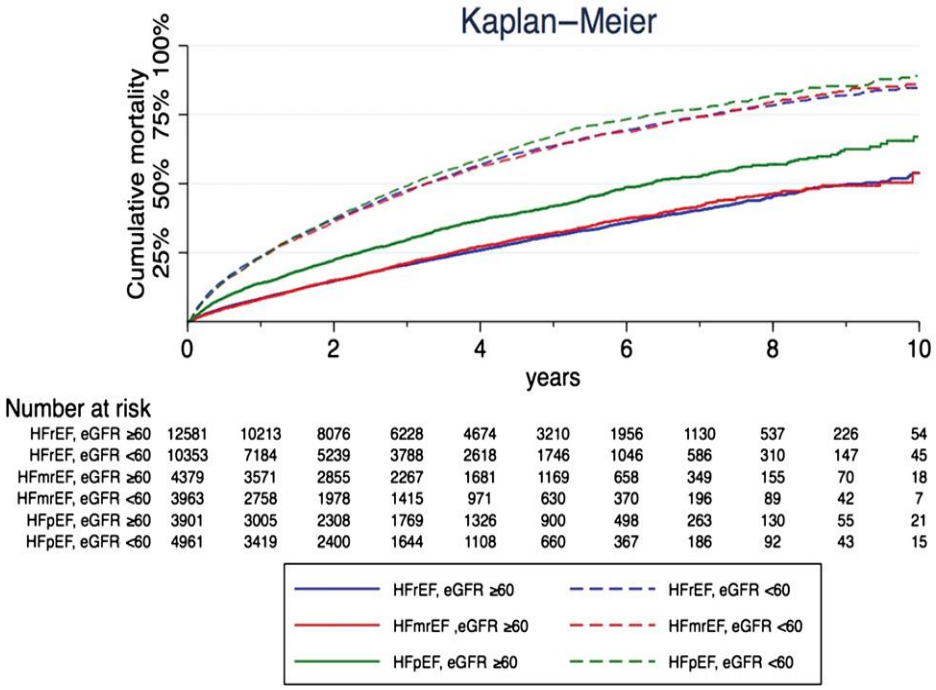
Associations between covariates and CKD

Associations were assessed between important baseline covariates and CKD, to elucidate the potential risk factors for CKD in the different EF groups (Figure 7). Many of the baseline variables were independently associated with CKD, including higher age, female sex, hypertension, diabetes and longer duration of HF and NYHA class. Anemia was strongly associated with CKD, whereas IHD and atrial fibrillation were less strongly associated with CKD after adjustments for covariates. Notably, the associations with CKD changed somewhat after multivariable adjustment, but were similar regardless of EF category. RAAS blockade was associated with lower odds of having CKD while beta blockers were associated with higher odds.

Associations between CKD and mortality

Over a median (IQR) follow-up of 900 (369-1669) days, there were 10 862 deaths overall. Patients with CKD had a worse outcome both in the short and long term in all EF groups (Figure 8). In the crude survival analyses patients with HFpEF, HFmrEF and HFrEF had similar poor prognosis in the presence of CKD, whereas in the absence of CKD, HFpEF had higher one year, five years, overall and long term mortality compared to HFmrEF and HFrEF. CKD was less strongly associated with mortality in HFpEF than in HFmrEF and HFrEF in the unadjusted analysis and remained less associated with mortality after multiple adjustments (p for interaction < 0.001) (Table 2).

**Figure 8 Kaplan–Meier curves for mortality in HFpEF, HFmrEF and HFrEF**




eGFR =estimated glomerular filtration rate.
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**Table 2 Association between CKD and mortality according to EF category**

| Model | HFpEF | | HFmrEF | | HFrEF | |
|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | **HR** | **95% CI** | **HR** | **95% CI** |
| Crude | 1,95 | 1,83 -2,08 | 2,64 | 2,46 -2,84 | 2,75 | 2,64 -2,88 |
| Adjusted age | 1,40 | 1,31-1,50 | 1,72 | 1,60-1,86 | 1,80 | 1,72-1,89 |
| Adjusted age and gender | 1,41 | 1,32-1,56 | 1,73 | 1,61-1,87 | 1,82 | 1,74-1,90 |
| Adjusted all baseline variables* | 1,32 | 1,24-1,42 | 1,51 | 1,40-1,63 | 1,49 | 1,42-1,56 |

*age, gender, civil status, cardiology ward, specialist follow-up, heart failure team follow-up, hypertension, diabetes, smoking, ischemic heart disease, atrial fibrillation, valvular heart disease, pulmonary disease, revascularization, hospitalization at diagnosis, heart failure duration > 6 months, NYHA class, haemoglobin , systolic blood pressure, heart rate, RAAS blockers, beta blockers, aldosterone antagonists, digoxin, statins, nitrats, oral anticoagulants and antiplatelet treatment **Löfman et al, EJHF 2017**. Reproduced with permission from Wiley

In ROC analyses of one year mortality, the prognostic discrimination of kidney function, measured as eGFR as a continuous variable, was stronger in HFrEF and HFmrEF than in the patients with HFpEF.

## Study III

Incidence of WRF

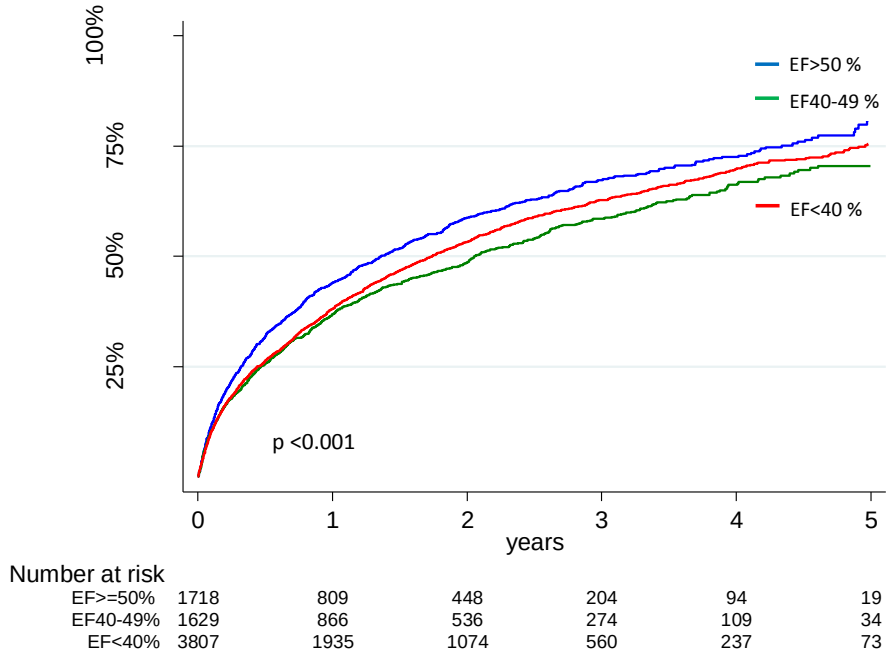
Of the 7,154 patients, 5,186 (72.5%) were discharged from hospital, while 1,986 (27.5%) patients were included at an out- patient visit. Within the first year, of patients discharged from hospital 41.2% developed WRF $\geq$ 25% and 14.4% WRF $\geq$ 50%, while of the out-patients, 23.5% developed WRF $\geq$ 25% and 6.4% WRF $\geq$ 50%.

Median (IQR) time to WRF $\geq$ 25% was 174 (52-439) days in HFpEF, 207(55-498) days in HFmrEF and 218 (57-503) days in HFrEF and to WRF $\geq$ 50% 350 (129-604) , 394 (147-772) and 396 (160-733) days respectively.

During the first year 41.6% of the patients with HFpEF vs. 34.5% and 35.4% with HFmrEF and HFrEF developed WRF $\geq$ 25%.

There was an increasing cumulative incidence of WRF during five year follow-up. At two years over 50% of the patients in all EF groups had WRF $\geq$ 25%, with a slightly higher proportion in HFpEF and a slightly lower in HFmrEF (Figure 9) and 25% of the patients had WRF $\geq$ 50%, even here a somewhat higher proportion in HFpEF.

**Figure 9 WRF ≥ 25% during follow-up, stratified on different EF groups**

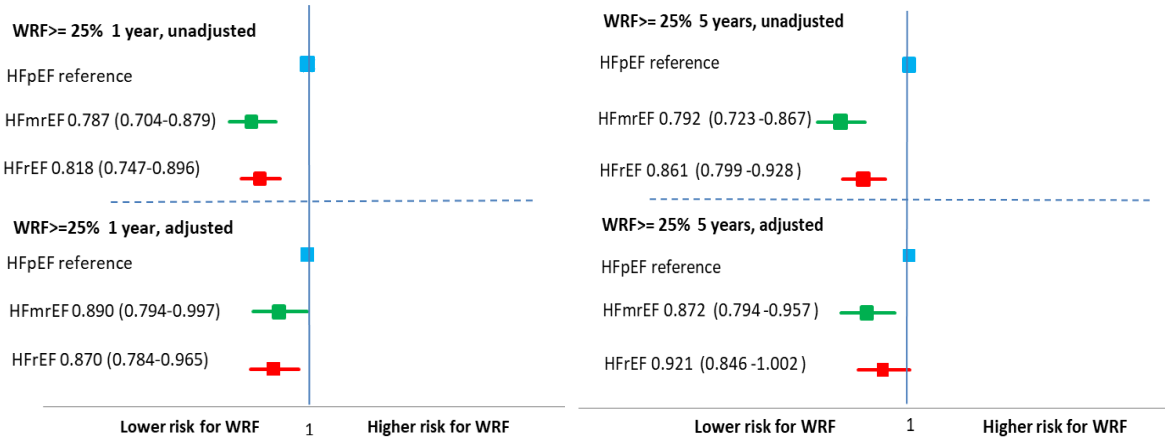



Associations between baseline variables and incident WRF

In all EF groups the patients with WRF ≥ 25% within the first year were older, had more often hypertension, atrial fibrillation, IHD, valvular heart disease, were more often hospitalized at inclusion, had more often higher NYHA class, more often anemia, COPD, less often eGFR ≥ 60 ml/min/1.73m2 but higher NT-proBNP and were more often treated with MRA and diuretics. In HFmrEF and HFrEF, patients with WRF ≥ 25% had also more frequently HF with duration > 6 months and only in HFrEF had the patients with WRF more often WRF during hospitalization.

In the multi-adjusted analyses, the risk for WRF ≥ 25% during the first year was higher in HFpEF (reference) than in HFmrEF and HFrEF (hazard ratio (HR) (95% CI) 1.0 vs 0.890 (0.794-0.997) and 0.870 (0.784-0.965)) and with similar trends during five years follow-up (Figure 10). In all EF groups, higher age, diabetes, enrolment at hospital discharge vs. as out-patient, NYHA class, use of MRA and diuretics were associated with WRF ≥ 25%. Even COPD and anemia, HF duration over 6 months, valvular heart disease, use of CRT, low systolic blood pressure and treatment with digoxin were associated with WRF ≥ 25%. There were few significant interactions when stratifying for EF groups. In HFrEF but not in HFmrEF and HFpEF, the duration of HF was associated with WRF.

**Figure 10 Risk for WRF within the first year and within five years, HR ( 95% CI)**

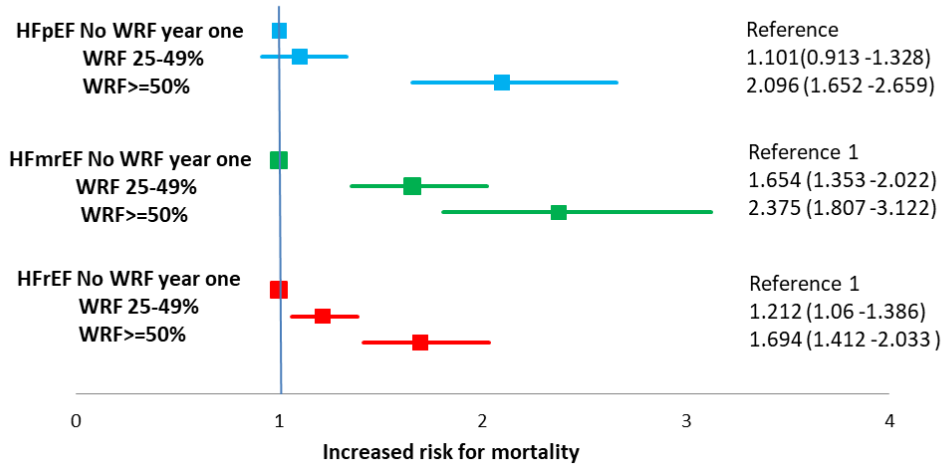



Associations between WRF and all-cause mortality

Within the first year after the index-HF event, 16.3%, 15.7% and 15.6% respectively of the HFpEF, HFmrEF and HFrEF patients died. Patients alive and with WRF ≥ 25% within year one had higher long-term mortality from year one than the patients with no WRF regardless of EF group.

There were clear associations between WRF 25-49% and WRF ≥ 50% within year one and mortality during follow-up, with the strongest association with WRF ≥ 50% in all EF groups, both unadjusted, after adjustment for baseline eGFR and in the fully adjusted analyses. In WRF 25-49% there was a lower mortality risk in HFpEF (HR, 95% CI) 1.101(0.913-1.328) than compared to HFmrEF 1.655 (1.354-2.024) and HFrEF, 1.212 (1.06-1.386) while in WRF ≥ 50% the multi adjusted mortality risk was similar in all EF groups.

**Figure 11 Mortality risk during follow-up with WRF 25-49% and WRF≥50% within year one in different EF groups, HR (95% CI)**



**Study IV**

Treatment with MRA

Of 45,071 patients with acute MI and HF, 4,470 (9.9%) patients had MRA prescribed at discharge, of which 4,269 (9.5%) had spironolactone and 204 (0.5%) had eplerenone. Those with MRA were somewhat younger, had more often STEMI on admission, had less often prior MI, HF and CKD, were less often treated with antiplatelet treatment, beta-blockers and diuretics on admission and had more often severely reduced EF compared with patients with no MRA. They were more often treated with inotropic drugs, intravenous diuretics and revascularization. At discharge, patients with MRA had more ACEi/ARB and diuretics, and slightly more often beta-blockers compared to patients without MRA.

Of 30,485 patients with a known LVEF, 9,895 (32.5%) had LVEF $\geq$ 50%, 7,921 (26.0%) had LVEF 40-49% and 12,669 (41.6%) had LVEF < 40%. Patients with lower LVEF were generally older, had more frequently diabetes mellitus, prior MI and HF, had higher rates of STEMI at admission and had lower eGFR. A total of 469 (4.7%) patients with LVEF $\geq$ 50% had MRA, while 722 (9.1%) of patients with LVEF 40-49% and 2,486 (19.6%) of patients with LVEF < 40% had MRA. In patients with LVEF $\geq$ 50%, baseline characteristics for those treated and not treated with MRA differed from those with LVEF 40-49% or LVEF < 40%. In this group, patients treated with MRA were older, had more often risk factors such as diabetes mellitus and hypertension, were more likely to have atrial fibrillation, and were more frequently treated with beta-blockers and diuretics on admission.

Of 43,163 with known kidney function, 20,904 patients (48.4%) had eGFR < 60 ml/min/1.73m2. Patients with CKD were older, more often female, had more frequently other risk factors and cardiovascular diseases. They were also less often treated with revascularization and ACEi/ARB, but more often treated with diuretics. A total of 1,802 patients (8.6%) with CKD were treated with MRA vs. 2,532 (11.4 %) of the patients without CKD. Regardless of kidney function the relative differences in baseline characteristics and other treatments between patients treated with and without MRA were similar.

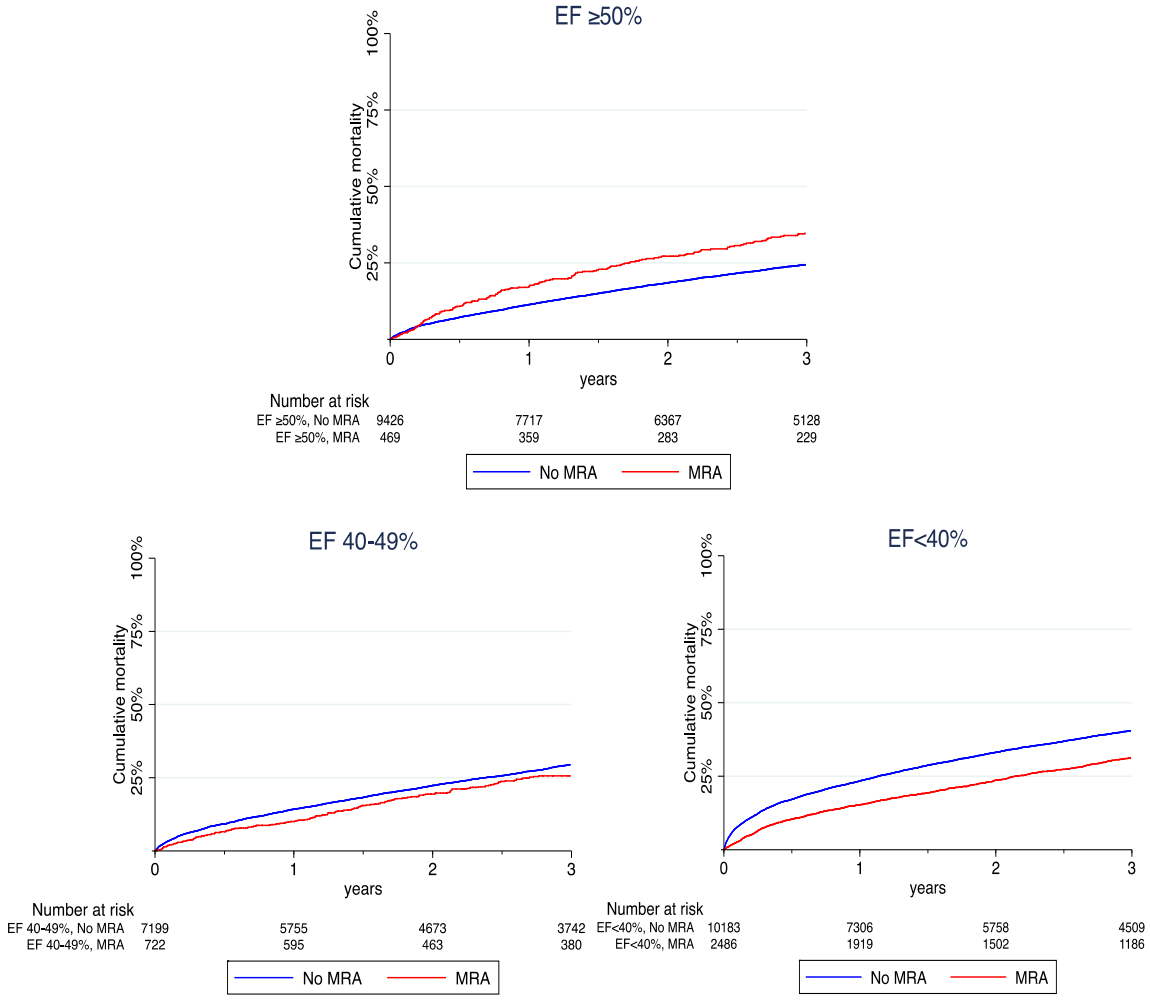
Mortality

The mortality rate was lower in patients treated with MRA during follow-up, 14.9 ((95% CI) 14.1-15.6) vs. 17.9 (17.6-18.2) per 100 person years in untreated patients resulting in HR (95% CI) of 0.83 (0.78-0.88). The association between MRA treatment and mortality was attenuated after adjustment but still significant (HR (95% CI) 0.94 (0.89-0.99)).

In the crude analysis when stratifying into different LVEF groups, MRA treated patients had lower mortality rates compared to the untreated patients in those with reduced LVEF (< 40 %) (13.2 (12.2-14.2) vs. 19.2 (18.6-19.8) per 100 person-years) and LVEF 40-49% (10.2 (8.6-11.8) vs. 12.2 (11.7-12.7) per 100 person years) (Figure 12). In those with LVEF $\geq$ 50%,

MRA treated patients had higher mortality rates compared to the untreated patients (15.1 (12.6-17.5) vs. 9.8 (9.3-10.2) per 100 person-years). In the adjusted analyses, there was a significant interaction between MRA and LVEF groups (p<0.0001), with a lower risk of death in MRA treated patients with LVEF < 40% (HR (95% CI) 0.81 (0.75-0.88)) and in patients with LVEF 40-49% (0.88 (0.75-1.03)) but not in those with LVEF ≥ 50% (1.29 (1.09-1.53)) (Figure 13).

**Figure 12 Mortality with and without MRA stratified on EF groups**

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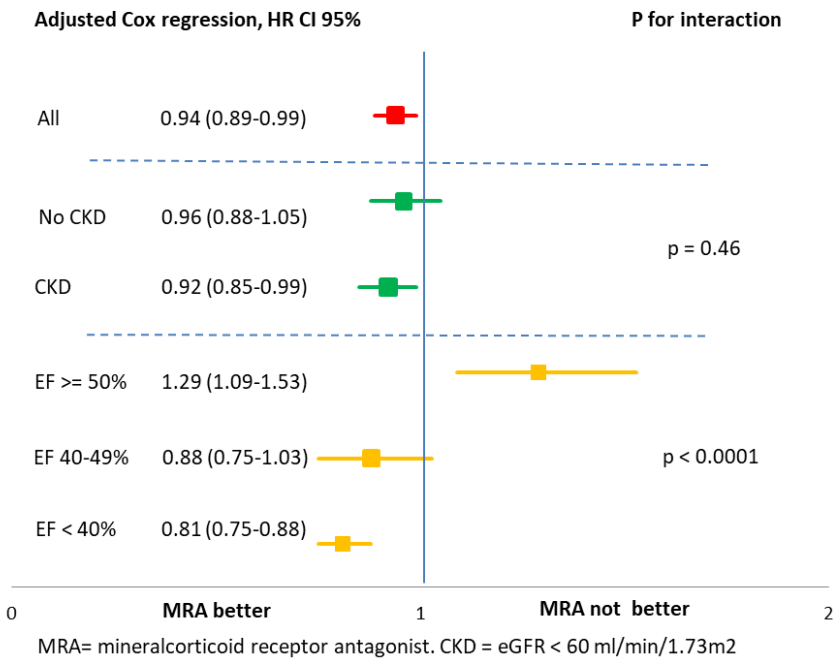
When the patients were divided into presence or not of CKD, MRA was associated with a lower mortality rate in patients with CKD (21.5 (20.0-23.1) vs. 26.9 (26.4-27.5) per 100 person-years), but not in patients without CKD (10.6 (9.7-11.5) vs. 10.7 (10.4-11.0) per 100 person-years). After adjustment there was no significant interaction between MRA and CKD (p=0.46) and there was no difference regarding the association between MRA treatment and outcome in patients with (HR (95% CI) 0.92 (0.85-0.99)) and without (0.96 (0.88-1.05)) CKD (Figure 13).

A sensitivity analysis, including only complete cases in the adjusted analyses, showed similar results with a significant interaction between MRA and LVEF, whereas there was no such interaction between MRA and CKD.

**Figure 13 Mortality risk with MRA use overall and stratified for LVEF and CKD**

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# DISCUSSION

Our main findings were that both CKD and WRF were common in unselected HF patients and most common in HFpEF. CKD and WRF were associated with similar co-variates in the different EF groups and both were strongly associated with long-term prognosis. In HFpEF the prognostic impact of CKD and WRF however was less strong than in HFrEF and HFmrEF. In unselected MI patients with HF, MRA was associated with better long-term survival in patients with reduced but not in preserved EF, while the association between MRA use and outcome was similar regardless of presence or not of CKD.

### Prevalence of renal dysfunction

The majority of HF patients have one or more comorbidities, CKD being most common followed by diabetes and anemia (51). The large meta-analysis of Damman et al. 2014 examining 57 studies of HF and including both RCTs, cohorts and registries, found a prevalence of CKD of 32% (5). In **study I** the prevalence of eGFR < 60 ml/min/1.73m2 was higher (51%), reflecting a real life HF population. In studies of AHF the prevalence of renal dysfunction is higher than in studies of CHF (5). In the American database ADHERE of AHF, the majority of patients had significant impairment of the kidney function (7). In the setting of AHF the predominantly driving force of renal impairment seem to be acute congestion with high CVP (1). CHF has been more studied than AHF and here the pathogenesis seems more complex and the reduction in renal blood flow of more importance with RAAS inhibitors partly blocking the kidney autoregulation (107). In **study I** a majority of patients with reduced renal function had HF with duration over 6 months. As many patients have an AHF incident on top of CHF, there is probably an overlap in the pathogenesis of acute and chronic HF.

The prevalence of renal insufficiency was found to be similar in the different EF groups in earlier registry data (83). **Study II** was the first large, generalizable, long term, comprehensive study of CKD in HFpEF, HFmrEF and HFrEF. We found that CKD was most common in HFpEF with a prevalence of 56%. This was higher than earlier noted and consistent with the unselective nature of SwedeHF compared to other registries (2, 83).

WRF has mostly been studied in acute hospitalized patients and less is known about the risk of long-term WRF after discharge. In **study III** we found that WRF was common and the cumulative incidence increased in HF both after discharge from hospital and in out-patients. During follow-up, half of the patients had an eGFR reduction of over 25% within two years and one quarter of the patients had a reduction of more than 50%. As with CKD, there was a higher risk for WRF in patients with HFpEF than in HFmrEF and HFrEF.

### Associations with renal dysfunction

In **study I** the patients with lower kidney function were older, had more often hypertension, diabetes mellitus, cardiovascular disease, long duration of HF and more severe NYHA class in keeping with previous studies (55, 86).

Renal dysfunction and HF potentiate each other by cardiorenal mechanisms and share similar risk factors. Diabetes and hypertension are (among RAAS and sympathetic activation, NO balance and inflammation) often referred to as cardiorenal connectors (1, 108). Both diabetes and hypertension are part of the pathogenesis in cardiorenal syndrome and promotes CKD disease progression by arteriosclerosis, tubular damage, albuminuria and nephron loss (109, 110).

In **study II** the HFpEF population was older, more often female, had more comorbidity, was more often included at hospitalization; all known risk factors for both HF and CKD (7, 54, 60). In **study II** there were interestingly in all three EF categories, almost similar associations between baseline characteristics and CKD after multivariable adjustments. Hemoglobin was independently associated with CKD, as was diabetes and hypertension. Even though the risk factors for CKD were similar in the different EF groups, the mechanisms leading to CKD and the impact of CKD in the different EF groups may vary.

### HFrEF and renal dysfunction

In HFrEF progress of HF is primarily due to loss of cardiomyocytes by ischemic heart disease and cardiomyopathies with subsequent RAAS and sympathetic activation and remodeling (57). The reduced cardiac function constitutes both forward and backward failure (111). Congestion of the kidney by high venous pressure, raised abdominal pressure and low stroke volume leads to reduced perfusion pressure in the glomeruli and reduced eGFR (13). With kidney congestion and reduced renal blood flow, the circulation in the kidney cortex and the tubules will be reduced, leading to varying degrees of tubular damage (112).

### HFpEF and renal dysfunction

In HFpEF the primary mechanism for disease progression is believed to be driven by the comorbidities. A new paradigm has been proposed for HFpEF where comorbidities induce an inflammatory state with microvascular dysfunction potentially leading to both cardiac and renal fibrosis (61, 113, 114). The direction of causality may however be in the opposite direction or bidirectional. There is a higher proportion of chronotropic insufficiency in HFpEF, which has shown a linear correlation with reduction in eGFR (115). In a study of HFpEF and echocardiography, CKD were associated with left atrial, left ventricular and right ventricular strain, proposing also a vicious circle where CKD and HFpEF are mutually

reinforced (116). There has been an increased understanding of HFpEF, where the combination of inflammatory state, hemodynamics and comorbidities is thought to induce right ventricular dysfunction which through increased central venous pressure deteriorate the kidney function further, explaining the high prevalence of renal dysfunction in HFpEF (64). The mechanisms in the progress of CKD in HFpEF seem therefore to be partially overlapping with the mechanisms in HFrEF and are accentuated by comorbidities and inflammation.

**HFmrEF and renal dysfunction**

In prior reports, HFmrEF has most often either been excluded as a grey area or included in the HFpEF or the HFrEF population (54, 55, 117). In **study II** we provide a detailed description of the HFmrEF group, where many clinical characteristics like age, proportion of female and hypertension were at a continuum between HFpEF and HFrEF but some characteristics like IHD and valvular disease were more similar to HFrEF than to HFpEF. This has later been confirmed in other studies of HFmrEF, where the main findings are that HFmrEF is similar to HFrEF regarding genesis of IHD and has a different response to treatment compared to HFpEF (118). The mechanism for CKD in HFmrEF is probably complex and similar to both HFpEF and HFrEF as HFmrEF is partly a transition between the two depending on the actual state of the HF. A proportion of HFmrEF seems to represent a prior or future HFpEF or HFrEF as different studies have shown that in 17-37% LVEF deteriorates and in 21-73 % it improves (119, 120).

In **study III** we examined the determinants of WRF and found similar associations as with CKD. Even here factors related to more severe HF were associated with WRF; higher age, valvular heart disease, registration at discharge from hospitalization vs. out-patient, HF over 6 months, CRT, NYHA class, anemia, low blood pressure, use of MRAs and diuretics were associated with WRF $\geq$25% after 1 year. We found few significant differences between the EF groups.

**Prognosis**

Patients with more than moderate decrease in kidney function have been excluded from clinical trials (57). The degree of kidney dysfunction and the impact of kidney dysfunction on outcomes in patients with HF have therefore earlier been under estimated.

In **study I** kidney function was strongly associated with short and long term mortality with an increasing mortality with decreasing eGFR. At five years, the cumulative probability of death was above 60% in those with moderate kidney dysfunction and above 80 % in patients with severe kidney dysfunction. The strong association with outcome was evident in all age groups, regardless of NYHA class, duration of heart failure, hemoglobin level and presence or not of diabetes mellitus. The high mortality in patients with HF and CKD may have multiple mechanisms. Both CKD and HF have similar risk factors associated with mortality;

like smoking, hyperlipidemia, anemia, hypertension and diabetes (85, 121, 122). CKD may be a marker for more severe heart failure as eGFR decreases with high venous pressure, ascites with increased abdominal pressure and forward failure (16, 17). Factors secondary to CKD, as endothelial dysfunction, secondary hyperparathyroidism, vascular calcifications, increased oxidative stress, chronic inflammation, metabolic acidity, deterioration of calcium-phosphate and electrolyte balance may also increase mortality (3). Patients with CKD are also less likely to receive evidenced based treatment because of fear of WRF and the uncertainty regarding optimal treatment doses (57, 123). In **study I** after adjustments for risk factors and factors related to severity of HF, impaired kidney function remained strongly associated with mortality confirming results from earlier observations showing that GFR is an independent predictor itself for outcome (86). When finally adjusting for treatment in our study, the association between kidney function and outcome remained unchanged; indicating that suboptimal treatment may not be so important for adverse outcome in patients with HF and reduced kidney function.

In **study II** CKD was strongly associated with mortality in all EF groups in line with earlier studies (5). The impact of CKD on prognosis in the different EF groups has varied according to different studies. In the meta-analysis of Damman et al of 80,000 patients, CKD was found to be a stronger predictor of death in HFpEF than in HFrEF, while the pooled study of McAlister et al. from the MAGGIC meta-analysis showed that renal dysfunction was a stronger predictor of all-cause mortality in patients with HFrEF than in HFpEF (5, 89). In study II we found in line with the MAGGIC meta-analysis that the mortality risk with CKD was lower in HFpEF in both the univariate and multivariate analyses than in the other EF groups. As CKD represents one of many comorbidities in HFpEF, the predictive role of impaired renal function may therefore be relatively lower in HFpEF than in HFmrEF and HFrEF.

In **study III** we found a weaker association between WRF and mortality in HFpEF compared to HFmrEF and HFrEF. In HFpEF and WRF the prognosis may be more related to comorbidities than in HFrEF, where progressive HF with subsequent kidney dysfunction may be more pronounced. **Study II** and **III** imply that in HFpEF both CKD and WRF are more common but seem to be less strongly associated with prognosis. In HFpEF there may be a parallel drive of CKD and HF by the comorbidities which lead to renal dysfunction being more frequent but less prognostic as it may not reflect a worse cardiac status. Whereas in HFrEF and HFmrEF, the kidney dysfunction may be secondary to more advanced HF and therefore comes later and is less frequent but once present, associated with greater risk. Even though there will be overlaps in the pathogenesis, as HFpEF and HFrEF have mutual cardiorenal connectors, this hypothesis may explain the observed differences in prevalence and prognosis in renal dysfunction between HFpEF and HFrEF .

**Heart failure treatment and prognosis in different EF groups**

In **study IV** the main finding was that MRA treatment was associated with a lower mortality in MI patients with reduced LVEF (< 40%) but not in patients with preserved LVEF (≥ 50%). Although the number of patients with EF ≥ 50% was small, and we do not know the indication for MRA treatment, the finding was noteworthy.

Earlier studies of MRA treatment in HFrEF are well in line with our results. Both RALES, study of spironolactone in patients with severe HF and LVEF ≤ 35% and EMPHASIS-HF, study of eplerenone in patients with mild HF and LVEF < 35% found that MRA in addition to standard therapy improved survival and morbidity (98, 124). In EPHESUS similar effects was found in patients with acute MI complicated by LVEF ≤ 40% and symptomatic HF or diabetes (99). In the STEMI guidelines 2017 MRA has a class I indication in patients with MI, HF and LVEF ≤ 40% (125). As **study IV** examines MRA treatment in non-selected real-life patients with acute MI and HF, it is noteworthy that only 19.6% of the patients with LVEF < 40% had MRA. Although this may be explained by the fact that MRA may be introduced after up-titration of ACEi/ARB and therefore prescribed after discharge from hospital, similar numbers have been noted in the US were only one out of seven eligible patients were prescribed MRA at discharge (126).

On the contrary, when looking at LVEF ≥ 50%, the means for comparing our results in the patients with preserved LVEF are lacking. There are no studies of MRA use in MI patients with HF and LVEF ≥ 50%. We may compare our findings with the results from the TOPCAT study of aldosterone antagonists in HFpEF (100). This study failed to show a reduction in the composite endpoint of cardiovascular death, aborted cardiac arrest and hospitalization with MRA, although a post-hoc analysis showed regional differences with benefits of spironolactone in the American patients (101). In **study IV** we found that patients with LVEF 40-49% had a tendency to lower mortality risk, which is in line with another sub-analysis from TOPCAT showing a potentially stronger beneficial effect at the lower end of the EF spectrum (127). The difference in survival with MRA treatment in LVEF ≥ 50% and LVEF < 40% is intriguing and also in line with earlier meta-analysis of MRA treatment in HF (128). Once again we are reminded that HFpEF and HFrEF are two different phenotypes with different pathogenesis. In HFpEF, pathogenesis is driven by comorbidities and inflammation while HFrEF are characterized by loss of myocytes due to ischemic heart disease or cardiomyopathies with neurohormonal activation (57, 61). Until now, all RCTs of HF treatment in HFpEF have failed to show improved survival (129). Aldosterone is part of the RAAS and RAAS blockade have not shown to have the same benefit in HFpEF as in HFrEF. Treatment with candesartan in CHARM-preserved did not reduce outcome (cardiovascular death and HF hospitalization) (130), indicating that neurohormonal activation is not as dominant part of pathogenesis in HFpEF as in HFrEF.

There may be differences in the comorbidities in HFpEF compared to HFrEF and also in the severity of HF in HFpEF that may affect the response to treatment. In a sub-analysis of Irbesartan in Heart Failure with Preserved Ejection Fraction Trial (I-PRESERVE), only HFpEF patients with modest NT-proBNP levels seemed to benefit from irbesartan suggesting that HFpEF patients with more advanced disease with the highest NT-proBNP and the worst prognosis were beyond potential medical treatment (131).

Patients with HFpEF have been found to die less from cardiovascular death and sudden cardiac death than HFrEF (132). This may also partly explain the lack of benefit of MRA in HFpEF as MRA has shown to reduce the risk of arrhythmias (98, 133).

**Heart failure treatment in patients with CKD**

The other main finding in **study IV** was that in patients with HF and CKD, there was no difference in mortality risk with MRA treatment compared to untreated patients. Patients with CKD have an increased mortality risk, predominantly from cardiovascular disease (134). As fibrosis of the heart, vessels and kidney are common in CKD, MRA represent a potential option to prevent cardiovascular complications (135). A meta-analysis of 12 CKD studies and over 4,000 patients showed that MRA treatment did benefit CKD patients regarding left ventricular muscular mass, all-cause mortality and cardio-vascular events and even patients in hemodialysis have been found to have reduced morbidity and mortality with MRA treatment (136, 137). There is a risk for hyperkalemia and WRF with MRA, which may explain why patients with CKD in the clinic often have MRA treatment withheld. Sub-analyses of EMPHASIS-HF and RALES found that MRA was of survival benefit despite WRF and surprisingly the greatest benefit was seen in patients with reduced eGFR (102, 138). Another sub-analysis of EMPHASIS-HF found MRA use to be efficient and safe in risk patients when they were well monitored (139). Criticism have been that in RCTs of MRA in addition to ACEi and beta blockers, the patients included are already selected as they have tolerated ACEi /ARB without hyperkalemia and there is therefore a potentially higher risk in unselected patients (139). In this setting future treatment with potassium binders may be feasible and facilitate MRA treatment (140). Even though our knowledge of MRA treatment in more pronounced kidney dysfunction is sparse, MRA seem to be underused, as only 8.6% of the patient with CKD had MRA. A recent study confirms that the most common factor associated to MRA underuse in HFrEF patients was CKD, this included even patients with only modest reduction of renal function (eGFR 30-59 ml/min/m2) where MRA was indicated (141). In **study IV** we examined an unselected real-life population and found that there was no higher mortality with MRA treatment in patients with CKD indicating that MRA may be used in MI patients with HF and reduced kidney function.

## Limitations

Both SwedeHF and Swedeheart are registries that reflect clinical practice. There may still be a certain selection of patients, as some patients may not have been transferred to the cardiology units and included in the registers because of frailty, co-morbidity or other reasons which may affect the generalizability of our studies. All studies were observational therefore causality cannot be proven. In all regression analyses we adjusted for a large number of confounders, but residual confounding may still exist due to unmeasured factors that could not be adjusted for.

The diagnosis of HFpEF is more contentious than diagnosing HFrEF. The criteria for diastolic dysfunction have changed over the years (142). Patients with CKD may have fluid retention and high filling pressures making it difficult to distinguish CKD from HFpEF (143). Many patients with diastolic dysfunction may also have alternative explanations for their dyspnea, such as obesity, pulmonary disease and ischemia (144). Taken together patients diagnosed with HFpEF are a heterogeneous group in which some may not have HF at all. However the patients that get a diagnosis of HFpEF may have a more severe HF than patients with HFrEF when they are taken into the cardiac units. This may have had an effect on the prevalence and prognosis of CKD in these patients.

In **study IV**, in analyses of MI and EF, a slightly reduced EF may be intermittent due to stunning, and the HF signs may have been temporary which is why we have to be cautious to extrapolate our results to a population of CHF. Regarding the MRA use; we do not know for sure if the patients continued with their medication during follow-up or if untreated patients were prescribed MRA later.

The EF measurements were according to local practice and not according to a core laboratory.

Even though there are limitations, **study I** and **II** included over 40,000 HF patients in Sweden during more than 10 years, **study III** included the majority of hospitalized HF patients in Stockholm during 5 years and **study IV** included almost all patients with acute MI and HF for a period of 10 years in a whole country, leading us to believe that the results should be highly generalizable.

# CONCLUSIONS

In unselected HF patients:

• Half of the patients have at least a moderate decrease in kidney function classified as CKD.

• Within two years, over half of the patients will have WRF of at least 25%.

• CKD and WRF are common in all EF groups and most common in patients with HFpEF.

• CKD is associated with similar covariates regardless of EF.

• Variables related to more severe HF are predictive of WRF in all EF groups.

• There is a strong graded association between renal dysfunction and both short- and long-term outcome.

• CKD is strongly associated with outcome in all EF groups, but less so in HFpEF than in HFmrEF and HFrEF.

• WRF is a strong negative prognostic factor in all EF groups, although in HFpEF only in patients with the most severe WRF.

In unselected patients with MI and HF:

• MRA may be underused in patients with reduced EF.

• MRA use is associated with better survival in patients with reduced EF but not in patients with preserved EF.

• The association between MRA use and outcome seems to be similar regardless of presence or not of CKD.

## Clinical perspectives

As CKD is the strongest risk factor in HF and WRF may have an impact on survival over many years it is an essential goal to preserve the kidney function in all HF patients. This includes early relief of decongestion when the patient is admitted to hospital and avoiding unnecessary examinations with contrast and nephrotoxic agents. As a simple measurement of creatinine is an indicator of patient prognosis, it is important to be observant to the laboratory tests. Estimation of GFR is easy and of uttermost value. Patients with HF and moderate renal dysfunction (eGFR 30-59 ml/min/1.73 m2) should not have optimal HF treatment, including MRA withheld. Collaboration with the nephrologists is important as are close-follow-up of the patients with laboratory controls after adjustment of the medication. Identifying patients at risk to prevent WRF may help in preserving renal function and improve clinical outcome. We still lack guideline recommended treatment in HFpEF, which is why it is essential to identify and treat the patients' comorbidities to decrease the risk of progressive renal dysfunction.

As CKD patients are at high risk of cardiovascular disease, early detection of cardiac symptoms and treatment of risk factors are important. Even here is a close collaboration with the cardiologist necessary so that the patients are not excluded from examinations and receive optimal treatment to avoid ischemic events and HF.

## Future studies

The renocardial part of CRS is less well described. It is unclear why some patients with CKD develop HFpEF with a transition towards a hypertrophic phenotype while others develop HFrEF in an earlier stage. These differences may be due to hemodynamic differences in filling pressures, preload and afterload, in inflammatory state and possibly underlying structural and premorbid differences that we do not know of and are in need of further studies.

The potential of reversing HF and CKD in CRS is also less well studied. Studies of kidney transplantation patients with HF have shown that EF may be improved when restoring renal function but we are in need of more knowledge of the pathophysiologic factors involved to be able to optimize patient selection (145).

**Study IV** implies that MRA may be used in the presence of CKD. Hopefully future RCTs of HF medications will be able to include patients with more severe renal dysfunction as there is a need for evidenced based treatment of patients with CKD.

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