UMEÅ UNIVERSITY

# Mineralocorticoid receptor antagonists in Heart Failure

***Exploring the gap between guideline-directed medical therapy and real-world practice***

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Umeå 2021

Responsible publisher under Swedish law: the Dean of the Medical Faculty

Dissertation for PhD
ISBN: 978-91-7855-650-2
ISSN: 0346-6612
New Series Number 2154
Cover design by Inhousebyrån
Electronic version available at: http://umu.diva-portal.org/
Printed by: CityPrint i Norr AB
Umeå, Sweden 2021

*To my family*

# Table of Content

# Original papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numbers as assigned below.

I. Jonsson A, Norberg H, Bergdahl E, Lindmark K. Obstacles to mineralocorticoid receptor antagonists in a community-based heart failure population. *Cardiovasc Ther*. 2018 Oct;36(5):e12459. doi: 10.1111/1755-5922.12459. Epub 2018 Aug 14. PMID: 30019390; PMCID: PMC6175311.

II. Jonsson A, Viklund I, Jonsson A, Valham F, Bergdahl E, Lindmark K, Norberg H. Comparison of creatinine-based methods for estimating glomerular filtration rate in patients with heart failure. *ESC Heart Fail*. 2020 Jun;7(3):1150-1160. doi: 10.1002/ehf2.12643. Epub 2020 Feb 13. PMID: 32052932; PMCID: PMC7261582.

III. Jonsson Holmdahl A, Wessberg G, Norberg H, Söderström A, Valham F, Bergdahl E, Lindmark K. Motives, predictors, and outcomes of MRA discontinuation in a real-world heart failure population. *Manuscript*.

IV. Jonsson Holmdahl A, Norberg H, Valham F, Bergdahl E, Lindmark K. Mineralocorticoid receptor antagonists use in patients with heart failure and impaired renal function. *PLoS One*. 2021 Oct 28;16(10):e0258949. doi: 10.1371/journal.pone.0258949. PMID: 34710128; PMCID: PMC8553049.

# Abstract

Heart failure is the possible end-result of a variety of different diseases, where ischemic heart disease and hypertension are the most common causes in high-income countries. In Sweden, heart failure has a prevalence of 2% in the adult population and rises to over 10% among people over 70 years of age. The 5-year all-cause mortality is about 50%. To put in context, the age-adjusted 5-year mortality, first hospitalization rate and premature life-year loss were shown to be similar to those of the most common forms of cancer combined. The triad of Angiotensin-Converting Enzyme Inhibitors (ACEIs) or Angiotensin II Receptor Blockers (ARBs), Beta-blockers (BBs), and Mineralocorticoid Receptor Antagonists (MRAs) are recommended in all patients with heart failure with reduced ejection fraction (HFrEF) to decrease mortality and morbidity rates. While most eligible patients get access to treatment with ACEIs/ARBs and BBs, national and international registry and observational studies have shown that MRA treatment is largely underused in patients with HFrEF. Treatment with MRAs has shown a 15-30% relative risk reduction of all-cause mortality in patients with HFrEF at a follow-up time of 16 to 24 months, but not even half of all eligible patients receive this treatment. The aim of this theses was to explore the pattern of MRA use in a real-world heart failure population and the reasons for MRA underuse.

With an observational retrospective study design, patients were included if they were diagnosed with heart failure at the Heart Centre or Department of Internal Medicine between January 2010 and January 2018. All patients were residents within the catchment area of the Umeå University Hospital, Sweden, and were identified by the hospital's medical records. All data were collected from medical records. Index data were collected at the time of diagnosis, and follow-up data were collected by the journal entry closest to the end of the data collection period (2016-2018).

From the medical record content analysis, we found that contraindications including renal dysfunction, hypotension and hyperkalemia were the most common reasons for not receiving treatment with MRAs. However, almost half of those patients did not meet the guideline-directed contraindications. After excluding patients with contraindications, the underutilization of MRAs was 10%. Patients without MRAs had been hospitalized for heart failure to a much lesser extent. It is possible that this group of patients were often overlooked, which is supported by the finding that nearly one-third of these patients never had a follow-up at the cardiology clinic. Overall, we estimated that about 60% of the patients with HFrEF would tolerate MRA treatment in the long-term, but only about 45% of the patients with HFrEF in our population were prescribed and maintained on MRAs.

Since renal dysfunction was the most common reason for not initiating MRA treatment, we wanted to evaluate how accurate eight different creatinine-based equations for estimated glomerular filtration rate (eGFR) were in heart failure patients. We showed that none of the exclusively creatinine-based equations for eGFR were accurate in predicting mGFR. All creatinine based eGFR equations overestimated the renal function. Our findings suggests that more accurate methods are needed for determining eGFR in patients with heart failure since overestimation causes an unnecessary risk of serious adverse effects and may also lead to patients not receiving optimal guideline-directed medical therapy.

We also found that half of all patients initiated on MRAs discontinued treatment. The most common reasons for discontinuation were renal dysfunction and elevated serum-potassium but again, a majority of those did not meet guideline-directed contraindications. Independent predictors of MRA discontinuation were lower eGFR, increased serum-potassium, lower blood pressure, higher comorbidity index and higher left ventricular ejection fraction. Patients who discontinued MRAs had a higher risk of all-cause mortality after adjusting for relevant covariates. One-third of all patients with moderately impaired renal function developed worsening renal function (WRF) but use of MRAs did not impact the risk. Furthermore, use of MRAs did not increase the adjusted overall risk of mortality even when experiencing WRF.

In conclusion, there seems to be a substantial avoidable under-treatment with MRAs especially for elderly patients that are admitted to the hospital for reasons other than heart failure as well as in patients with moderately impaired renal dysfunction with mild hyperkalemia. We suggest that the risk of inadequate means of follow-up restrains optimal use of MRAs, especially in patients with moderately impaired renal function and or mild hyperkalemia that require frequent and regular laboratory monitoring to assure the safe use of MRA. In addition, better methods are needed to accurately estimate renal function in heart failure patients. These findings contribute to the understanding of the underlying reasons behind the gap between the guideline-directed use of MRAs and real-world practice.

# Abbreviations

| | |
|---|---|
| $^{51}$Cr-EDTA | $^{51}$Chromium-51-ethylenediaminetetraacetic acid |
| ACEI | Angiotensin-Converting Enzyme Inhibitor |
| ARB | Angiotensin II Receptor Blocker |
| ARNI | Angiotensin Receptor-Neprilysin Inhibitor |
| BB | Beta-Blocker |
| BIOSTAT-CHF | The Biology Study to Tailored Treatment in Chronic Heart Failure |
| CCI | Charlson Comorbidity Index |
| CG-IW/AW | Cockcroft-Gault's ideal weight/actual weight equation |
| CHAMP-HF | Change the Management of Patients with Heart failure |
| CKD | Chronic kidney disease |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration equation |
| CRS | Cardio-Renal Syndrome |
| CRT | Cardiac Resynchronization Therapy |
| ECG | Electrocardiography |
| eGFR | estimated Glomerular Filtration Rate |
| EMPHASIS-HF | The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure |
| EPHESUS | Eplerenone Post-Myocardial Heart Failure Efficacy and Survival Study |

| | |
|---|---|
| ESC | European Society of Cardiology |
| ESC-HF-LT | ESC Heart Failure Long-Term Registry |
| HFmrEF | Heart Failure with mildly reduced Ejection Fraction |
| HFpEF | Heart Failure with preserved Ejection Fraction |
| HFrEF | Heart Failure with reduced Ejection Fraction |
| IDMS | Isotope-Dilution Mass Spectrometry |
| LM-rev | the revised Lund-Malmö equation |
| LVEF | Left Ventricular Ejection Fraction |
| MDRD | Modification of Diet in Renal Disease study equation |
| mGFR | measured Glomerular Filtration Rate |
| MR | Mineralocorticoid Receptor |
| MRA | Mineralocorticoid Receptor Antagonist |
| NT-proBNP | N-terminal pro-b-type Natriuretic Peptide |
| NYHA | New York Heart Association functional classification |
| RAAS-I | Renin-Angiotensin-Aldosterone-System Inhibitor |
| RALES | Randomized Aldactone Evaluation Study |
| RCTs | Randomized Controlled Trials |
| SGLT2 | Sodium-Glucose Co-Transporter 2 |
| SNS | Sympathetic Nervous System |
| WRF | Worsening Renal Function |

# Enkel sammanfattning på svenska

Hjärtsvikt är ett komplext kliniskt syndrom som blir allt vanligare. I Sverige har cirka 2 % av befolkningen hjärtsvikt och diagnosen blir vanligare med högre ålder. Hjärtsvikt är förknippad med hög dödlighet, då cirka 50% avlider inom 5 år från diagnos. Flera läkemedel har visat sig öka överlevnaden och minska sjukligheten för patienter med hjärtsvikt, men behandlingen är komplex och kräver att olika läkemedel kombineras och dosjusteras över tid. Dessutom krävs regelbundna uppföljande kontroller efter insättning för att behandlingen ska vara säker och optimal behandlingsstrategi ska nås. Vid den tidpunkt då våra studier genomfördes bestod basbehandlingen vid hjärtsvikt, primärt av tre läkemedelsgrupper: angiotensinkonverterande enzymhämmare (ACE-hämmare) eller angiotensin II-receptorblockerare (ARB), Betablockerare (BB) och mineralkortikoidreceptorantagonister (MRA). Flera nationella och internationella registerstudier och observationsstudier har visat att de flesta patienter behandlas med ACE-hämmare/ARB och BB men att mindre än hälften av de patienter som skulle vara lämpliga för MRA får behandling. Detta trots att kliniska prövningar har visat att behandling med MRA minskar risken för död med 15–30 % vid en uppföljningstid på 16–24 månader. De stora kliniska prövningarna har ofta inkluderat patienter som är både yngre och med mindre samsjukligheten än den verkliga hjärtsviktspopulationen. Det kan därför vara svårt för den behandlande läkaren att applicera resultaten från en klinisk prövning till verkliga patienter med hjärtsvikt, vilket kan skapa en osäkerhet i den kliniska verkligheten kring hur olika risker med läkemedelsbehandlingen ska hanteras. Syftet med den här avhandlingen var att bättre förstå hur utbredd underbehandlingen med MRA var i en verklig hjärtsviktspopulation och vad skillnaden mellan riktlinjebaserad rekommenderad läkemedelsbehandling och klinisk verklighet beror på.

Avhandlingen baseras på journaldata från Norrlands Universitetssjukhus (NUS), Umeå, Sverige. Alla patienter som fått en hjärtsviktsdiagnos via Hjärtcentrum eller Medicinkliniken mellan 2010 och 2018 och var folkbokförda inom NUS primära upptagningsområde inkluderades. Journaldata insamlades från två tillfällen, så nära diagnos som möjligt och så nära slutet på datainsamlingen som möjligt (mellan år 2016–2018).

Hjärtsviktspopulationen vi studerade hade en hög medelålder (80 år) och samsjukligheten med bland annat högt blodtryck, ischemisk hjärtsjukdom, diabetes och nedsatt njurfunktion var hög. I vår första studie initierades och bibehölls behandling med MRA hos ca 45 % av patienterna fastän vi uppskattade att åtminstone 60 % av patienterna bör ha tolererat behandlingen. Genom journaltextanalyser fann vi att den vanligaste anledningen till att inte förskriva

MRA var att den behandlande läkaren bedömde att patienten hade en eller flera kontraindikationer, där de vanligaste var nedsatt njurfunktion, högt kalium och lågt blodtryck. Däremot nådde knappt hälften av patienterna de gränser för njurvärde och kalium då MRA-behandling är kontraindicerad, vilket innebär att många i gruppen med kontraindikationer egentligen borde ha tolererat behandlingen. Vi fann ingen orsak i journalen till utebliven MRA-behandling hos ytterligare 1 av 10 patienter som var lämpliga för behandling med MRA och inte hade kontraindikationer. Dessa patienter var äldre, hade färre sjukhusinläggningar för hjärtsvikt, färre behandlades eller nådde måldoser av ACE-hämmare/ARB och BB och färre hade sviktpacemaker, jämfört med patienterna som hade MRA-behandling. Dessutom hade en tredjedel inte något uppföljande besök på kardiologmottagning. Vi drog därför slutsatsen att äldre patienter med mindre symptomgivande hjärtsvikt verkar ha en risk att bli förbisedda och att patienter med lätt till måttlig nedsatt njurfunktion underbehandlas med MRA.

Njurfunktionen räknas oftast ut indirekt genom olika ekvationer som tar hänsyn till nivån av blodprovet kreatinin, ålder, kön och ibland vikt. I vår andra studie undersökte vi hur väl åtta av dessa ekvationer överensstämde med ett uppmätt njurfunktionsvärde hos patienter med hjärtsvikt. Utöver en ekvation som frånsett kreatinin även använder blodproven urea och albumin, uppfyllde ingen av ekvationerna som enbart var baserade på kreatinin kraven på noggrannhet och precision. Alla ekvationer baserade på enbart kreatinin överskattade njurfunktionen och gav ofta värden som avvek mer än 30% från det uppmätta njurfunktionsvärdet. Vi drog därför slutsatsen att bättre metoder krävs för att räkna ut njurfunktionen hos patienter med hjärtsvikt. Det är viktigt att få en så korrekt uppskattning av njurfunktionen som möjligt, eftersom värdet på njurfunktionen kan avgöra vilken typ av läkemedelsbehandling som ges.

I den tredje studien visade vi att över hälften av patienterna som fick förskrivet MRA avslutade behandlingen. Även om många som avslutat behandlingen gjorde ett förnyat insättningsförsök, avslutades MRA ofta på nytt. Återigen var den vanligaste anledningen till att sätta ut behandlingen måttligt nedsatt njurfunktion och förhöjt kalium men drygt hälften av dessa patienter nådde inte beslutsgränsen för dosminskning eller utsättning av MRA. I en överlevnadsanalys där vi justerat för andra bidragande anledningar till ökad dödlighet såsom ålder, samsjuklighet och njurfunktion, såg vi att gruppen med utsatt MRA hade ökad risk för död jämfört med gruppen som fortsatt med MRA. Vi drog slutsatsen att MRA ofta sätts ut trots att njurfunktionen och kaliumnivåerna tillåter fortsatt behandling och att utsättning av MRA är förknippat med en lägre överlevnad.

Eftersom måttligt nedsatt njurfunktion var en vanlig anledning till utebliven eller avslutad behandling valde vi i den fjärde studien ut en grupp patienter med

hjärtsvikt och minst måttligt nedsatt njurfunktion, för att se hur MRA-behandling påverkade risken för ytterligare försämrad njurfunktion och överlevnad. Vi fann att en försämrad njurfunktion drabbade ungefär en tredjedel av denna selekterade hjärtsviktspopulation, utan någon skillnad mellan gruppen som behandlades med MRA och gruppen som inte behandlades med MRA. En justerad riskanalys visade att det inte heller var någon skillnad i dödlighet mellan grupperna. Vi drog därför slutsatsen att MRA inte ökar risken för försämrad njurfunktion eller ger ökad dödlighet i gruppen med minst måttligt nedsatt njurfunktion och hjärtsvikt.

Sammanfattningsvis fann vi att det fanns en påtaglig åtgärdbar underbehandling av MRA i hjärtsviktspopulationen vi studerade. Särskilt äldre med mindre symptomgivande hjärtsvikt riskerar att bli förbisedda. En stor del av patienterna behandlas inte enligt gällande riktlinjer, särskilt inte de mest sköra patienterna med högst risk för biverkningar. De kreatinin-baserade metoderna som används för att uppskatta njurfunktionen hos patienter med hjärtsvikt har otillräcklig noggrannhet och kan leda till både under- och överskattning av njurfunktionen, vilket försvårar möjligheterna till optimal läkemedelsbehandling. Våra resultat bidrar med förklaringar till skillnaden mellan riktlinjebaserade behandlingsrekommendationer och den kliniska vardagen. Mer forskning behövs för att hitta metoder som förbättrar förskrivning, följsamhet och uppföljning av MRA-behandling.

# Introduction

There are several medical treatments that have proven survival benefits in heart failure. However, the medical treatment for HFrEF is complex and requires sequential addition of drugs and dose titration over a long period. In addition, close monitoring of laboratory data is required for safety reasons after optimal medical therapy is reached.

When the studies were conducted, the triad of ACEIs or ARBs, BBs and MRAs were recommended in all patients with HFrEF to decrease mortality and morbidity. In three landmark randomized controlled trials (RCTs), MRAs has shown a 15-30% risk reduction of all-cause mortality. Despite this fact, studies have shown that less than half of all eligible patients receive treatment with MRAs.

MRA treatment has been strongly associated with increased risk of hyperkalaemia and WRF. In perspective of the real-world heart failure population of elderly patients with a high degree of comorbidities including renal dysfunction, these risks are important considerations. Since RCTs have strict selection criteria causing limited generalizability and external validity, the actual tolerability of MRAs in real-world patients with heart failure remains uncertain. In everyday clinical practice, it is challenging to apply the results from RCTs to the diversified real-world patients, which could cause more arbitrary and cautious treatment decisions. This discrepancy between real-world setting and the tightly controlled setting of a RCT stresses the importance of further research on actual real-world patients.

To better understand the reasons of the underuse of MRAs in heart failure, a summary of the heart failure syndrome, the linkage between heart failure and renal dysfunction and the development of heart failure treatment with focus on MRAs is presented.

# Background

## Definition of heart failure

Heart failure is the possible end-result of a variety of different diseases. Rather than being a specific disease, it is a clinical syndrome with different aetiologies and pathophysiology. The exact definition of heart failure has varied widely (1, 2). In 2021, a consensus document for a universal definition and classification of heart failure was published by selected members from The Heart Failure Society of America, the Heart Failure Association, the European Society of Cardiology (ESC) and the Japanese Heart Failure Society (1). The definition was:

"Heart failure is a clinical syndrome with current or prior

- Symptoms and/or signs caused by structural and/or functional cardiac abnormality (Figure 1)
- And corroborated by at least one of the following:
  - Elevated natriuretic peptide levels
  - Objective evidence of cardiogenic pulmonary or systemic congestion"

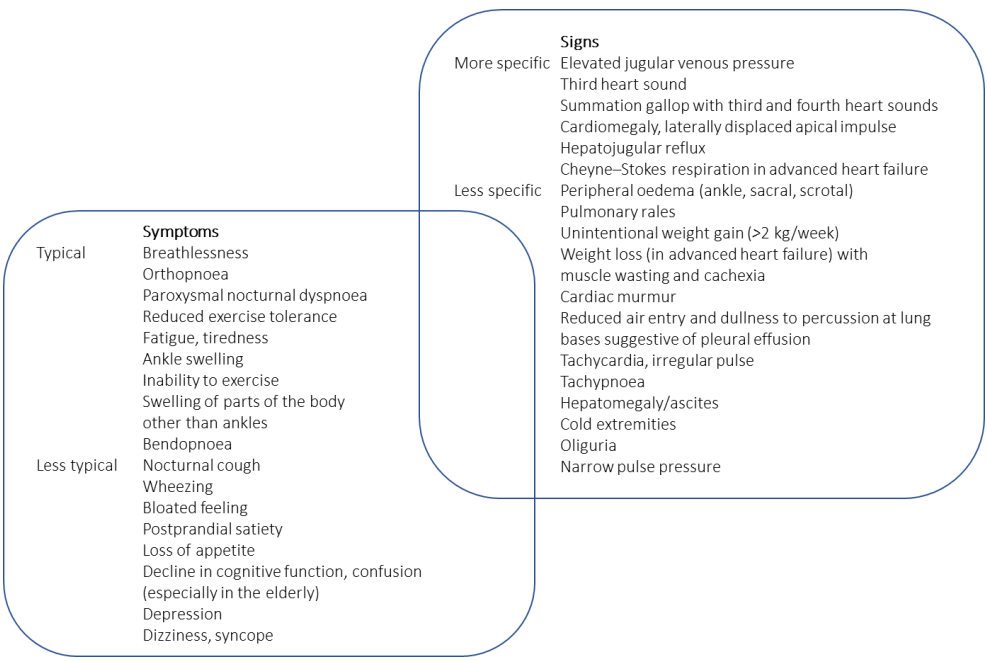


*Figure 1. Symptoms and signs of heart failure (1).*

These recent definitions of heart failure require not only symptoms or signs, but also objective measurements. These objective measurements are discussed in further details in the following chapters.

## Epidemiology and prognosis

Heart failure is a complex clinical syndrome with a prevalence of 1-2% of the adult population in developed countries and rises to >10% among people over 70 years of age (3). To put in context, the age-adjusted 5-year mortality, first hospitalization rate and premature life-year loss were shown to be similar to those of the most common forms of cancer combined (4).

In Sweden, the age-adjusted annual incidence rate of heart failure/1000 inhabitants is about 3% and the 1-year all-cause mortality is about 31% in women and 26% in men (5). The most common causes of death were chronic ischaemic heart disease, myocardial infarction, progressive heart failure and atrial fibrillation.

Of note, the age-adjusted annual incidence of heart failure has decreased since the mid-1990s, whereas the prevalence has increased (5-7). The decreased incidence could be explained by improvements in managing cardiac disorders such as myocardial infarction (MI), valvular heart disease, arrhythmias, and their associated risk factors (2, 5, 8, 9).

## Diagnosis of heart failure

### *Clinical evaluation*

The diagnosis of heart failure is challenging since none of the symptoms and signs are entirely sensitive or specific. The symptoms and signs raise suspicion of heart failure rather than giving a definitive diagnosis. Worsening dyspnoea is a cardinal symptom with a high sensitivity (89%) but a low specificity (51%) since dyspnoea can be caused by many other medical conditions. Other symptoms or signs have high specificity such orthopnoea (89%), oedema (72%), elevated jugular venous pressure (JVP) (70%), cardiomegaly (85%), added heart sound (99%), lung crepitation (81%) and hepatomegaly (97%); however, the sensitivity of these features is low and can even be absent in over 50% of the patients (10). Additional weigh gain is common due to volume retention, but in advanced heart failure unintended weight loss due to malnutrition and/or cachexia can be prominent (11). Another cardinal symptom is fatigue, which is partly caused by reduced cardiac output but also due to a changed metabolism. Further, symptoms and signs are more difficult to identify in the elderly and in patients with additional comorbidities such as chronic lung disease or obesity (12).

### *Initial investigations*

*Natriuretic Peptides*
Natriuretic peptides are biomarkers for heart failure diagnosis. B-type natriuretic peptide (BNP) is released from the cardiomyocytes due to stretch. Since the ventricles have a predominance of cardiomyocytes, BNP mainly reflects ventricular stretch. Cleavage of the precursor protein, proBNP, produces the biologically active BNP and the biologically inactive N-terminal pro-b-type natriuretic peptide (NT-proBNP) (13). The biologically active BNP causes natriuresis, diuresis, vasodilation, and smooth muscle relaxation.

BNP and NT-proBNP are reasonably correlated, and although both values can be used, NT-proBNP is the most used marker in Sweden. The upper limit normal for NT-proBNP in a non-acute setting is <125 pg/mL and <300 pg/mL in an acute-setting. The negative predictive value is 0.94-0.98 in both acute and none-acute settings, but the positive predictive value is lower, 0.44-0.57, in none-acute setting and 0.66-0.67 in acute settings (14). Hence, NT-proBNP is used to rule out heart failure and not to establish the diagnosis (12).

Several other cardiovascular and non-cardiovascular diseases can cause elevated NT-proBNP such as valvular heart disease, pulmonary hypertension, ischemic heart disease, atrial arrhythmias, and renal failure. Further, the natriuretic peptides levels increase with age, while obesity can cause disproportionally low levels (2).

*Electrocardiography*
Electrocardiography (ECG) is often abnormal in heart failure. An abnormal ECG has an 89% sensitivity and a 56% specificity for heart failure diagnosis. When compared, NT-proBNP are more accurate than ECG in the diagnosis in heart failure (10). Nevertheless, ECG is part of the initial evaluation of a suspected heart failure patient since it provides important information such as causes of heart failure as well as information that affects treatment strategies (Figure 2) (2).

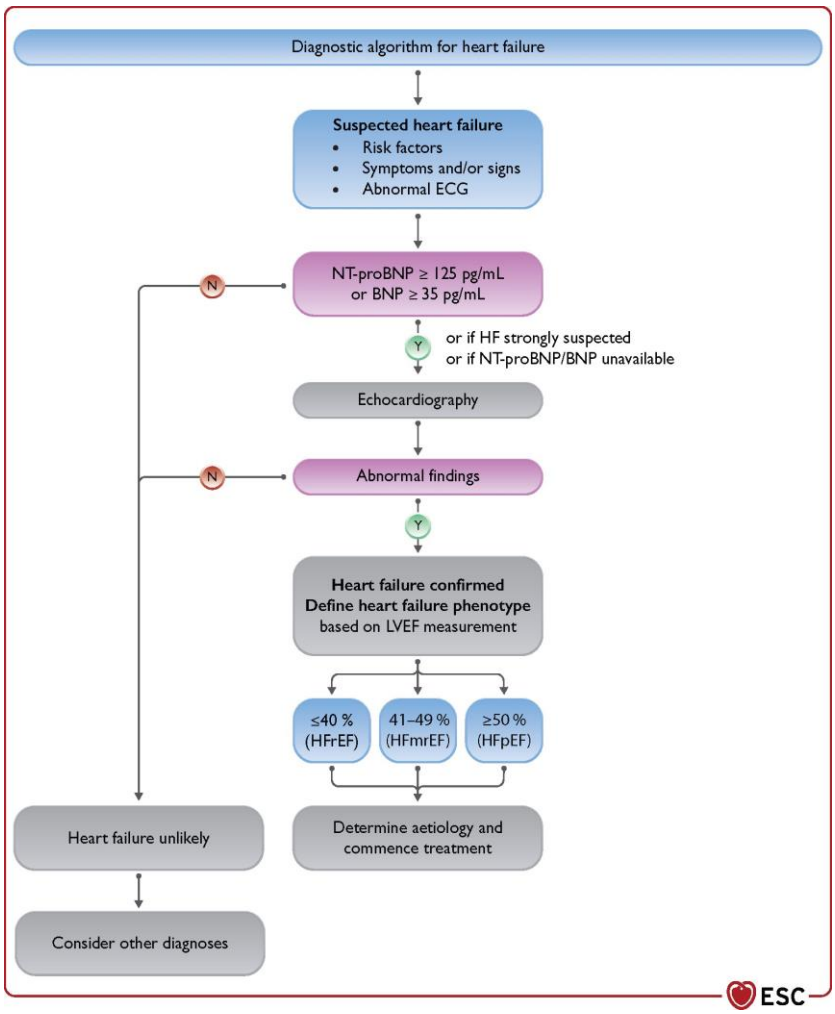


*Figure 2. The diagnostic algorithm for heart failure. BNP = B-type natriuretic peptide; ECG = electrocardiogram; NT-proBNP = N-terminal pro-B type natriuretic peptide; LVEF = left ventricular ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction. Reprinted from (3), by permission of Oxford University Press on behalf of the European Society of Cardiology.*

### *Echocardiography*

In echocardiography, ultrasound is used to produce two-dimensional imaging of the heart. In transthoracic echocardiography, an ultrasound transducer is placed on the patient's chest and high frequency soundwaves traverse through internal body structures, interact with tissues, reflect back to the transducer, and are then processed by microcomputers to generate an image. An examination by transthoracic echocardiography provides data on the size and shape of cardiac

chambers, cardiac morphology, function of cardiac valves, and assessment of the systolic and diastolic function. By using the Doppler principle, in which ultrasound that is reflected from red blood cells moving towards the emitter will return at a higher frequency while ultrasounds reflected from red blood cells moving away from the transducer will return at a lower frequency, it is possible to calculate the velocity of the intracardial blood flow and to quantify myocardial motion. The transthoracic echocardiography examination is highly dependent on the operator, both for acquisition of ultrasound images as well as for interpretation. Ultrasound penetrates poorly through air and bone and since the heart is surrounded by lungs and the rib cage, the ability to circumvent these obstacles depends highly on the operator's skills (2).

Transthoracic echocardiography plays a central role in the diagnosis of heart failure and to distinguish between the three different subtypes. The most common method to assess the left ventricular systolic function is to calculate left ventricular ejection fraction (LVEF).

LVEF = (end diastolic volume-end systolic volume)/end diastolic volume.

The volumes can be calculated by several methods, where the modified biplane Simpson's method is the most used (12). This method uses the apical four- and two-chambers and measures the diameter and height in axial slices that are equally distributed along the ventricle. The volume of each axial slice is calculated, and the sum of all axial slices gives the total chamber volume. The accuracy is affected by imaging plane, image quality, endocardial border definition, and heart rate. For example, foreshortening of the ventricle can be caused by a minor change in the angle or position of the transducer, which can reduce the measured volume. Further, it relies on geometric assumptions that are not generalizable to all patients. These drawbacks contribute to loss of reproducibility and to inter- and intra-observer variability (15).

### *Classification according to ejection fraction*

Classification based on LVEF is important since it differentiates patients with heart failure according to demographics, comorbid condition, aetiologies, response to therapies, and prognosis, and because most clinical trials select patients based on LVEF (12, 13). The LVEF is a critical measure of heart failure since it is used to divide patients into three main definitions (Table 1).

*Table 1. Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction, and preserved ejection fraction (3).*

| Type of HF | | HFrEF | HFmrEF | HFpEF |
|---|---|---|---|---|
| CRITERIA | 1 | Symptoms ± Signs[a] | Symptoms ± Signs[a] | Symptoms ± Signs[a] |
| | 2 | LVEF ≤40% | LVEF 41–49%[b] | LVEF ≥50% |
| | 3 | - | - | Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c] |

*HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction. Reprinted from (3), by permission of Oxford University Press on behalf of the European Society of Cardiology.*

A normal LVEF is considered LVEF ≥50% and patients with normal LVEF but symptoms and signs of heart failure in combination with diastolic dysfunction or raised left ventricular filling pressures is defined as Heart Failure with preserved Ejection Fraction (HFpEF) (16). HFrEF was previously referred to as systolic heart failure, and HFpEF was referred to as diastolic heart failure. Since patients with HFrEF can have elements of diastolic dysfunction and patients with HFpEF can have elements of systolic dysfunction, criteria based on LVEF are preferred over the term "systolic" or "diastolic" dysfunction (12).

*Heart Failure with reduced Ejection Fraction*

The diagnosis is made upon symptoms and signs, and an echocardiogram that reveals a LVEF ≤40%. Definitions has varied over time from LVEF ≤40% to LVEF ≤35%, which is why many previous RCTs have mainly enrolled patient with LVEF ≤35%. Furthermore, those with HFrEF often have elements of diastolic dysfunction. (13)

*Heart Failure with mildly reduced Ejection Fraction*

The diagnosis is based upon criteria composing symptoms and signs of heart failure and LVEF 41-49%. Heart failure with mildly reduced ejection fraction (HFmrEF) was previously called heart failure with moderately reduced ejection fraction. HFmrEF was renamed in in the updated ESC heart failure guidelines from 2021 since clinical trials suggests that these patients benefit from similar therapies as patients with HFrEF (3).

*Heart failure with preserved Ejection Fraction*

The diagnosis is based on symptoms and signs of heart failure, LVEF ≥50%, elevated natriuretic peptides and additional echocardiographic criteria. Echocardiographic criteria are relevant structural heart disease (left ventricular

hypertrophy and/or left atrial enlargement) or/and signs of diastolic dysfunction. Diastolic dysfunction can be described as impaired left ventricular relaxation and increased left ventricular stiffness. The structural alterations seen on echocardiography are enlargement of the left atrial (left atrial volume index >34 mL/m$^2$) or ventricular hypertrophy (left ventricular mass index $\geq$115 g/m$^2$ for men and $\geq$ 95 g/m$^2$ for women). A key functional alteration is an E/e' ratio at rest >9, e' septal velocity <9 cm/s, mitral E velocity <90 cm/s, pulmonary artery pressure at rest >35 mmHg, or tricuspid regurgitation >2.8 m/s (3). An elevated E/e' ratio represents an elevated left ventricular end diastolic pressure, which is a sign of diastolic dysfunction (2, 12). Diastolic dysfunction is not always evident at rest; therefore, a diastolic stress test with echocardiography can be performed in cases of uncertainty.

### *Heart Failure grading*

Grading systems are used to categorize the degree of symptoms and to monitor a patient's status over time. Currently, the most accepted system is the New York Heart Association functional classification (NYHA) (Table 2).

*Table 2. New York Heart Association functional classification based on severity of symptoms and physical activity (12).*

| NYHA class | Patient Symptoms |
|---|---|
| I | No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations. |
| II | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations. |
| III | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in undue breathlessness, fatigue, or palpitations. |
| IV | Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased. |

The NYHA classification is functioning as a framework for clinician communication and patient prognostication. It also functions as a tool for risk stratification, inclusion criteria for clinical trials and to determine eligibility for certain therapies such as cardiac resynchronization therapy (CRT) and left ventricular assist devices (2, 17). NYHA has a low reproducibility (56%) and validity (51%) when tested compared with treadmill performance (18). Also, NYHA classes II and III were shown to be poor discriminators of functional impairment in comparison to objective heart failure parameters and further to have wide variation as a predictor of adverse outcomes (17). Despite these shortcomings, it is a commonly used tool in clinical practice and heart failure research.

## The left ventricular function

### *Determinants of left ventricle function*

Cardiac output is the product of heart rate and stroke volume, where stroke volume is defined as the amount of blood ejected from the ventricle per heartbeat. Cardiac output is measured in litres per minute. The cardiac output is determined by five main factors – contractility, relaxation, preload (or Frank-Starling mechanism), afterload, and heart rate (19).

*Contractility and relaxation*

Contractility or the inotropic state of the heart is the capacity of contraction of the myocardium independently of the loading condition. An increased inotropic state is caused by enhanced myofilament $Ca^{2+}$ sensitivity or enhanced $Ca^{2+}$ transient. Increased contractility is associated with an enhanced rate of lusitropic effect or the rate of myocardial relaxation. The diastolic function is the totality of an active process of relaxation due to myofilament dissociation and calcium reuptake and a passive process related to the viscoelastic properties of the myocardium (20). Left ventricular dysfunction can either be caused by systolic dysfunction (impaired contraction) or diastolic dysfunction (impaired relaxation) (19).

*Preload and afterload*

Preload is the degree of myocardial distension before contraction has started and is represented by the left ventricular end diastolic volume. Afterload is the forces that are opposing the left ventricular ejection; it could be described as the aortic impedance or the ventricular wall stress during systole (2).

*Heart rate and force-frequency relationship*

The force of ventricular contraction is enhanced with increased heart rate. This is caused by changes in sodium and calcium in the myocyte. Increased calcium influx, rate of sarcoplasmic reticulum calcium uptake and amount of sarcoplasmic reticulum calcium released during each heartbeat amplify both inotropic and lusitropic effects. Normally, pacing rates up to 150-170 beats/min attenuate the force-frequency relationship, while higher rates result in decreased left ventricular function (2).

*The Frank-Starling mechanism*

The Frank-Starling mechanism explains how the heart responds and adapts to changes in preload and afterload to maintain adequate cardiac output. The Frank-Starling mechanism is the length-tension relationship of the cardiac muscle cells. Increased sarcomere length augments contraction by increased calcium sensitivity of the myofilaments (2). This explains why the force of contraction and thereby stroke volume increase to an elevated preload to a certain

maximum, where the contraction capacity of the heart reaches a plateau (21). However, in heart failure, stroke volume only increases slightly due to increased preload due to ventricular dysfunction. After a certain point, the heart muscle decompensates and further increased preload instead causes a decrease in stroke volume (19).

*Wall stress/Laplace's law*
According to Laplace's law, wall stress = pressure x radius/(2x wall thickness). This expression causes two main points: wall stress can increase either due to left ventricular size (radius) or intraventricular pressure. Increased wall stress causes increased consumption of oxygen. Laplace's law explains how a hypertrophic heart compensates for increased pressure by increased wall thickness. Further, in a dilated heart, increased radius causes increase wall stress (2).

## Aetiology

A wide range of cardiac conditions and systemic diseases can result in heart failure. Ischemic heart disease and hypertension are the predominant causes of heart failure in high-income countries (2, 22). Other causes are valve diseases, atrial or ventricular arrhythmias, and congenital heart diseases. Dilated cardiomyopathy is comprised of familiar cardiomyopathies, endocrine and metabolic causes (obesity, diabetes, thyroid disease), toxic cardiomyopathies (alcohol, drugs, cardiotoxicity related to cancer therapies) and cardiomyopathies due to inflammation (myocarditis, human immunodeficiency virus, chagas disease), non-infectious inflammation induced cardiomyopathies (rheumatological, connective tissue disorders, peripartum cardiomyopathy), stress-induced cardiomyopathy (Takotsubo cardiomyopathy) and cardiomyopathies caused by other systemic diseases such as hemochromatosis, amyloidosis and sarcoidosis (13).

### *Acute versus decompensated heart failure*

Patients can have an acute presentation of heart failure that requires hospitalization or urgent care. Most of these patients have a chronic heart failure that is progressively worsening. It has been suggested that these patients should be categorized as 'decompensated heart failure' rather than acute heart failure. However, a rapid onset or progressively escalating symptoms or signs of heart failure requires acute diagnosis and treatment. Further, some of the acute presentation of heart failure such as peripartum, myocarditis, cardiotoxicity cardiomyopathy, hypertensive emergency or acute myocardial infarction require specialized treatment targeting the underlying aetiology, (1). The focus of this thesis is on chronic HFrEF, and the diagnosis and treatment strategies for acute decompensated heart failure will not be discussed further.

## Pathophysiology of heart failure

### *Heart failure as a neuroendocrine syndrome*

Until William Harvey 1668 described the circulation, the heart was thought of as a source of heat (23). The understanding that the blood circulated and that the heart was the propelling power advanced the thinking of 19th century physiologists. For example, Lancisi recognized how valvular regurgitation causes ventricular dilation and that dilation seemed to weakens the heart. (24). For a long time, a dilated ventricular was considered the cause of heart failure until E.H. Starling in 1918 published "Law of the Heart" (25). Starling introduced the Frank-Starling curve, named after him and Otto Frank who had done measurements on how systolic pressure varied with diastolic volume in frog's heart. The Frank-Starling's law of the heart stated that increased end-diastolic volume enhances cardiac performance, but the law was met with a lot of scepticism as it contradicted the idea that ventricular dilation weakened the heart (23). It was not until 1955 when the description of "Families of Starling Curves" by S.J. Sarnoff was published that the idea of contractility was presented where presented. S.J. Sarnoff argued that the "contractile" state of the heart was the major regulator of cardiac performance and defined the slope of the Frank-Starling curve (26). This naturally led to clinical trials trying to develop better inotropic drugs for heart failure than the already existing digoxin, but they all had to be stopped prematurely because the drugs did more harm than good, appearing to first favour short-term hemodynamic benefits at the expense of acceleration of heart failure progression (27). Therefore, the treatment for heart failure remained mainly symptomatic.

Until the 1980s, the Starling's law of the heart and the neuroendocrine response in heart failure were considered compensatory mechanism. This consensus changed when studies demonstrated that the neuroendocrine response in heart failure was not a specific mechanism to counteract heart failure, it was a mechanism to maintain arterial pressure – the same mechanism that could be seen in exercise, vasodilation or severe bleeding (28). With the idea that a chronically active sympathetic system could have a negative effect on the heart in the long-term, along came the idea that the renin-angiotensin-aldosterone-system (RAAS) and the sympathetic nervous system (SNS) could damage the function and structure of the myocytes (29). This overactivation could be inhibited by ACEIs and BBs, which were successfully introduced in the late 1980s (30-37). The medical treatment was further improved ten years later by the discovery of the 'aldosterone escape', which could be treated by MRAs (38-40). Since then, until 2010s, ACEIs, BBs and MRAs have been the medical

cornerstones in the pharmacological treatment of heart failure (12). Heart failure was proven to be a neuroendocrine syndrome.

In summary, after an index event that produces a decline in the pumping capacity of the heart, a variety of compensatory mechanisms are activated that include the RAAS, SNS and the cytokine systems. These systems are initially able to compensate for the decrease in cardiac output and preserve homeostasis. However, sustained activation of these neuroendocrine systems in chronic heart failure causes secondary end-organ damage with worsening left ventricular remodelling, cardiac decompensation, and heart failure progression (2, 41).

### *Sympathetic nervous system activation and parasympathetic nervous system withdrawal*

Activation of the SNS is an adaption to reduced cardiac output. An inadequate cardiac output is sensed by baroreceptors in the left ventricle, aortic arch, carotid sinus, and renal afferent arterioles. Loss of inhibitory impulses from the baroreceptors causes a sustained activation of the SNS and RAAS. As the SNS is activated, the parasympathetic tone is withdrawn. Activation of the SNS causes increased activity of the $Beta_1$-adrenergic receptors, causing a positive inotropic effect combined with peripheral arterial vasoconstriction. However, long-term activation of the SNS may trigger ventricular tachycardia or sudden death. Consequently, short-term activation of the SNS is beneficial, but it becomes maladaptive when activated over long-term. Decreased parasympathetic activity is associated with increased inflammation, decreased nitric oxide levels, increased SNS activity and worsening left ventricular remodelling (2).

### *Renin-angiotensin-aldosterone system*

The RAAS is responsible for maintaining cardiac output through several mechanisms – retention of sodium and water, peripheral arterial vasoconstriction, and increased cardiac contractility. Heart failure leads to a decreased cardiac output, which causes renal hypoperfusion. Renal hypoperfusion combined with increased sympathetic stimulation causes renin release from the kidney. Renin is an enzyme that splits angiotensinogen into angiotensin I. Angiotensin I is converted to Angiotensin II by the angiotensin-converting enzyme (ACE). Angiotensin II binds to Angiotensin type 1 and Angiotensin type 2 receptors, which both are present in the myocardium. Activation of angiotensin type 1 receptors causes vasoconstriction, cell growth, catecholamine release and aldosterone secretion. Angiotensin type 2 receptors cause vasodilation, inhibition of cell growth, natriuresis and bradykinin release. In heart failure, there is a sustained activation of the RAAS, which leads to an excessive production of aldosterone and Angiotensin II (2). On short-term, activation of the RAAS is important to maintain circulatory homeostasis.

Nonetheless, sustained activation of Angiotensin II is maladaptive and causes fibrosis of the heart and kidney, which worsens activation of the SNS and overproduction of aldosterone. When aldosterone binds to the mineralocorticoid receptor (MR), it supports the maintenance of the circulatory haemostasis in the short-term by increased sodium retention and potassium loss in the nephron. However, sustained activation causes reduced myocardial perfusion, myocardial interstitial fibrosis, increased peripheral vascular resistance and baroreceptor dysfunction and thereby worsening heart failure (42-46).

### *Left ventricular remodelling*

The neurohormonal concept does not completely explain the progress of heart failure. Ventricular remodelling is a central part in the pathophysiology in progressive heart failure. This includes pathologic myocyte hypertrophy, myocyte apoptosis, myofibroblast proliferation and interstitial fibrosis that are associated to increased volume and altered chamber configuration of the ventricles. The ventricular modelling develops after all forms of myocardial injury and increased wall stress. Activation of the RAAS and SNS, proinflammatory cytokines, endothelin and increased oxidative stress are contributing factors. These systems are upregulated due to increased left ventricular wall stress, haemodynamic derangement, or after a myocardial injury. Inhibition of the RAAS and beta-adrenergic blockade have been shown to attenuate or reverse left ventricular remodelling (2, 47).

## Comorbidities in Heart Failure and Charlson comorbidity index

Multiple concomitant diseases are common in heart failure, which complicates management and contribute to increased morbidity, mortality, and an impairment of quality of life. Data from a European cohort of outpatients with chronic heart failure showed that 74% of all patients had at least one comorbidity. Chronic kidney disease (CKD) (41%), anaemia (29%) and diabetes (29%) were the most common comorbidities (48). A large observational study from England showed a mean number of comorbidities of 5.4 per patient with over 79% of all patients experience three or more comorbidities. In this study, the most common cardiovascular comorbidities were hypertension, ischaemic heart disease and atrial fibrillation (Figure 3) (7).

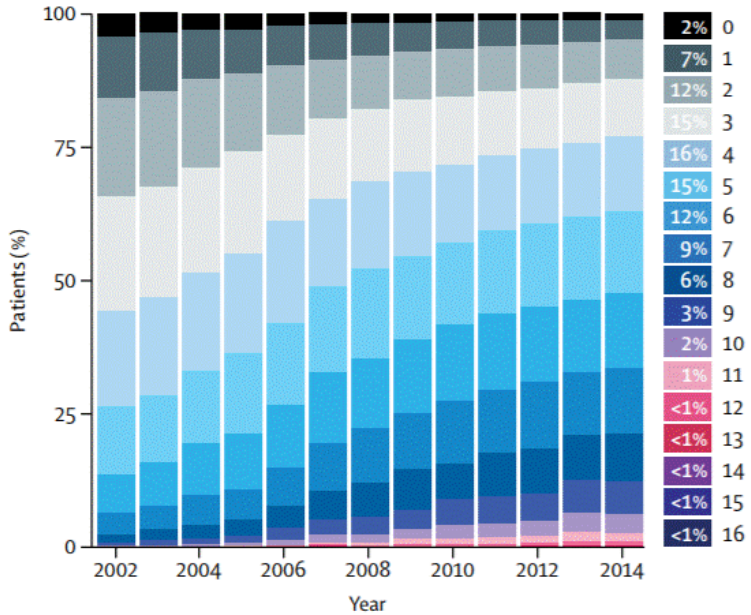


*Figure 3. Number of comorbidities, out of 17 major conditions, affecting patients with incident heart failure over time. Copyright © 2018 Nathalie Conrad et al. Published by Elsevier Ltd. Reproduced from (7), licensed under CC-BY 4.0, https://creativecommons.org/licenses/by/4.0/.*

The Charlson comorbidity index (CCI) is a tool to measure comorbid disease status in health care databases. It was developed by Charlson et al. by assessing numerous clinical conditions through reviewing hospital charts and assessing their relevance in prediction of 1-year mortality (49). A weighted score for 17 comorbidities was created based on their risk of 1-year mortality. The sum of the score quantifies the disease burden and is an estimator of mortality. Few studies have evaluated CCI in heart failure. Studies on the prognostic impact on CCI on the elderly's first acute heart failure hospitalization and newly diagnosed heart failure identified CCI as an independent risk factor for 1-year and 3-years mortality (50, 51).

## Cardiorenal syndrome

Renal dysfunction is one of the most common comorbidities in heart failure. The prevalence of moderate impaired renal function in HFrEF, defined as eGFR below 60 ml/min/1.73 $m^2$, is over 50% (52, 53). Heart failure and CKD share many risk factors and aetiologies. In addition, the failing heart and kidney can worsen each other's prognosis. The interaction and mechanisms in how the heart and kidney affect each other is complex and includes several mechanisms.

A definition of cardio-renal syndrome (CRS) was proposed by the Consensus conference on Acute Dialysis Quality Initiative Group (54). In this classification, CRS can be divided into two groups – cardio-renal and reno-cardial CRS. From this, the cardiorenal syndromes were categorized into five types based on the organ presumed to be the primary precipitant at the time of progression (Table 3).

*Table 3. Classification of cardio-renal syndrome (54).*

| Type | Deno-mination | Description | Example |
|---|---|---|---|
| 1 | Acute cardiorenal CRS | Heart failure leading to acute kidney injury | Acute coronary syndrome resulting in cardiogenic shock and to acute heart and kidney failure |
| 2 | Chronic cardiorenal CRS | Chronic heart failure leading to CKD | Chronic heart failure |
| 3 | Acute renocardiac syndrome | Acute kidney injury leading to acute heart failure | Heart failure in the setting of acute kidney injury from volume overload, inflammatory surge, and metabolic disturbances in uremia |
| 4 | Chronic renocardiac syndrome | CKD leading to chronic heart failure | Left ventricular hypertrophy and heart failure from CKD-associated cardiomyopathy |
| 5 | Secondary CRS | Systemic process leading to heart and renal failure | Sepsis, cirrhosis, diabetes mellitus, amyloidosis |

*CKD = chronic kidney disease, CRS= Cardiorenal syndrome. Copyright © 2017 Cardiological Society of India. Published by Elsevier B.V. Reproduced from (9) licensed under CC BY-NC-ND 4.0, http://creativecommons.org/licenses/by-nc-nd/4.0/.*

In clinical practice, these five types of CRS have been difficult to define since starting from clinical description limits the ability to distinguish the individual patient's predominant pathophysiology. A clinical challenge is to distinguish if volume overload results from worsening heart failure or decreased glomerular filtration, or how to evaluate increase serum-creatinine (S-creatinine) in patients with CRS. In a decompensated patient, increased venous pressure caused by congestion decreases glomerular filtration and increased S-creatinine. Increased S-creatinine could as well be due to up titration of the RAAS-inhibitors (RAAS-I), BBs or loop diuretics, which rather reflect changes in hemodynamic than intrinsic kidney function. A previous study showed that if RAAS-I are withheld for 48 h, S-creatinine decreases but instead NT-proBNP and cardiac volumes increases, which in time could increase S-creatinine (55). Simultaneously, adhering to the RAAS-I over time decrease S-creatinine as the cardiac output improves and development of renal and cardiac fibrosis is reduced. In addition, loop-diuretics could either increase eGFR by activating the RAAS or decrease eGFR by reducing venous hypertension. In summary, differentiating between

true and pseudo worsening renal function in heart failure is difficult, and requires judgement of the clinical context.

Due to this clinical difference in using previously defined subtypes of CRS, suggestions have been made to rather focus on the common pathophysiological pathways across the various subtypes. Cardiovascular and renal disorders could be viewed as results from systemic diseases reflecting their shared risk factors (dyslipidaemia, atherosclerosis, hypertension, tobacco use, diabetes mellitus, obesity, amyloidosis) and the related neurohormonal, inflammatory, immunologic, and fibrotic response, which have varying expressions in the heart and kidneys (56).

### *Glomerular filtration rate and creatinine*

Glomerular filtration rate (GFR) is measured as the clearance of an exogenous filtration marker. The 'gold standard' for measured GFR (mGFR) is the urinary clearance of inulin during a continuous intravenous infusion (57). This method is expensive and difficult to perform in a daily clinical basis. Consequently, alternative filtrations markers and clearance methods have been developed such as urinary iothalamate clearance, plasma clearance of iohexol or plasma clearance of $^{51}$Chromium-51-ethylenediaminetetraacetic acid ($^{51}$Cr-EDTA). $^{51}$Cr-EDTA is a radioisotope whose clearance was shown to correspond well with inulin clearance, which is why this method is commonly used in clinical practice for mGFR (58).

However, all clearance methods for mGFR are complex, time-consuming, and expensive to conduct on a routine basis in a large number of patients, which is why eGFR should be used for initial assessment (59). Creatinine-based eGFR is still the most widely used endogenous filtration marker, although Cystatin C is an alternative marker. Measurement of S-creatinine should be used by a specific assay with calibration traceable to the international standard reference materials and be minimal biased compared to isotope-dilution mass spectrometry (IDMS) reference methodology, in order to maintain international standardisation (60).

Creatinine is a breakdown product of the muscle metabolism. The concentration of S-creatinine is not only affected by GFR, but other physiological processes also including creatinine generation by dietary intake, muscle mass, tubular creatinine secretion and extrarenal creatinine elimination by the gastrointestinal tract influence S-creatinine levels. Demographic data such as sex, ethnicity and age also affect S-creatinine concentrations. Further, GFR must be matched to kidney size, which in turn is related to Body Surface Area (BSA). The value of 1.73m$^2$ reflects the average body surface area of a study population from 1927 in

the USA and is kept due to normalization purposes. Interpretation of mGFR and eGFR is therefore based on adjustment to the body surface area of 1.73m$^2$ (57).

To adjust for factors affecting S-creatinine concentrations, numerous equations have been developed in order to estimate GFR from S-creatinine. These equations include age, sex, ethnicity, body size and sometimes weight. Further, it is preferable if the equations have been developed using traceable reference methods compared to IDMS reference methodology (59).

eGFR is one of the most essential measurements to assess renal function. Renal dysfunction is common in heart failure and eGFR is considered before initiating, dose adjusting and discontinuing RAAS-Is (3). Further, lower eGFR is associated with higher morbidity and mortality in heart failure (61).

### *Creatinine in patients with heart failure*

Several creatinine-based equations have been developed for estimating glomerular filtration rate (eGFR) in patients with CKD and/or for the general population, but a majority of these equations have not been validated for patients with heart failure. In heart failure, several factors influence the precision and accuracy of creatinine-based eGFR equations. Muscle mass is the most important determinant of creatinine generation, and previous studies have showed that muscle wasting (sarcopenia) had a prevalence of 20% in patients with chronic heart failure and was more common with lower LVEF (62). Therefore, patients with heart failure may have low creatinine levels despite low GFR which might cause an overestimation of creatinine-based eGFR. Further, in patient with decompensated heart failure, fluid retention causes weight gain without an increase in lean body mass which might affect weight-dependent eGFR equations (63).

## Prevention of disease progression in chronic HFrEF

The foundation of the preventive pharmacological treatment in HFrEF is to interfere with the exaggerated activation of the RAAS and SNS. By targeting these systems, ACEIs/ARBs, BBs and MRAs stabilize left ventricular remodelling, improves symptoms, and prolong survival in patients with HFrEF(3).

### *Angiotensin-Converting Enzyme inhibitors and Angiotensin II Receptor Blockers*

ACEIs reduces mortality and morbidity in symptomatic patients with HFrEF. In 1987, the Cooperative North Scandinavian Enalapril Survival Study (CONCENCUS) was the first study that showed decreased mortality in HFrEF by an ACEI. It included patients in NYHA IV and the enalapril group had a 40%

reduction in mortality (p=0.002) and an improvement in NYHA classification (p=0.001) compared to the placebo group (30). In the following Studies of Left Ventricular Dysfunction (SOLVD), patients with LVEF ≤35%, congestive heart failure and NYHA I-III were included. In the enalapril group the risk reduction in mortality was 16% (95% CI; 5-26%; p=0.0036) and the risk reduction in hospitalization due to worsening heart failure was 26% (95% CI; 18-34%; p<0.001) compared to placebo (31). Evidence also supports ACEI use in asymptomatic patients with left ventricular dysfunction, with fewer hospitalizations and decreased development of symptomatic heart failure (64-66). ACEIs inhibit the enzyme conversing angiotensin I to angiotensin II. They also inhibit kininase II, causing upregulation of bradykinin, which further enhances the angiotensin suppression. Side effects includes hypotension, renal dysfunction, hyperkalemia and angioedema. Another common side effect is non-productive cough (10-15% of patients), which may be caused by elevated levels of bradykinin and substance P that otherwise would have been degraded by endogenous angiotensin-converting enzymes (2, 67).

ARBs are indicated in patients who are intolerant to ACEIs. ARBs block the effect of angiotensin II on the angiotensin type 1 receptor, which is the subtype responsible for the adverse biologic effects of angiotensin II on cardiac remodelling. Side effects are similar to ACEIs and includes hypotension, renal dysfunction and hyperkalemia. Three ARBs – candesartan, losartan, and valsartan, have been excessively evaluated in clinical trials. In the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM-Alternative) trial, symptomatic patients with LVEF ≤40% and NYHA II-IV who could not tolerate ACEIs were included. Candesartan was compared to placebo and showed a combined cardiovascular mortality or heart failure hospitalization rate reduced by 23% (unadjusted HR 0.77 (95% CI; 0.67–0.89, p<0.001)) (68). In the Valsartan heart Failure Trial (VAL-HeFT), patients with LVEF ≤40% and NYHA II-IV with ACEIs and/or BBs were included. Valsartan was compared to placebo in a double-blind, parallel-group trial. Overall mortality was similar in both groups, but incidence of the composite end point on mortality and morbidity was 13.2% (95% CI; 0.77-0.97, p=0.009) lower in the valsartan group compared to the placebo group. In the subgroup analysis, mortality was reduced in patients not receiving ACEIs or BBs. Among patients who received both ACEIs and BBs, valsartan increased mortality and morbidity compared to placebo (69). The combined results from the VAL-HeFT trial and the CHARM-Added trial, which showed increased risk of adverse side effects when adding ARBs to ACEIs, have resulted in that the combination of ACEIs and ARBs should be restricted to selected group of HFrEF receiving a beta blocker who are unable to tolerate an MRA and must be used under strict supervision (12).

***Beta blockers***

BBs reduced mortality and morbidity in patients with HFrEF. BBs and ACEIs are complementary and can be started simultaneously. The mechanism of the beneficial effects of BBs use in HFrEF are due to the interferences of the harmful effects of sustained activation of the SNS. Decreased activation of the SNS counteracts cardiac remodelling from myocyte hypertrophy, interstitial fibrosis and apoptosis, lowers heart rate, decreases myocardial oxygen consumption and reduces atrial and ventricular arrhythmogenesis, in particular by competitively antagonizing the $Beta_1$- adrenergic receptor (70)

The up titration of BBs should be slower than ACEIs/ARBs since initiation and increased dose can cause worsening fluid retention due to the withdrawal of adrenergic support. BBs can have a negative inotropic effect, which increases the risk of heart failure decompensation in the short-term. The first survival benefit was shown in 1979, but it was not until 1993 that the first placebo-controlled multicentre trial was conducted. The slow induction was due to the negative inotropic effect. The first clinical trial, Metoprolol in Dilated Cardiomyopathy, used short-acting metoprolol versus placebo and showed a reduction of 34% of in death or need for cardiac transplantation but failed to reach significance. In 1995, Hall et al. showed that after a first month of initial mild reduction in function, long-term therapy with metoprolol resulted in reverse remodelling of the left ventricle and subsequent improved LVEF over time (71). In 1999, the Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF) trial and the Cardiac Insufficiency Bisoprolol Study II (CIBIS II) were published. The MERIT-HF used metoprolol (succinate) CR/XL (controlled released) with longer half-life versus placebo and showed a significant relative risk reduction of 34% (95% CI; 0.53-0.81; $p<0.001$) in mortality in patients with NYHA II-IV and LVEF $\leq$40%. The CIBIS II trial used bisoprolol versus placebo in patients with NYHA III-IV and LVEF $\leq$35% and showed reduced all-cause mortality of 34% (95% CI; 0.54-0.81, $p<0.001$). In 2001, the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial was published. It studied carvedilol versus placebo in patients with NYHA IV and LVEF <25% and showed a reduced combined risk of death or hospitalization for heart failure by 31% (95% CI; 19% to 41%, $p<0.001$) (72).

Not all studies with BBs have been successful, which suggests that the effects of BBs should not be viewed as class effect. The adverse effects of BBs, besides an increased risk of initial fluid retention, are feelings of general fatigue or weakness. Moreover, it can cause bradycardia and exacerbate heart block (2).

## Mineralocorticoid receptor antagonists

### *Aldosterone and the mineralocorticoid receptor*

The two adrenal glands lie superior to the two kidneys. The adrenal glands are composed of the adrenal cortex and the adrenal medulla. The adrenal medulla secretes hormones related to the SNS, and catecholamines (epinephrine and norepinephrine), and the adrenal cortex secretes another group of hormones, the corticosteroids. Corticosteroids are synthesised from the steroid cholesterol, and are further divided into three groups – mineralocorticoids, glucocorticoids, and androgens.

The primary and most important mineralocorticoid, considering the importance of normal endocrine function of the body, is aldosterone. Aldosterone is produced in the Zona Glomerulosa (73). The Zona Glomerulosa contains the enzyme aldosterone synthase, which is necessary for the synthesis of aldosterone. The major regulators of aldosterone secretion are angiotensin II and potassium and sodium ion concentration in the extracellular fluid. Adrenocorticotropic hormone from the anterior pituitary gland is necessary for aldosterone secretion but has less effect in controlling the rate of secretion. Aldosterone binds to the MR, which is a ligand-dependent transcription factor that is part of the nuclear receptor family (74). The MR is expressed in epithelial cells of the renal nephron and in the distal colon, salivary and sweat glands where it regulates the fluid balance. However, MR is also expressed in non-epithelial cells in the heart, the kidney, coronary and vascular smooth muscle cells, fibroblasts, and inflammatory cells (75). Cortisol, the primary glucocorticoid, can also bind to MR with a high affinity. The plasma concentration of cortisol is about 2000 times that of aldosterone. Overstimulation of MR is prevented by the enzyme 11β-hydroxysteroid dehydrogenase type 2 which converts cortisol to cortisone (75, 76). Cortisone has a lower affinity to MR, which explains why cortisol in the end does not exert significant mineralocorticoid activity.

Aldosterone executes its major physiological function of maintaining sodium and potassium balance and blood pressure control by binding to the MR in the connecting tubule and cortical collecting duct in the kidney. Activation of the MR in the kidneys causes sodium reabsorption and potassium secretion. In the principal cells of the renal collecting duct, aldosterone diffuses into the cell because of its lipid solubility. In the cytoplasm, aldosterone binds to MR, the receptor complex dimerizes and migrates to the nucleus where it binds to a specific portion of the DNA sequence to form mRNA. The mRNA diffuses back to the cytoplasm where it causes protein formation in conjunction with the ribosomes. In the renal collecting duct principal cell, the sodium ions enter the cell through the amiloride-sensitive apical sodium channels and are extruded into

the peritubular space by the sodium pump ($Na^+$-$K^+$-ATPase) in the basolateral membrane, in exchange for potassium. The apical sodium channels and the basolateral $Na^+$ pumps are regulated by the proteins activated by activation of MR. In short, aldosterone does not have an immediate effect on sodium transport; rather, the effect is performed after the sequence of events that leads to the formation of the proteins that are required for the sodium transport. About 75 minutes after aldosterone enters the cell, the sodium transport begins to increase and reaches its maximum effect after several hours (76, 77).

Two pathway of MR activation has been described. The genomic pathway in which aldosterone bind to the MR, the hormone-receptor complex dimerizes, migrates to the nucleus, and binds to specific DNA sequency which trigger transcription of target genes. The other pathway of aldosterone is the rapid non-genomic pathway. Receptors in the cytoplasm and cellular membrane mediate the effect, where the action of aldosterone is exhausted within 10 minutes. By this pathway, aldosterone is thought to have a rapid, positive inotropic action of the myocardium and increases the systemic vascular resistance (78, 79). However, the precise structure of receptors responsible for the rapid effect of aldosterone has not been determined, nor physiological significance or the clinical relevance.

Besides the function of regulate fluid balance in order to control blood pressure homeostasis, MR has been shown to execute structural and functional changes in the heart, kidney, and blood vessels. In the vascular system, MR is located in the endothelial and vascular smooth muscle cells. In the heart, MR is found in cardiomyocytes, endothelial cells, fibroblasts and macrophages (80). The function of MR in a healthy heart may include regulation of cardiomyocyte growth and cardiac electrophysiology but is not yet fully understood. However, in patients with heart failure, the myocardial expression of MR is increased. Chronic activation of MR in the heart is associated with fibrosis, inflammation, and oxidative stress (77, 81). Harmful effects of aldosterone in the heart includes ventricular remodelling, proarrhythmogenic effects, myocardial hypertrophy, ventricular remodelling, reduced coronary blood flow and myocardial injury. In patients with renal failure where MR expression also is increased, the deleterious effect of aldosterone includes glomerular hypertrophy, glomerulosclerosis, proteinuria, reduced renal blood flow and renal injury (Figure 4) (75).

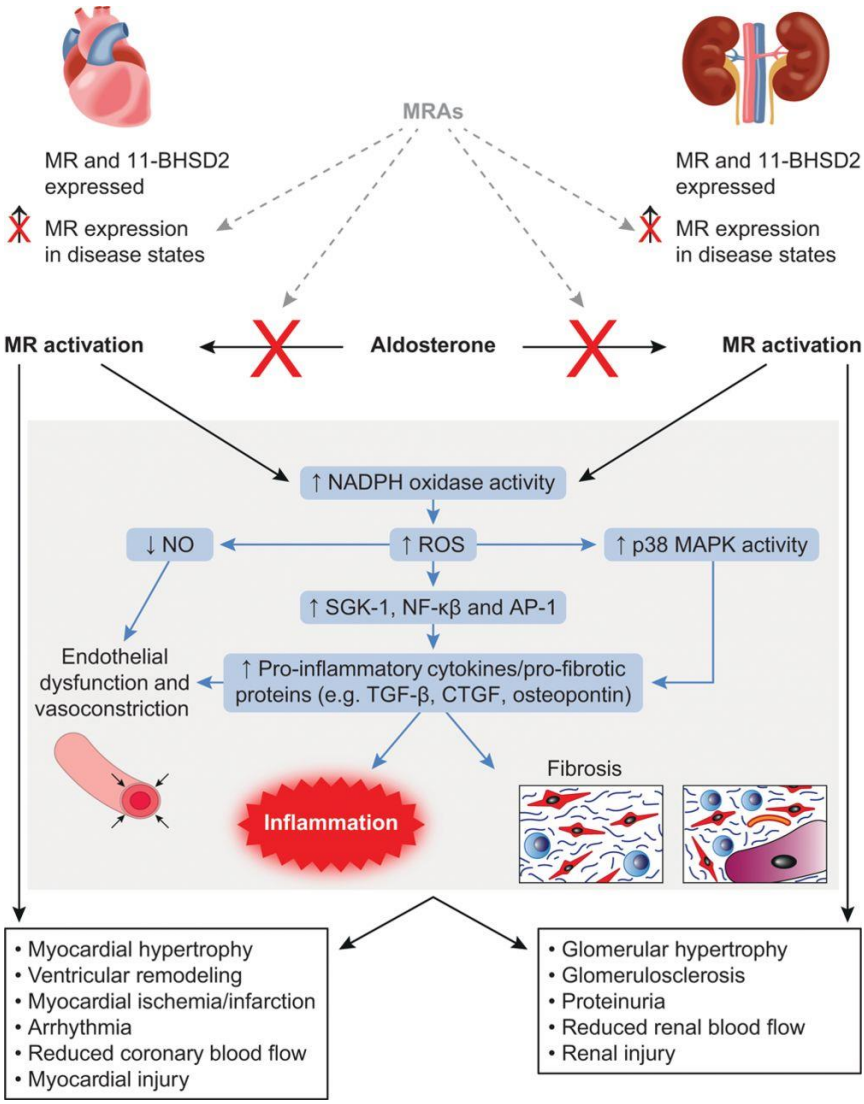


*Figure 4. The direct deleterious effects of aldosterone/MR activation in the heart and kidneys and the common pathophysiological mechanisms involved. The benefits of MRAs in interrupting these pathways are also illustrated. Copyright © 2014 American Heart Association, Inc. Reproduced from (75) with permission from Wolters Kluwer Health, Inc, https://doi.org/10.1161/HYPERTENSIONAHA.114.04488. 11-BHSD2 = 11β-hydroxysteroid dehydrogenase type 2, AP-1 = activator protein-1, CTGF = connective tissue growth factor, NADPH oxidase = nicotinamide adenine dinucleotide phosphate-oxidase, MAPK = mitogen-activated protein kinase, MR = mineralocorticoid receptor, MRA = mineralocorticoid receptor antagonist, NF-κB = nuclear factor-κB, NO = nitric oxide, ROS = reactive oxygen species, SGK-1 = serum- and glucocorticoid-induced protein kinase-1, and TGF-β = transforming growth factor-β.*

### *Development of MRAs*

Spironolactone was developed in 1959, 30 years before the mineralocorticoid receptor had been molecular characterized (82). In 1960s, Spironolactone was approved as a diuretic drug with indications for hypertension, oedematous conditions and primary aldosteronism (74). Adverse effects including gynecomastia, impotence and menstrual disturbances in pre-menstrual women were reported early. The most likely explanation for these side effects is the unspecific selectivity of spironolactone for MRAs since it also inhibits androgen and progesterone receptors (83). At high concentrations, it can also interfere with the glucocorticoid receptor. Uncertainties about optimal dose and unacceptable side effects explained why spironolactone was not a candidate for large scale RCTs between 1970 and 1990. Eplerenone, which is an anti-aldosterone with more selectivity than spironolactone, was discovered in the early 1980s with the synthesis of several 9-11alfa-epoxyderivates of spironolactone (Figure 5). Eplerenone was shown to be an effective anti-mineralocorticoid drug in comparison with spironolactone (84). Eplerenone is less potent (40x less) than spironolactone but is more selective to MR (77). However, it was not until understanding of the mineralocorticoid receptor's role in cardiac fibrosis, that both spironolactone and eplerenone in the late 1990s became subjects for further research interest (85).

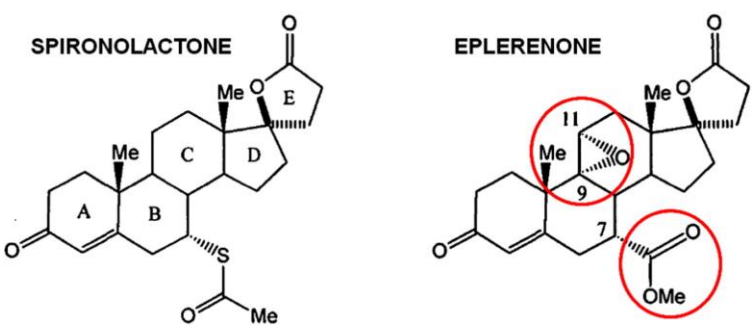


*Figure 5. Chemical structure of spironolactone and eplerenone. Reprinted with permission from (86), copyright © 2015, with permission from Elsevier.*

### *Pharmacokinetic*

One of the most striking differences between spironolactone and eplerenone is their differences in half-life. Spironolactone is rapidly metabolized into its two active compound – 7alfa-thiomethylspironolactone and canrenone that have half-lives in healthy individuals of 13.8 and 16.5 h, respectively. Eplerenone has no active metabolites and a half-life of 4 h in steady states; however, it has been shown to have increased $Na^+/K^+$ ratio in over 12 h. A possible explanation is that

the natriuresis of eplerenone is maximum plasma concentration ($C_{max}$) driven, in contrast to area-under-the-curve (AUC)-driven (87).

When a MRA is bound to MR, the MR is destabilized, followed by ubiquitination and degradation. It is speculated that it is the half-life of MR itself rather than the half-life of MRAs that determines the period of natriuresis. The blood pressure lowering effect of eplerenone is improved when given twice daily in comparison to once daily, which is why it is concluded that the natriuresis may be driven by $C_{max}$ while blood pressure control involves an AUC-driven mechanism (Table 4) (87).

*Table 4. Differences in pharmacodynamic and pharmacokinetic properties of Spironolactone and Eplerenone.*

| | **Spironolactone** | **Eplerenone** |
|---|---|---|
| Structural features | Based on progesterone, γ-lactone ring as substituent at C-17 | 17α-Thoacetyl group of spironolactone replaced with carbomethoxy group; 9,11-epoxide added to lactone ring |
| Bioavailability | 80-90% | 69% |
| Plasma protein binding | 88% (bound to albumin) | 49% (bound to α1-acid glycoprotein) |
| $T_{1/2}$ | 1.4*, 16.5*, 13.8*, 15 h* | 3-4 h |
| Distribution | 90% bound to plasma proteins | 50% bound to plasma proteins |
| Metabolic pathway | Hepatic | Hepatic |
| Active metabolites | Yes | None |
| Tissue distribution | Renal concentration 6x higher than cardiac concentration | Renal concentration 3x higher than cardiac concentration |
| Elimination | Primary urine, secondary by biliary faeces excretion | CYP3A4 |

** Spironolactone, canrenone, 7alfa-TMS and 6betahydroxy-7alfa-TMS, respectively. $T_{1/2}$ = Half-life.*

### *Pharmacodynamics*

ACEIs have been shown to suppress the production of aldosterone only temporarily, a phenomenon called 'aldosterone escape' (88, 89). As mentioned, an overactivation of the MR leads to increased sodium retention and potassium loss. However, it also causes reduced myocardial perfusion, myocardial interstitial fibrosis, increased peripheral vascular resistance, baroreceptor dysfunction and causes electrical remodelling that increases the risk of ventricular arrhythmias in patients with chronic heart failure (43-45, 77). This explains why MRAs do not only lower the risk of further hypervolemia and hypertension but are also cardio protective (42, 90).

### *MRAs in clinical trials*

In three landmark RCTs, MRA treatment was shown to produce major clinical benefits in patients with HFrEF (Table 5).

*Table 5. Study design and outcomes of landmark MRA trials.*

| | **RALES** | **EPHESUS** | **EMPHASIS-HF** |
|---|---|---|---|
| Year | 1999 | 2003 | 2011 |
| No. Of participants | 1663 | 6642 | 2737 |
| Inclusion criteria | Heart failure, 6 weeks before enrolment | 3-14 days post-MI, LVEF ≤40%, symptoms of heart failure or diabetes | Heart failure, age ≥ 55 years |
| NYHA | III-IV | I-IV | II |
| LVEF (%) | ≤35, 6 months before enrolment | ≤40 | ≤30 or ≤35 if a QRS duration of >130 msec |
| Major exclusion criteria | S-creatinine >220 μM, S-K >5.0 | S-creatinine >220 μM, S-K >5.0 | eGFR <30 mL/min/173m², S-K >5.0, NYHA III or IV |
| Mean age (years ± SD) | 65 ± 12 | 64 ± 12 | 69 ± 8 |
| eGFR equation | Not used | Cockcroft-Gault | MDRD-6 |
| Other medical therapy | ACEIs, loop diuretics, digitalis | ACEIs/ARBs, BBs | ACEIs/ARBs, BBs |
| MRA | spironolactone | eplerenone | eplerenone |
| Dose (mg/day) | 25-50 | 25-50 | 25-50 |
| Mean daily dose (mg) | 26 | 43 | 39 |
| Mean follow-up | 24 months | 16 months | 21 months |
| Primary end point | Death from any cause | Death from any cause and time to death from cardiovascular causes or hospitalization for cardiovascular event | A composite of death from cardiovascular causes or a first hospitalization for heart failure |
| **Outcomes, unadjusted** | | | |
| All-cause mortality | RR 0.70 (95% CI 0.60-0.82) | RR 0.85 (95% CI 0.75-0.96) | HR 0.78 (95% CI 0.64-0.95) |
| Cardiovascular mortality | RR 0.69 (95% CI 0.58-0.82) | RR 0.83 (95% CI 0.72-0.94) | HR 0.76 (95% CI 0.62-0.96) |
| Hospitalization for HF | RR 0.65 (95% CI 0.54-0.88) | RR 0.85 (95% CI 0.74-0.99) | HR 0.61 (95% CI 0.50–0.75) |

*RALES = Randomized Aldactone Evaluation Study (38), EPHESUS = Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (40), EMPHASIS-HF = The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (39), MI = Myocardial infarction, NYHA = New York Heart Association function class, LVEF = Left ventricular ejection fraction, eGFR = estimated glomerular filtration rate, S-K = serum-potassium, MDRD-6 = 6-variable Modification of Diet in Renal Disease study equation, ACEI = Angiotensin-converting enzyme-inhibitor, ARB = Angiotensin II receptor blocker, BB = beta blocker, MRA = mineralocorticoid receptor antagonist, SD = Standard deviation, RR = Relative risk, HF = Heart failure, HR = Hazard ratio, CI = Confidence interval.*

In the Randomized Aldactone Evaluation Study (RALES) (1999), patients with LVEF ≤35% and NYHA IV were included. Spironolactone reduced the relative risk of all-cause mortality by 30% (p<0.001) (Figure 6). Further, 41% in the spironolactone group versus 33% in the placebo group showed improvement in NYHA-class (p<0.001). The reduced mortality rate was mainly attributed to lower risk of death from progressive heart failure and of sudden death from cardiac causes. In terms of safety, serious hyperkalemia (Serum-potassium (S-potassium) ≥6.0 mmol/L) was uncommon, occurring in 10 patients (1%) in the placebo group and in 14 patients (2%) in the spironolactone group (p=0.42). Median creatinine concentration increased significantly in the spironolactone group by 4-9 µmol/L. (38).

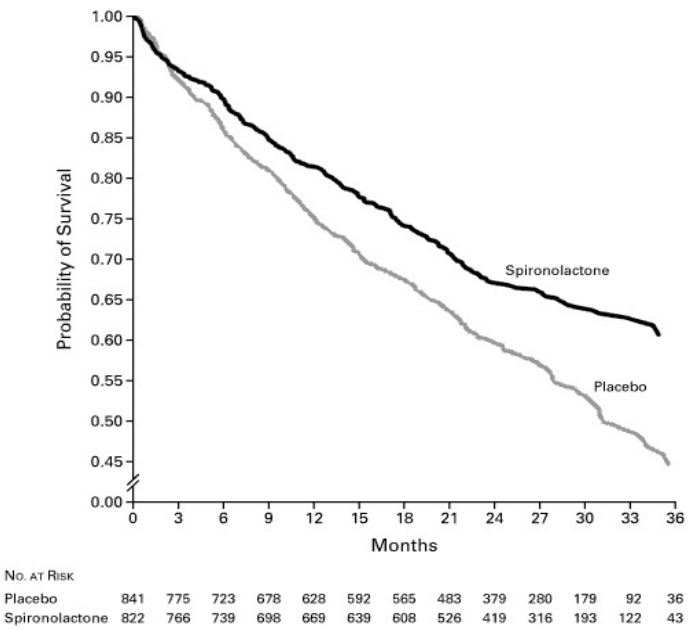


*Figure 6. Kaplan–Meier Analysis of the Probability of Survival among Patients in the Placebo Group and Patients in the Spironolactone Group. Reproduced with permission from (38), Copyright © Massachusetts Medical Society.*

In the Eplerenone Post-Myocardial Heart Failure Efficacy and Survival Study (EPHESUS) (2003), patients with LVEF ≤40% after an acute myocardial infarction were included. Most patients had treatment with ACEIs or ARBs, BBs, and diuretics. Eplerenone reduced the relative risk of all-cause mortality by 15% (Figure 7). Serious hyperkalemia (S-potassium ≥6.0 mmol/L) was seen more commonly in the eplerenone group compared to the placebo group (5.5% vs 3.9% p=0.002). S-creatinine concentration increased by 1.8 µmol/L in the placebo group and 5.3 µmol/L in the eplerenone group (p<0.001). (40).

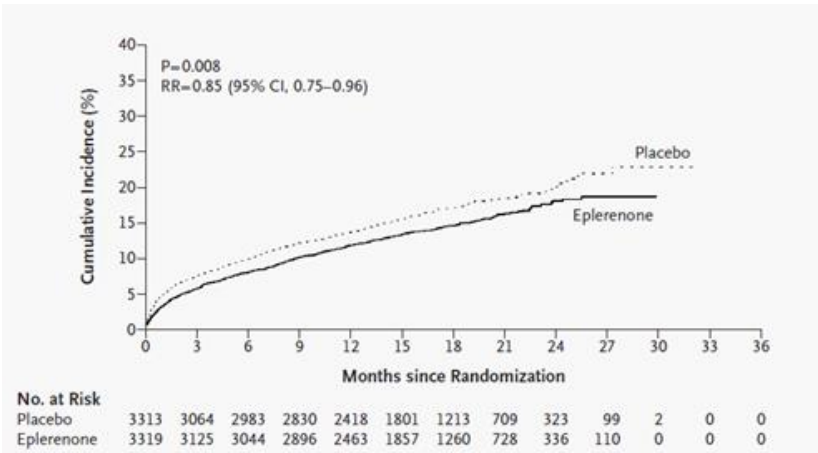


*Figure 7. Kaplan–Meier Estimates of the Rate of Death from Any Cause. Reproduced with permission from (40), Copyright © Massachusetts Medical Society.*

In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) (2011), patients with LVEF ≤30% (or ≤35% if QRS width >130 ms) and NYHA II were included. Most patients were treated with ACEIs or ARBs and BBs. The study demonstrated an adjusted risk reduction in all-cause mortality of 24% (Figure 8). In terms of safety, mean changes in serum creatinine levels form baseline were 8.0 ± 32.7 µmol per litre in the eplerenone group and 3.5 ± 35.4 µmol per litre in the placebo group. A S-potassium >6.0 mmol/L was reported in 2.5% of the patients in the eplerenone group and 1.9% in the placebo group (p=0.29) (39).

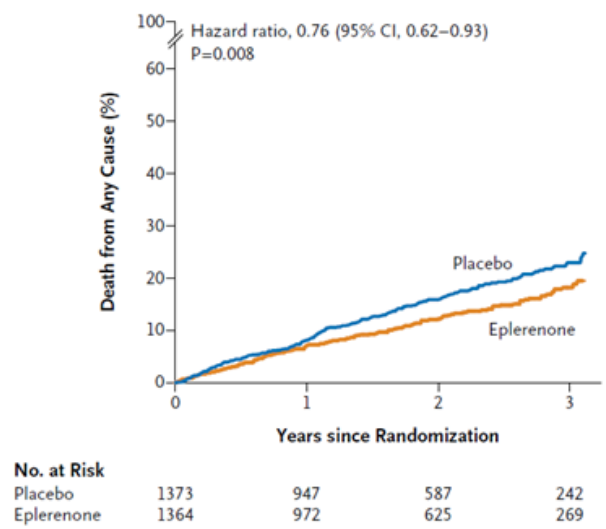


*Figure 8. Cumulative Kaplan–Meier Estimates of Rates of death from any cause. Reproduced with permission from (39), Copyright © Massachusetts Medical Society.*

### *Implementation in clinical practice*

MRAs are potentially indicated in all patients with persisting symptoms (NYHA class II-IV) and LVEF ≤35% despite treatment with ACEIs or ARBs and BBs. Further, MRAs are recommended to patients with LVEF ≤40% post-MI who developed symptoms of heart failure or have a history of diabetes mellitus. To date, eplerenone and spironolactone are used interchangeably due to limited data of studies comparing these MRAs in patients with heart failure.

All three RCTs evaluating MRAs in HFrEF excluded patients with S-creatinine >220 μM or eGFR <30 ml/min/1.73 $m^2$ and S-potassium >5.0 mmol/L. These exclusion criteria now serve as guidelines for when MRAs can be safely initiated. Both ESC and ACC guidelines recommend that patients should have an initial eGFR ≥30 ml/min/1.73 $m^2$ and S-potassium ≤5.0 mmol/L before MRA initiation in order to avoid life-threatening hyperkalemia. In terms of dosing, ESC guidelines make no differences in initial renal function or class of MRA when recommending a starting dose of 25 mg once per day and target dose of 50 mg once per day of both Eplerenone and Spironolactone. However, ACC guidelines have a more specific up-titration schedule that also considers initial renal function, which is in line with the study procedure of EMPHASIS-HF (12, 13).

When initiating MRAs, potassium sparing diuretics and supplements should be looked out for, as well as trimethoprim/trimethoprim-sulfamethoxazole (acts like the potassium sparing diuretic amiloride) and strong CYP3A4 inhibitors such as ketoconazole, itraconazole, nefazodone, telithromycin, clarithromycin, ritonavir and nelfinavir when using eplerenone (12).

### *Side effects of MRAs*

*Hyperkalemia*

The major concern with the use of MRAs is hyperkalemia. Both eplerenone and spironolactone are associated with dose-related increase in S-potassium levels, where patients with underlying renal dysfunction are at greater risk. In RALES, EPHESUS and EMPHASIS-HF, the incidences of serious hyperkalemia were 1-5.5%; this may not reflect the heterogeneous reality of clinical practice as elderly patients with CKD were poorly represented among the patients included in the RCTs. After the publication of RALES, a Canadian pharmacoepidemiologic study from 2004 noted an increased incidence of hyperkalemia-associated hospitalizations, which also correlated with an increase in prescription of MRAs (91). It has been speculated if the increased rate of hyperkalemia was related to MRA use in patients that were excluded from RALES, for example in those with lower eGFR (74). On the other hand, a longitudinal study from Scotland indeed showed increased rates of MRA prescription, but without increased rates of

hospitalization for hyperkalemia and lower rates of outpatient hyperkalemia. Nevertheless, careful monitoring of S-potassium in patients prescribed MRAs is important to avoid increased rates of hyperkalemia (92). In an observational study from Sweden on patients with heart failure on MRAs, the 1-year incidence of mild hyperkalemia (S-potassium >5.0 mmol/L) was 26% and of moderate hyperkalemia (S-potassium >5.5 mmol/L) was 11%. Most of the events of hyperkalemia occurred within the first 3 months of MRA treatment (Figure 9) (93).

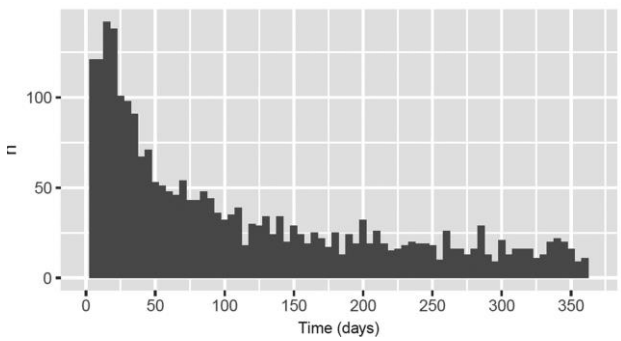


*Figure 9. The time distribution to any hyperkalaemia after MRA initiation (K+ > 5.0 mmol/L). Copyright © 2018 Marco Trevisan et al. European Journal of Heart Failure published by John Wiley & Sons Ltd on behalf of European Society of Cardiology. Reproduced from (93), licensed under CC BY-NC 4.0, https://creativecommons.org/licenses/by-nc/4.0/.*

*Worsening renal function*

WRF is most commonly defined as an increase in S-creatinine of more than 26.5 µmol/L or over 25%, or as a decrease in eGFR over 20% (94). In a subgroup analysis of the RALES trial, WRF occurred in 17% of the spironolactone group and in 7% of the placebo group ($p<0.001$). Of note, WRF was defined differently in this study, i.e. as a 30% reduction of eGFR from baseline. eGFR declined at 4 weeks in the spironolactone group; however, after 6 months, there were no longer significant difference in eGFR between the groups (95). In the subgroup of the EPHESUS trial, WRF (eGFR reduction >20%) occurred in 17% vs 15% in the eplerenone and placebo groups ($p=0.017$) in the first month. The difference in eGFR appeared at the first month and were persistent during the study time. However, after the initial decline, the mean annual changes in eGFR were similar in both groups. Hence, eplerenone did not alter the long-term decline in renal function (Figure 10) (96).

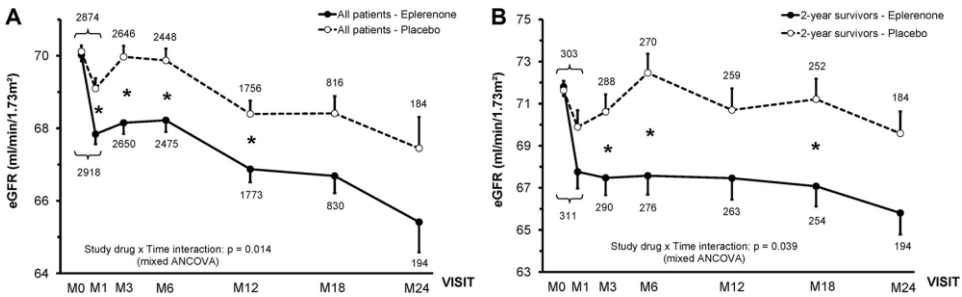


*Figure 10. Adjusted estimated glomerular filtration rate (eGFR) changes during the 24-month (M) follow-up between the eplerenone and placebo groups. A, All patients. Study drug x time interaction; probability of the difference of eGFR changes over time between groups. Dots and bars are least-square means and their SE estimated from adjusted mixed ANCOVA models. B, Sensitivity analysis of 2-year survivors. *Significant pairwise differences between placebo and eplerenone group levels adjusted for multiple testing. Copyright © 2011 American Heart Association, Inc. https://doi.org/10.1161/CIRCULATIONAHA.111.028282. Reproduced from (96) with permission from Wolters Kluwer Health, Inc. eGFR = estimated glomerular filtration rate.*

Finally, in the subgroup analysis of EMPHASIS-HF, WRF (eGFR reduction >20%) occurred in 30% vs 24% in the eplerenone and placebo groups (p<0.001). As in other studies, patients on eplerenone had an early, significant, and persistent decline in eGFR (Figure 11) (97).

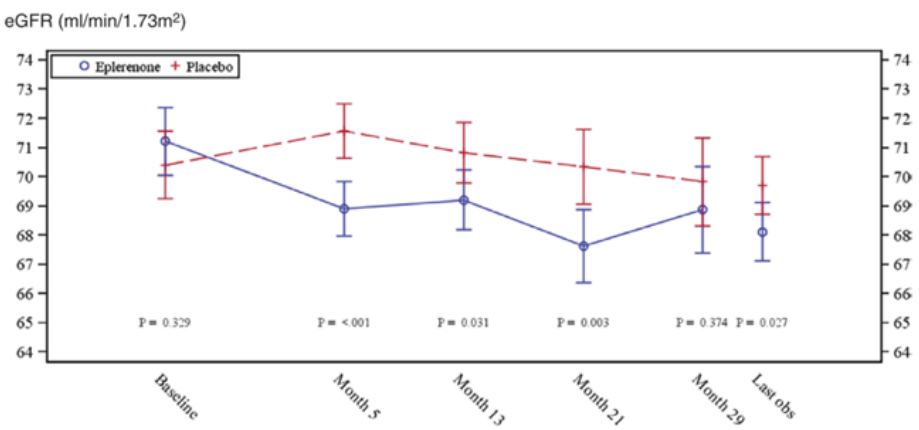


*Figure 11. Estimated glomerular filtration rate (eGFR; mL/min per 1.73 m2) kinetics between treatment groups. Copyright © 2013 American Heart Association, Inc. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000792. Reproduced from (97) with permission from Wolters Kluwer Health, Inc. eGFR = estimated glomerular filtration rate.*

Presumably, the early decline in renal function that occurred in all three trials could be due to a functional hemodynamic effect from blockade of the RAAS, supported by the observed association between plasma volume change and early

renal function decline, but without long-term adverse effect of eplerenone on renal function (96).

*Hypotension*

In the RALES trial, there were no differences between spironolactone and placebo in blood pressure during the study time. In the EMPHASIS-HF trial, the Eplerenone group had a significantly smaller increase of blood pressure than the placebo group (at one year blood pressure (systolic/diastolic) increased by 8/4 mmHg in the placebo group and 5/3 mmHg in the eplerenone group $p<0.01$). In the EPHESUS trial, systolic blood pressure decreased more in the eplerenone group compared to the placebo group (reduction of 2.5 mmHg vs 0.3 mmHg ($p=0.001$) (38-40). Eplerenone versus spironolactone was evaluated in one clinical trial. It was reported that there were greater blood pressure changes with twice daily 50 mg spironolactone compared with twice daily 50 mg of eplerenone (Figure 12) (98).

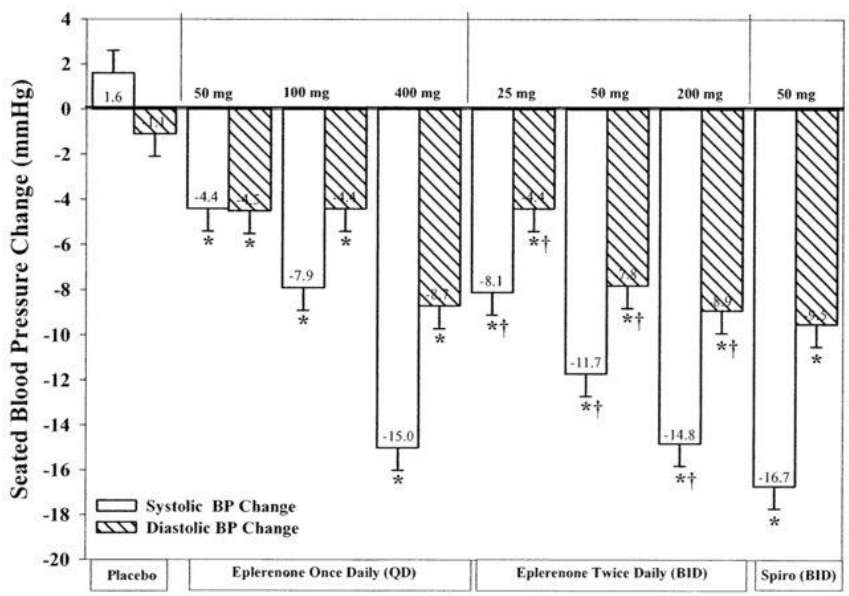


*Figure 12. Change from baseline in systolic and diastolic blood pressure (BP) (seated). Adjusted means are from the analysis of covariance model with treatment and center as factors and baseline as covariate. *P <0.05 vs placebo; †P <0.05 vs everyday dose. Copyright © 2002 by the American Journal of Hypertension, Ltd. Reprinted from (98) by permission of Oxford University Press.*

*Endocrine effects*

Spironolactone is an unspecific MRA that has an affinity for the androgen receptor, the progesterone receptor, and the glucocorticoid receptor, which causes sexual side effects that are less associated with eplerenone due to its

specificity to MR. The binding to progesterone and androgen receptors causes side effects including gynecomastia and sexual dysfunction in men and breast pain and disturbance of the menstrual cycle in women (86). In RALES, gynecomastia or breast pain was reported in 10% of the spironolactone treated patients compared to placebo treated patients, a side effects which caused MRA withdrawal in 2% versus 0.2% of the patients (38). Sexual side effects in women were not reported. In the EMPHASIS-HF and the EPHESUS trials, gynecomastia in patients treated with Eplerenone was reported to a lesser extend (0.7% and 1%) (39, 40).

***Monitoring MRAs***

Due to the risk of side effects including hyperkalemia and WRF, careful monitoring is important, especially the first months after initiation. ESC guidelines recommend S-potassium and S-creatinine checks at 1, 4, 8 and 12 weeks after starting/increasing dose and then that at 6, 9, and 12 months. After the first year, monitoring is recommended 4-monthly (3). Further, if S-potassium rises above 5.5 mmol/L or creatinine rises to 221 µmol/L (2.5 mg/dL)/eGFR <30 mL/min/1.73 $m^2$, the dose should be halved. If S-potassium rises to >6.0 mmol/L or S-creatinine to >310 µmol (3.5 mg/dL)/eGFR <20 mL/min/1.73 m2, MRAs should be discontinued immediately (12). Nevertheless, studies have shown that laboratory monitoring after MRA initiation often do not meet guideline recommendations (99).

***MRAs in patients with impaired renal function***

Moderate impaired renal function, eGFR <60 ml/min/1.73 $m^2$, is common in HFrEF and has been reported in about 50% of the patients (52, 100). eGFR <60 ml/min/1.73$m^2$ was associated with increased mortality in post-hoc analyses of RALES, EPHASUS and EMPHASIS-HF. Further, patients on MRAs had increased risks of developing early WRF compared to placebo. In EPHESUS, early WRF was associated with worse cardiovascular outcome including all-cause mortality. However, there was no interaction between early WRF and the beneficial effects of eplerenone on cardiovascular death and hospitalization (p=0.77) or for hospitalization for heart failure progression (p=0.82) (96). In RALES, WRF was associated with increased mortality in the placebo group but not in the spironolactone group (95). Finally, in EMPHASIS-HF, WRF was associated with increased mortality but eplerenone did not change the outcome in the setting of WRF. Hence, the beneficial effect of eplerenone was consistent and independent of WRF occurrence (97).

MRAs have been suggested to have reno-protective effects. In patients with type 2 diabetes, eplerenone in combination with ACEIs was shown to reduce albuminuria (101). In patients with diabetes and maximally recommended doses

of ACEIs or ARBs, spironolactone was shown to reduce albuminuria by 33% without correlation to blood pressure (102, 103). These findings are supported by a study from Swedish Heart Failure Registry that showed that patients with HFrEF and severe CKD (eGFR <30 ml/min/1.73 m$^2$) had survival benefits when treated with RAAS-I (104). However, even though use of MRAs has been proven beneficial in patients with kidney failure, the associated side effect, including hyperkalemia, is a main limitation for broad implementation in patients with both renal- and cardiovascular disease (74).

## Additional therapies for HFrEF

ESC Guidelines for diagnosis and treatment of acute and chronic heart failure have a clear treatment strategy for patients with HFrEF (Figure 13) (3).

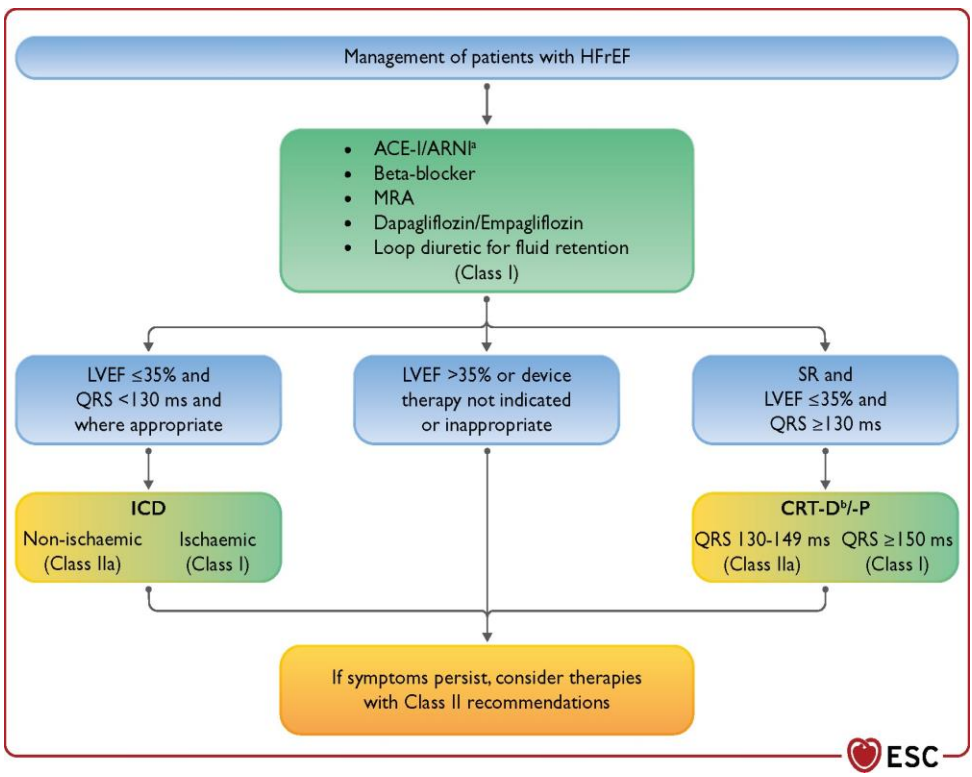


*Figure 13. Therapeutic algorithm of Class I Therapy Indications for a patient with heart failure with reduced ejection fraction. ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; CRT-D =cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; ICD = implantable cardioverter-defibrillator; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; QRS = Q, R, and S waves (on a 12-lead electrocardiogram); SR = sinus rhythm. a) As a replacement for ACE-I. b) Where appropriate. Reprinted from (3), by permission of Oxford University Press on behalf of the European Society of Cardiology.*

In brief, all patients with HFrEF should be consider for treatment ACEIs and BBs. ARBs are given to patient with intolerance to ACEIs. In previous ESC guidelines from 2016, MRAs should be initiated if the patient is still symptomatic and has LVEF ≤35% (12). In the updated ESC guidelines from 2021, MRAs should be given to all patients with HFrEF in addition to ACEIs and BBs. If the patient is still symptomatic after they have been given the cornerstone therapies of ACEIs, BBs and MRAs, the guidelines recommend a switch from ACEIs to angiotensin receptor-neprilysin inhibitor (ARNI). However, in the updated guidelines ARNI can be considered as the first-line treatment instead of ACEIs/ARBs. ARNI is a class of drug resulting from the combination of Sacubitril/valsartan which is an ARBs (Valsartan) combined with an inhibitor of neprilysin (Sacubitril) (105). In the Angiotensin-neprilysin inhibitor versus enalapril in heart failure (PARADIGM-HF) trial, sacubitril/valsartan was compared to enalapril in patients with HFrEF in NYHA class II-III. Sacubitril/valsartan reduced the composite endpoint of cardiovascular death and heart failure hospitalization by 20% (HR 0.80; 95% CI 0.73-0.87; p<0.001) (106). Further, the updated guidelines recommend sodium-glucose cotransporter 2 (SGLT2) given as either Dapagliflozin or Empagliflozin to all patients with HFrEF, to reduce the risk of cardiovascular death and worsening heart failure. In the Dapagliflozin in patients with heart failure and reduced ejection fraction (DAPA-HF) trial, dapagliflozin was compared to placebo in patients with HFrEF with LVEF ≤40% and NYHA II-IV. Most patients had standard therapy of ACEIs/ARBs or ARNI, BBs and MRAs. The study showed a 26% reduction (HR 0.74; 95% CI 0.65-0.85, p<0.001) of the primary outcome of worsening heart failure and death from cardiovascular causes. Of note, these effects were seen in patient with and without diabetes. (107). In the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial, empagliflozin reduced the combined primary endpoint of cardiovascular death or heart failure hospitalization by 25% in patients with HFrEF with NYHA class II-IV (108). The mechanism of action behind its cardiovascular benefits is not clear but its renal protective mechanisms was suggested as a possible explanation (109).

In addition, all patients with LVEF ≤35% should be considered for Implantable cardioverter-defibrillator (ICD), especially in patients with ischaemic aetiology. CRT with or without defibrillator should be considered if the ECG shows QRS-complex broader than 130 ms. Diuretics is recommended for symptom relief in case of fluid retention (108).

## Patterns of MRA use

Consequently, the therapy strategies in heart failure are both comprehensive and complicated. With so many treatment options for such a large patient population that is often old and frail with many co-morbidities, heart failure treatment has

become more and more complex. Studies from Europe and USA have shown that most patients get access to ACEIs/ARBs and BBs, but MRAs are underused. In a large prospective registry study from USA from 2005-2007, published just after the first guidelines recommended MRAs in heart failure, 33% of all eligible patients received MRAs at hospital discharges after being treated for heart failure (110). In The Heart Failure Pilot Survey (ESC-HF Pilot) study (2009-2010) – a prospective, multicentre, observational survey from 12 European countries, 33% of ambulatory patients with chronic heart failure had MRAs in Northern Europe without any further analysis on eligibility (111). In a retrospective post-hoc analysis of The Biology Study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF) – a European multicentre prospective study including patients from 2010-2012, 56% of all eligible patients had a MRA prescribed at baseline and 63% after 9 months (112). In a study from the Swedish Heart Failure Registry (SwedeHF) that included patients from 2003-2012, the use of MRAs decreased from 53% in 2003 to 42% in 2012 ($p<0.001$) (Figure 14) (113). Further, nearly 30% discontinued MRA treatment before the first and last visit.

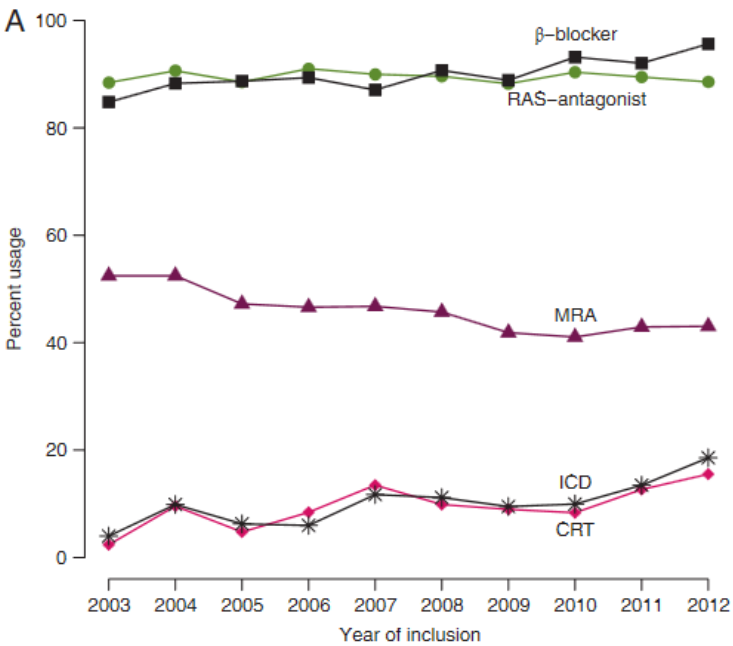


*Figure 14. Crude proportions of patients receiving evidence-based treatments over time. Copyright © 2016 The Authors. European Journal of Heart Failure © 2016 European Society of Cardiology. Reproduced from (113), with permission from John Wiley & Sons, Inc. RAS= renin-angiotensin system, MRA = mineralocorticoid receptor antagonist, ICD = implantable cardioverter defibrillator, CRT = cardiac resynchronization therapy.*

In the ESC Heart Failure Long-Term Registry (ESC-HF-LT) (2011-2013), a prospective observational registry from 21 European and/or Mediterranean

countries, 51 % of all outpatients with chronic heart failure in the Nordic countries (Lithuania and Sweden, n=421) were treated with MRAs (114). However, this study included a limited number of participants and included all patients with chronic heart failure independent on LVEF. In the Change the Management of Patients with Heart failure (CHAMP-HF) (2015-2017), a registry study including outpatients (n=3518) in United States with chronic HFrEF, 33% of all patients were prescribed MRAs (115).

The Swedish National Board of Health and Welfare are doing regular evaluations of the adherence to the national guidelines on cardiac care. The most recent evaluation was done in 2015 and showed that the MRA treatment in patients with heart failure had decreased from 19% 2008 to 16% 2013. More males than females were treated with MRAs, with a difference of 5 percent units. However, the evaluation did not include patients in primary care (116).

In a recent observational cohort study of patients with HFrEF from Sweden, United Kingdom and United States, the pattern of use for guideline-directed medical therapy between 2016-2019 (117). The patients had to be new users and had to have a recent hospitalization for heart failure. In 68172 new users of heart failure drugs, 17421 received an MRA (26%). In the Swedish cohort of 23407 patients, 9172 patients (39%) received MRAs. In the total population, the MRA dose was titrated to target dose (50 mg once daily) in <5% of patients and the discontinuation rate was 40%.

## Knowledge gap

The underuse of MRAs has been presented in several registry and observational studies; the risks of hyperkalaemia and renal dysfunction often serve as possible explanations. In perspective of the real-world heart failure population of elderly patients with a high degree of comorbidities including renal dysfunction, these risks are important considerations. Since RCTs have strict selection criteria causing poor generalizability and external validity, the actual tolerability of MRAs in real-world patients with heart failure remains uncertain. In the everyday clinical practice, it is challenging to apply the results from RCTs into clinical practice. The discrepancy between the real-world setting and the tightly controlled setting of a RCT stresses the importance of further research on actual real-world patients with heart failure.

# Aims

The overall aim of this thesis is to explore why a large group of patients with heart failure fail to receive optimal guideline-directed treatment with MRAs.

Specific aims in papers I-IV are as follows:

I. What is the pattern of use for MRAs in a real-world heart failure population and what are the reasons for non-prescription of MRAs?

II. Which method for estimating glomerular filtration rate (eGFR) is most accurate in patients with heart failure?

III. What are the reasons for discontinuation of MRA treatment in patients with HFrEF?

IV. What are the outcomes in terms of worsening renal function and mortality for patients with HFrEF and impaired renal function who are treated with MRAs?

# Materials and Methods

## Study population

This thesis is based on medical record data from Umeå University Hospital, Sweden. Patients that were diagnosed with heart failure at the Heart Centre or Department of Internal Medicine between January 2010 and January 2018 were retrospectively included. All patients had at least one specialist clinic visit, either as out clinic patient or hospitalized. Both incident and prevalent patients were included. Postal codes were used to find all patients living within the hospital primary catchment area.

The medical records were used to identify patients that had been diagnosed with heart failure, either as a primary or contributory diagnosis according to the International Classification of Disease (ICD) 10$^{th}$ revision codes I50.X, I42.0, I42.6, I42.7, I42.9, I11.0, I13.0, and I13.2. The diagnosis had to be signed or countersigned by a specialist in cardiology or internal medicine.

Umeå University Hospital serves around 130 000 residents and is the only cardiology clinic within the primary catchment area. The residents within the area of the hospital are comprised of mixed urban and rural populations. Residents living in Umeå are generally younger and have higher level of education compared with residents in the other cities of the primary catchment area.

## Data collection

The start of data collection was June 2015, and the end of data collection was February 2019. We manually collected data from the medical records regarding medical therapy for heart failure, laboratory data (S-Sodium, S-Potassium, S-creatinine, S-hemoglobin, S-NT-proBNP), clinical parameters (blood pressure, weight, length), comorbidities (coronary heart disease, diabetes, hypertension, atrial fibrillation), echocardiogram (LVEF, left ventricular end systolic diameter, left ventricular end diastolic diameter, tricuspid annular plane systolic excursion, septal wall motion, valvular heart disease, posterior wall thickness), ECG parameters (rhythm, frequency, QRS duration, left bundle branch block), and electronic devices (pacemaker (PM), implantable cardioverter defibrillator (ICD), CRT, CRT-Defibrillator). Index data were collected at the time of diagnosis, and follow-up data were collected for the journal entry closest to the end of the data collection period (2016-2018). For patients diagnosed before 2010, their baseline data were collected by the journal entry closest to January 2010.

Renal function classes were defined as normal to mildly reduced renal function (eGFR $\geq$60 ml/min/1.73 m$^2$), moderately impaired renal function (eGFR $\geq$30-59

ml/min/1.73 m$^2$), severely impaired renal function (eGFR ≥15-29 ml/min/1.73 m$^2$), and renal failure (eGFR <15 ml/min/1.73 m$^2$) (57).

All patients alive on March 1, 2016 with a LVEF between 30-40% were reassessed by a specialist in cardiology to validate patients with borderline heart failure classes. One researcher performed an additional data collection, according to the standardized protocol, on a minor proportion of the medical records to validate the collected data.

## Study design

***Paper I***

Obstacles to treatment with MRAs in patients with HFrEF. All patients who were alive at the end of March 2016 with LVEF of 40% or less either at index or follow-up were included. Two groups were identified – patients that never had MRAs (no MRA at index, between index and follow up, or at follow-up), and patients that were treated with MRAs at follow-up. Medical records from the cardiology and/or internal medicine clinics were read for all patients without MRAs in order to determine the reasons for non-prescription of MRAs for each particular case. In cases where no reasons for non-prescription of MRAs were mentioned, patients were screened for guideline-directed contraindications (renal impairment, hyponatremia, hyperkalaemia, or hypotension). Contraindications were either mentioned in the medical records by the treating physicians or by consistently increased laboratory values above or under the reference interval. Systolic blood pressure under 100 mmHg was defined as hypotension. When a reason for non-prescription of MRA was mentioned in the medical records, the text was highlighted and copied into another document. The codes for reasons of non-prescription were set after the reading of the medical records.

***Paper II***

Comparison of S-creatinine based equations for eGFR with mGFR in all patients with heart failure. All patients who underwent plasma clearance with $^{51}$Cr-EDTA between 2010 and 2018 were identified. The eGFR equations were chosen based on that they had been used in the most important RCTs for MRAs, are recommended by international guidelines or national assessments, or if they were suitable to the characteristics of our heart failure database (57, 118). The equations are summarized in Table 6.

*Table 6. Description of the different creatinine-based equations used in Paper II.*

| | $CG_{AW}$/$CG_{IW}$(63) | CKD-EPI (119) | MDRD/sMDRD (120) | sMDRD-IDMS (121) | FAS (122) | BIS1 (123) | LM-rev (124) |
|---|---|---|---|---|---|---|---|
| **Patients** | n=236, 18-92 y | n=8254, mean age 47 y | n=1628, mean age 50.6 y | See MDRD/sMDRD | n=6870 > 2 years old | n=610, mean age 76 y | n=850, mean age 60 y |
| **Population** | 96% males, single centre | GFR >60, from 10 studies | Chronic kidney disease | See MDRD/sMDRD | Wide range of age, multi-centre | >70 y, population-based cohort | >18 y, Swedish, two-centre |
| **Mean mGFR (ml/min/1.73m²)** | ** | 68 | 39.8 | See MDRD/sMDRD | 58-95 | 60 | 55 |
| **Reference method** | 24 h U-creatinine | $^{125}$I-Iothalamate (urine) | $^{125}$I-Iothalamate (urine) | See MDRD/sMDRD | Inulin, iohexol, iothalamate clearance | Plasma Iohexol clearance | Plasma Iohexol clearance |
| **Variables** | Age, sex, weight | Sex, age, race | Age, sex, race, s-urea nitrogen*, s-albumin* | Age, sex, race. | Age, sex | Age, sex | Age, sex |
| **Standardized method*** | No | Yes | No | Yes | Yes | Yes | Yes |
| **Publication year** | 1976 | 2009 | 1999 | 2007 | 2016 | 2012 | 2011 |

** Excluded in the sMDRD, ** Presented for as mean creatinine excretion mg/kg/24 h for each decade of age. $CG_{IW}$ and $CG_{AW}$ = Cockcroft-Gault's ideal and actual weight, CKD-EPI = The Chronic Kidney Disease Epidemiology Collaboration, MDRD/sMDRD= The Modification of Diet in Renal Disease Study / simplified MDRD, IDMS = Isotope-Dilution Mass Spectrometry, FAS = Full Age Spectrum, BIS1 = Berlin Initiative Study 1, and LM-rev= The revised Lund-Malmö equation, GFR = glomerular filtration rate, y = years.*

Additional data required for the equations were collected from the medical records. Values of S-creatinine, S-urea and S-albumin were recorded as close as possible to the time of the $^{51}$Cr-EDTA measurement. Data for length and weight were collected from the $^{51}$Cr-EDTA measurement. The medical records were examined if any patient was treated with trimethoprim and/or dronedarone at the time of the $^{51}$Cr-EDTA measurement since these medications cause higher S-creatinine levels.

### *Paper III*

Determining the motives, predictors and outcomes of MRA discontinuation in patients with HFrEF. All patients who were alive at the end of March 2016 and had LVEF of 40% or less at index or follow-up were included. All patients treated

with MRAs were included and further divided into two groups depending on whether or not they discontinued MRAs during the follow-up time. The medical records from cardiology and/or internal medicine were read for all patients that discontinued MRAs. The text from the medical records were analysed with direct content analysis and the specialty of the physician (e.g. cardiologist, internist, other) who initiated the withdrawal of the MRA was documented (125). Data on S-creatinine, S-potassium and blood pressure were gathered from the time of discontinuation. CCI-index was calculated by searching for corresponding ICD-codes for each comorbidity (Table 7) (126). The outcomes for Paper III were MRA discontinuation and all-cause mortality.

*Table 7. Diagnostic categories, weighted scores, and corresponding ICD-10-AM codes (126).*

| **Condition** | **Weights** | **ICD-10-AM** |
|---|---|---|
| Acute myocardial infarction | 1 | I21, I22, I252 |
| Congestive heart failure | 1 | I50 |
| Peripheral vascular disease | 1 | I71, I790, I739, R02, Z958, Z959 |
| Cerebral vascular accident | 1 | I60, I61, I62, I63, I65, I66, G450, G451, G452, G458, G459, G46, I64, G454, I670, I671, I672, I674, I675, I676, I677 I678, I679, I681, I682, I688, I69 |
| Dementia | 1 | F00, F01, F02, F051 |
| Pulmonary disease | 1 | J40, J41, J42, J44, J43, J45, J46, J47, J67, J44, J60, J61, J62, J63, J66, J64, J65 |
| Connective tissue disorder | 1 | M32, M34, M332, M053, M058, M059, M060, M063, M069, M050, M052, M051, M353 |
| Peptic ulcer | 1 | K25, K26, K27, K28 |
| Liver disease | 1 | K702, K703, K73, K717, K740, K742, K746, K743, K744, K745 |
| Diabetes | 1 | E109, E119, E139, E149, E101, E111, E131, E141, E105, E115, E135, E145 |
| Diabetes complications | 2 | E102, E112, E132, E142 E103, E113, E133, E143 E104, E114, E134, E144 |
| Paraplegia | 2 | G81 G041, G820, G821, G822 |
| Renal disease | 2 | N03, N052, N053, N054, N055, N056, N072, N073, N074, N01, N18, N19, N25 |
| Cancer | 2 | C0, C1, C2, C3, C40, C41, C43, C45, C46, C47, C48, C49, C5, C6, C70, C71, C72, C73, C74, C75, C76, C80, C81, C82, C83, C84, C85, C883, C887, C889, C900, C901, C91, C92, C93, C940, C941, C942, C943, C9451, C947, C95, C96 |
| Metastatic cancer | 3 | C77, C78, C79, C80 |
| Severe liver disease | 3 | K729, K766, K767, K721 |
| HIV | 6 | B20, B21, B22, B23, B24 |

***Paper IV***

Outcomes for patients with HFrEF on MRAs with moderately impaired renal function. All patients who had LVEF of 40% or less at index or follow-up and index eGFR <60 ml/min/1,73m$^2$ were included. Patients were divided into two groups depending on if they had treatment with MRA at index and follow-up or if they never had treatment with MRAs. The outcomes were decline in renal function, WRF (defined as a decrease in eGFR over 20% between index and follow-up), and all cause-mortality.

## Statistics

The statistical analyses were performed with SPSS version 24 (Paper I), and version 25 (Papers II-IV) (Armonk, NY, USA). The level of significance was set at 0.05.

***Descriptive and comparative statistic***

Continuous variables were presented as means with standard deviations and were analysed with Student's t test. Continuous variables without normal distribution were presented as medians with interquartile ranges and analysed with Mann-Whitney U test. Categorical variables were presented with frequencies and percentages and analysed with chi-square or fisher's exact test when suitable.

***Tests for agreements***

In Paper II, the agreement was assessed between eight different equations for eGFR against mGFR. A Pearson's correlation coefficient (r) was performed to test the relationship between the different equations for eGFR and mGFR. The precision was considered acceptable if r >0.8. Since the correlation describes the linear relationship between two methods and not their agreement, it is not recommended as a method for assessing the comparability between two methods. To find the differences between the methods, Bland-Altman plots were used. Bland-Altman plots is a graphical method that plots the differences of two paired measurements against the mean of the two measurements. The Y-axis shows the difference between the two paired measurements (A-B) and the X-axis represents the average of these two measurements ((A+B)/2) (127). In order to quantify the accuracy between the measurements, limits of agreement were constructed. These were calculated as the mean and the standard deviations of the differences between the two methods. The accuracy was defined as the percentage of patients with eGFR within $\pm$30% of mGFR (P30), calculated as [eGFR-mGFR]-100/mGFR, and was considered acceptable if >75 % of the eGFR was within $\pm$30% of mGFR.

Finally, eGFR <30 ml/min/1.73 m² is a threshold for RAAS-I treatment in patients with HFrEF, including MRAs. Therefore, the McNemar test was performed for all equations to compare the proportion of patients that were falsely divided into the wrong eGFR-group compared to mGFR. The groups were defined by eGFR or mGFR over 30 ml/min/1.73 m² or not.

***Regression analysis***

In paper III-IV, multivariable logistic regression was used to assess factors associated with MRA discontinuation and WRF, respectively. Since we did not aim to build a predictive model but rather evaluate how different covariates affected the outcome, we included all relevant covariates simultaneously in the statistical analysis. In Paper III, we did a subgroup analysis excluding patients that met the guideline-directed contraindication of MRAs, in order to evaluate which factors that were associated with MRA discontinuation in patients not meeting the guidelines.

***Survival analysis***

Kaplan-Meier curve estimated survival function depending on MRA use and log-rank test were used to compare differences in survival. Cox proportional hazard model was performed to further evaluate the association of all-cause mortality and MRA use when adjusting for clinically relevant covariates. In Cox proportional hazard model, assumptions of proportionality of hazard were verified by log-log plots.

***Direct content analysis***

Direct content analysis was used in Paper III (125). Prior research and guidelines were used to identify key concepts and variables as initial coding categories (Table 8) (12, 13). Operational definitions for each coding category were determined using prior research. Data were collected in two steps. First, each patient's medical records were read in order to find texts or values that at the first impression appeared to represent the predefined codes. The relevant parts of the texts from the medical records were copied into a separate document. Second, the content of the text was categorized into the predetermined codes. If text passages were found that could not be categorized into the initial codes, a new code was created. The highlighted texts from the medical records were coded by two different researchers. Further, each patient could have up to three codes.

*Table 8. Operational definitions for direct context analysis.*

| Operational definitions | Number |
|---|---|
| **Renal dysfunction (elevated S-creatinine) – commented as the reason by the treating physician** | 1 |
| **Renal dysfunction (elevated S-creatinine) – in the laboratory data. Inclusion if S-creatinine increased by 20% compared to previous values** | 2 |
| **Hyperkalemia – commented as the reason by the treating physician** | 3 |
| **Hyperkalemia – in the laboratory data. Inclusion if S-potassium was ≥5.0 mmol/L** | 4 |
| **Hyponatremia – commented as the reason by the treating physician** | 5 |
| **Hyponatremia – in the laboratory data. Lower limit 133 mmol/L** | 6 |
| **Gynecomastia** | 7 |
| **Other patient reported side effect** | 8 |
| **Improved LVEF** | 9 |
| **Low blood pressure – commented as the reason by the treating physician** | 10 |
| **Low blood pressure – in the laboratory data. Upper limit for systolic blood pressure 110 mmHg** | 11 |
| **Patient refusal of trying MRAs/fear of side effects** | 12 |
| **Patient reported side effect** | 13 |
| **Unknown reason** | 14 |
| **Orthostatic hypotension** | 15 |
| **Heart transplantation** | 16 |
| **Prescribing errors** | 17 |
| **Palliative care** | 18 |

*MRAs = mineralocorticoid receptor antagonists, LVEF = left ventricular ejection fraction.*

## Ethics

All studies in this thesis complied with the Declaration of Helsinki and were approved by the Regional Ethical Review Board in Umeå, Sweden (registration number 2015/419- 31 and registration number 2016-233-32M).

Patients' medical records are protected by confidentiality by the Public Access to Information and the Secrecy Act but can be available for research purposes after approval by an Ethical Review Board.

A paper stating that information from the health care visit could be used in research and quality registries was placed at the outpatient cardiology clinic, the cardiology care unit and cardiology ward. We did not obtain informed consent from the included patients, which was waived by the Ethical Review Board. Since health care data are classified as especially sensitive information, the responsibility for none-disclosure is essential. The non-anonymized database was

stored on a computer protected by the firewall of Umeå University Hospital. The responsible researcher gave each patient a specific code, and the anonymous coded database was used in all statistical analyses. No individual data could be identified in the results since all statistical analyses were presented on a group level.

# Results

## Study population and data validity

In Paper I, the database had 3636 included patients. During the time between Paper I and Papers II-IV, more patients were included, which is why the database grew to 4449 patients (Table 9).

*Table 9. Patient included in the different papers.*

| Inclusion | Paper I | Papers II-IV |
|---|---|---|
| **Database (n)** | 3636 | 4449 |
| **mGFR (n)** | - | 149 |
| **Alive 2016 January*-march** (n)** | 2029 | 2955 |
| **LVEF ≤40% (n)** | 812 | 1137 |

**Papers III-IV, **Paper I. mGFR= measured glomerular filtration rate, LVEF = left ventricular ejection fraction.*

There was a high compliance between the reassessment of a minor sample (200 patients) of the collected data and the original data collection.

## Paper I

There were 812 patients with HFrEF included. Mean LVEF was 33% and one-third of the patients were women. Nearly half (48%) of the patients had a creatinine clearance under 60 ml/min. Nearly all patients had treatment with ACEIs/ARBs and BBs (91% and 90%, respectively) (Table 10).

*Table 10. Characteristics of the HFrEF population.*

| Characteristics | Patients with EF ≤ 40 % (N=812) |
|---|---|
| **Sex - *n* (%)** | |
| **Male** | 563 (69) |
| **Female** | 249 (31) |
| **Age - year, mean (SD)** | 75 ± (12) |
| **Systolic blood pressure - mmHg, mean (SD)** | 126 ± (19) |
| **Diastolic blood pressure - mmHg, mean (SD)** | 74 ± (11) |
| **Ejection fraction - %, mean (SD)** | 33 ± (6) |
| **Heart rate - beats/min, mean (SD)** | 75 ± (15) |
| **Body-mass index - kg/m², mean (SD)** | 27 ± (5) |

| **Laboratory values** | |
|---|---|
| **NT-proBNP - pg/mL, median (IQR)** | 1224 (432-2899) |
| **Potassium - mmol/L, mean (SD)** | 4.4 ± (1.5) |
| **Serum creatinine - µmol/L, mean (SD)** | 108 ± (60) |
| **Creatinine clearance - mL/min, mean (SD)** | 68 ± (33) |
| **Creatinine clearance - *n* (%)** | |
| **≥90 mL/min** | 182 ± (22) |
| **60-89 mL/min** | 235 ± (29) |
| **30-59 mL/min** | 305 ± (38) |
| **15-29 mL/min** | 76 ± (9) |
| **<15 mL/min** | 6 ± (1) |
| **Medical history - *n* (%)** | |
| **Atrial fibrillation** | 387 (48) |
| **Diabetes** | 185 (23) |
| **Hypertension** | 554 (68) |
| **Coronary disease[a]** | 386 (48) |
| **Medications and devices - *n* (%)** | |
| **ACE inhibitor** | 383 (47) |
| **ARB** | 353 (43) |
| **Beta-blocker** | 730 (90) |
| **Diuretics** | 497 (61) |
| **Digitalis** | 95 (12) |
| **Implantable cardioverter-defibrillator[b]** | 108 (13) |
| **Cardiac resynchronization therapy[b]** | 105 (13) |

*ACE = angiotensin converting enzyme inhibitor, ARB = angiotensin II receptor blocker; IQR, interquartile. Creatinine clearance was calculated with Cockcroft-Gault equation. Values are means and standard deviation (SD), no. (%), or median (interquartile range (IQR)) when appropriate.*

[a] *Coronary artery disease defined as either previous myocardial infarction or documented stenosis of at least 50 %.*

[b] *Including patients with Cardiac Resynchronization Therapy Defibrillator (CRT-D).*

There were 553 patients (68%) who had tried MRAs at some point. Of these, 184 patients discontinued treatment and 369 (45%) remained on MRA. The remaining 259 patients (32%) had never tried MRAs (Figure 15).

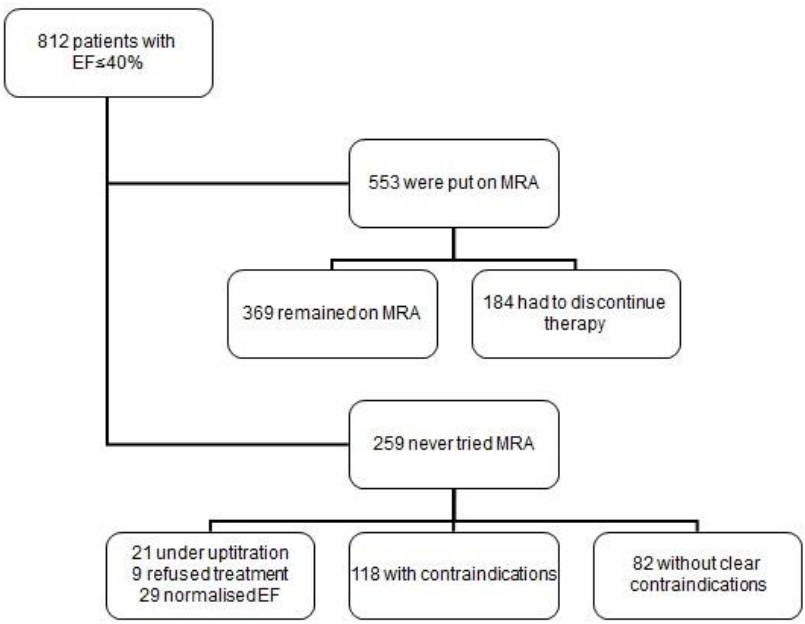


*Figure 15. Flowchart of patient distribution in Paper I.*

The medical record review showed that contraindications were the most common reason for not receiving MRAs. Renal dysfunction (93 patients) was the most common contraindication, followed by hypotension (28 patients) and hyperkalemia (25 patients). Of the 93 patients with renal dysfunction, 26 patients (28%) had a creatinine clearance under 30 ml/min. Nineteen of the 25 patients with hyperkalemia also had renal dysfunction listed as a contraindication. The mean S-potassium was 5.2 $\pm$ 0.4 mmol/L for patients with hyperkalemia as a contraindication and 12 patients has S-potassium $\leq$5.0 mmol/L. When excluding patients with creatinine clearance under 30 ml/min, S-potassium >5.0 mmol/L and hypotension from the 118 patients with contraindications, there were 51 patients without clear contraindications. Eighty-two patients with indication for MRAs had no contraindications or other obstacles to MRA treatment. Compared to the patients who were on MRAs at follow-up, the MRA naïve patients had less treatment with ACEIs/ARBs and BBs and fewer patients reached target doses. In addition, 26 of the 82 patients did not have any follow-up at the cardiology clinic. MRA naïve patients were older (77 $\pm$13 vs 72 $\pm$ 11, $p<0.001$), had higher systolic

blood pressure, higher LVEF, lower body mass index (BMI), less treatment with CRT and ICD and fewer had been hospitalized owing to heart failure compared to the patients who were on MRAs. Further, mean S-potassium for the MRA naïve patients were slightly lower but within normal reference values in both groups. No difference in creatinine clearance was found between groups.
Considering the 82 patients (10%) without MRA and no contraindications together with the 51 patients (6%) in the contraindication group without guideline-directed contraindications, we estimated that there was an underuse of MRA in 16% of the patients with HFrEF.

## Paper II

eGFR is an important measure in heart failure care. However, it is unknown which creatinine-based method is the most accurate in patients with heart failure, and we decided to investigate this in our real-world population. In our heart failure population, 146 patients out of the 4449 patients in the database, had undergone a $^{51}$Cr-EDTA measurement. The reasons for conducting $^{51}$Cr-EDTA measurement was malignancy (37%), CKD (33%), and heart/lung/renal transplantation (29%). The mGFR was conducted before starting cytostatic drugs and after the renal transplantations, where a majority had the mGFR conducted several years after the renal transplantation. All patients with heart failure, independent of LVEF, were included. Comparing the characteristics of the 146 patients to the whole heart failure population, the most striking difference was that the study group had a higher S-creatinine than did the total heart failure group (median S-creatinine 116 vs 97 μmol/L, $p<0.001$). The study group was younger (70 $\pm$ 14 vs. 81 $\pm$ 13 years $p<0.001$) and had a higher prevalence of diabetes (39% vs. 25%, $p<0.001$). The two groups had no significant difference in LVEF, male sex, and treatment with ACEI/ARB, BBs, MRAs or loop diuretics ($p>0.05$). There were no differences in the percentage of patients categorized in HFrEF and HFpEF between the study group and the total heart failure population (33% vs 27% and 47% vs 44%, $p>0.05$).

The mGFR from the $^{51}$Cr-EDTA measurement was 42 ml/min/1.73 m$^2$ in the study group. All equations showed a higher mean eGFR compared to mGFR, except for the Modification of Diet in Renal Disease study equation (MDRD) (Table 11). To note, the MDRD equation required serum-urea (S-urea) and serum-albumin (S-albumin), which was only available in 69 patients with impaired renal function. The Berlin Initiative Study 1 equation (BIS1) included 71 patients since all patients under 70 years of age were excluded.

*Table 11. mGFR and eGFR for the total study group and by LVEF.*

| GFR-method | Study group (n=146) | HFrEF (n=48) | HFmrEF (n=29) | HFpEF (n=68) |
|---|---|---|---|---|
| $^{51}$Cr-EDTA | 42 ± 24 | 43 ± 24 | 44 ± 26 | 39 ± 23 |
| CG-AW | 55 ± 30 | 59 ± 30 | 60 ± 36 | 50 ± 28 |
| CG-IBW | 49 ± 27 | 52 ± 27 | 53 ± 33 | 44 ± 24 |
| MDRD | 28 ± 16 | 35 ± 18 | 27 ± 13 | 23 ± 14 |
| sMDRD$^{IDMS}$ | 54 ± 31 | 58 ± 30 | 60 ± 38 | 49 ± 27 |
| CKD-EPI | 53 ± 28 | 57 ± 27 | 57 ± 31 | 49 ± 27 |
| LM-rev | 48 ± 25 | 52 ± 24 | 51 ± 28 | 44 ± 23 |
| BIS1 | 44 ± 17 | 43 ± 19 | 43 ± 18 | 46 ± 15 |
| FAS | 52 ± 27 | 56 ± 27 | 57 ± 34 | 47 ± 24 |

*HFrEF = Heart Failure with Reduced Ejection Fraction, HFmrEF = Heart Failure with Mid-Range Ejection Fraction, HFpEF = Heart Failure with Preserved Ejection Fraction, GFR= Glomerular filtration rate, $^{51}$Cr-EDTA = 51Chromium-51-ethylenediaminetetraacetic acid $CG_{IW}$ and $CG_{AW}$ = Cockcroft-Gaults ideal and actual weight, CKD-EPI = The Chronic Kidney Disease Epidemiology Collaboration, MDRD/sMDRD= The Modification of Diet in Renal Disease Study / simplified MDRD, FAS = Full Age Spectrum, BIS1 = Berlin Initiative Study 1 and LM-rev= The revised Lund-Malmö equation. eGFR or mGFR are in ml/min/1.73 m$^2$. All values reported as mean ± standard deviation.*

The accuracy (P30) was highest for MDRD (80%), followed by LM-rev (68%) and the Cockcroft-Gault's ideal weight equation (CG-IW) (63%). None of the equations except MDRD med the 75% cut-off for acceptable accuracy. All equations except for MDRD falsely categorized patients with a real mGFR under 30 ml/min/1.73 m$^2$ into an eGFR over 30 ml/min/1.73 m$^2$ ($p<0.001$). The equation with the highest precision was MDRD (r=0.9), followed by the revised Lund-Malmö equation (LM-rev) (r=0.88). All equations, except for MDRD, overestimated eGFR (Figure 16). One of the most commonly used equation, the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), had a quite low accuracy of 58% and overestimated eGFR by a mean of 26 %.

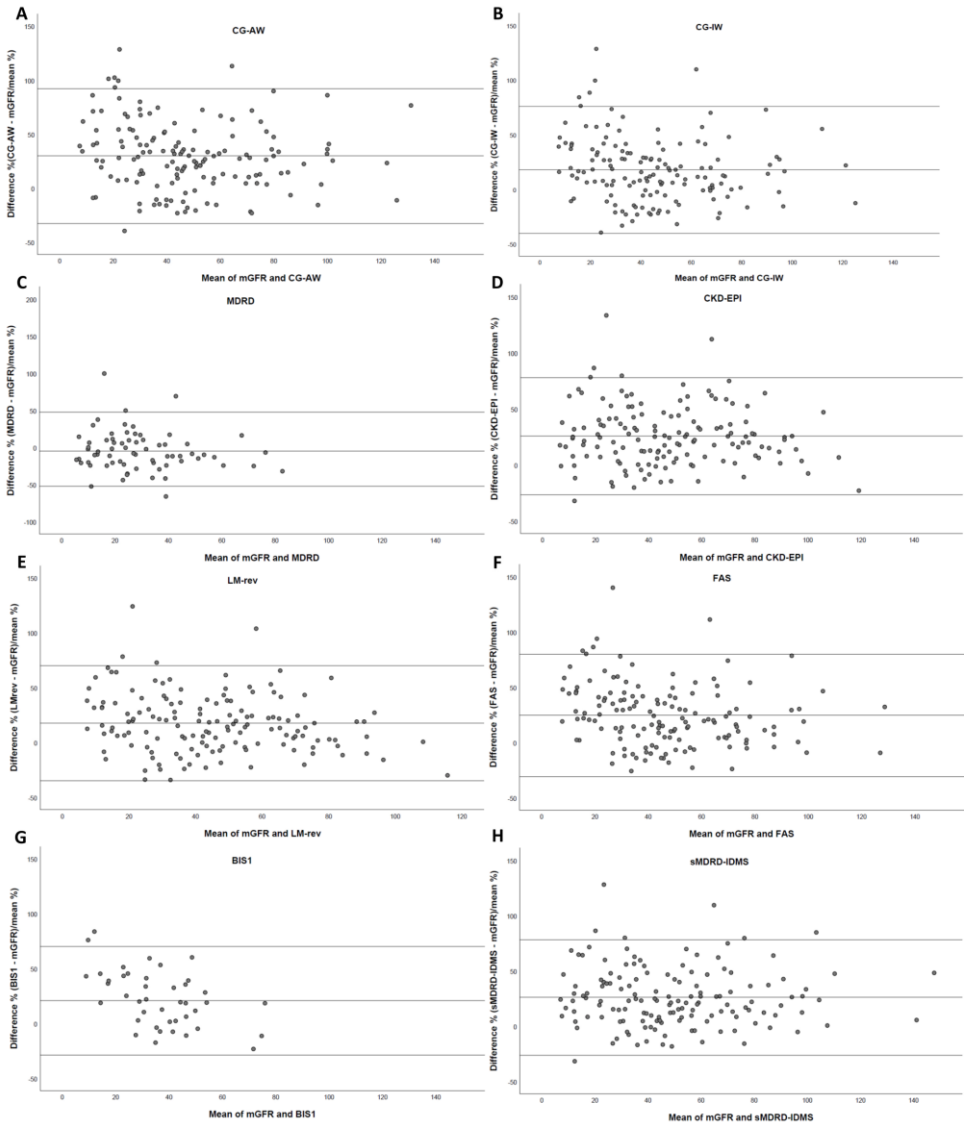


*Figure 16. Bland-Altman scatterplots of the distribution of the true $^{51}$Cr-EDTA measured GFR (mGFR) and each creatinine-based equation for eGFR. The y-axis shows the mean difference in % and the x-axis the average of the mGFR and the estimated glomerular filtration rate. The lines represent the mean difference in % and the upper and lower limits of agreement.*

## Paper III

To explore the motives, predictors and outcomes of MRAs discontinuation, a further study was conducted with 572 patients included. The group that discontinued MRAs had MRAs at index and not at follow-up, while the group that continued MRAs had MRAs at index and follow-up. There were 297 patients (52%) who discontinued MRAs during the mean follow-up time of 2 years and 3 months. However, during this relatively short follow-up time 124 patients (42%) reinitiated MRAs; but of these, 43% had another discontinuation (Figure 17).

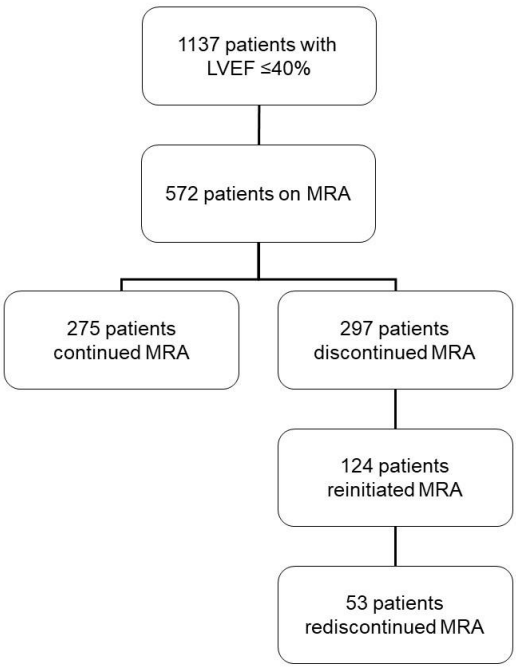


*Figure 17. Flowchart of patient's distribution in Paper III.*

The group that discontinued MRAs were more often women (36% vs 26%, p=0.008), had slightly higher age (77 ± 12 vs 72 ± 11 years, p<0.001), higher systolic blood pressure, NT-proBNP, and had a lower mean eGFR (50 ± 19 vs 59 ± 17 ml/min/1.73 $m^2$, p<0.001) compared to patients that continued MRAs. Further, patients that discontinued MRAs had a higher CCI-index (p<0.001). Notably, there was no difference between groups in treatment with ACEI/ARB/ARNI, BB or loop-diuretics (p<0.05).

The most common reasons for discontinuing MRAs were renal dysfunction (n=97, 33%), elevated S-potassium (n=71, 24%) and low blood pressure (n=56, 19%) (Figure 18).

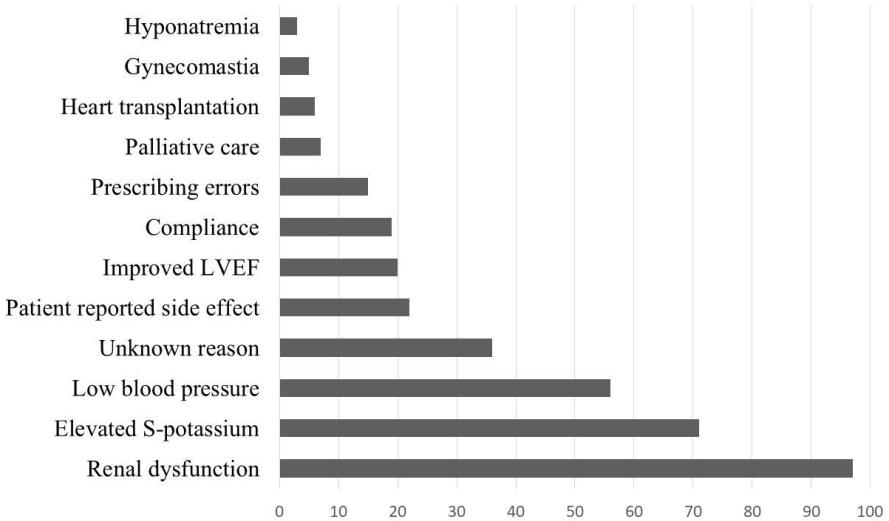


*Figure 18. Reasons for MRA discontinuation (n=297). LVEF = Left ventricular ejection fraction.*

Of the patients with renal dysfunction, 44% had eGFR ≥30 ml/min/1.73 m² when discontinuing MRAs and 98% had eGFR <60 ml/min/1.73 m². In patients with renal dysfunction as a reason for discontinuation and eGFR ≥ 30 ml/min/1.73m², 19 cases (48%) were withdrawn by a cardiologist, 12 cases (30%) by a general practitioner, and 4 cases (10%) by an internist. In comparison to the 57 (59%) patients with an eGFR <30 mL/min/1.73 m² 28 cases (49%) were withdrawn by a cardiologist, 13 cases (23%) by a general practitioner, and 12 cases (21%) by an internist.

In the group with elevated S-potassium (n = 71), 48 patients (68%) had S-potassium ≤5.5 mmol/L and 38 patients (53%) also had renal dysfunction listed as a contraindication. S-potassium >6.0 mmol/L at discontinuation was found in 10 patients (14%). Of the 23 patients with S-potassium >5.5 mmol/L at MRA withdrawal and elevated S-potassium as a reason for discontinuation, 12 cases (52%) were withdrawn by a cardiologist, 3 cases (13%) by a general practitioner, and 6 cases (26%) by an internist. In comparison to the 48 patients with S-potassium ≤5.5 mmol/L at MRA discontinuation, 14 cases (29%) were withdrawn by a cardiologist, 21 cases (44%) by a general practitioner, and 6 cases (12%) by an internist.

38 patients had both renal dysfunction and elevated s-potassium listed as reasons for discontinuation which means that 130 patients in total was listed with renal dysfunction and/or hyperkalemia. Of these 130 patients, there were 78 patients (60%) that had eGFR >30 mL/min/1.73 m2 and S-potassium ≤5.5 mmol/L.

In the group with low blood pressure, the mean systolic blood pressure at discontinuation was 97 ± 17 mmHg when the group with orthostatic hypotension was excluded.

Renal dysfunction and increased S-potassium could be identified by either the medical records or laboratory data. There were no differences between renal dysfunction identified by the medical records or by laboratory data (mean eGFR mean eGFR 30 vs 31 mL/min/1.73 m², p=0.873). Also, there were no differences if elevated S-potassium was identified by the medical records or by the laboratory data (mean S-potassium 5.4 vs 5.3 mmol/L, p=0.858).

In the multivariable logistic regression with MRA discontinuation as outcome, predictors of MRA discontinuation were increased S-potassium, lower eGFR, lower systolic blood pressure, higher LVEF, and higher CCI-index (Figure 19).

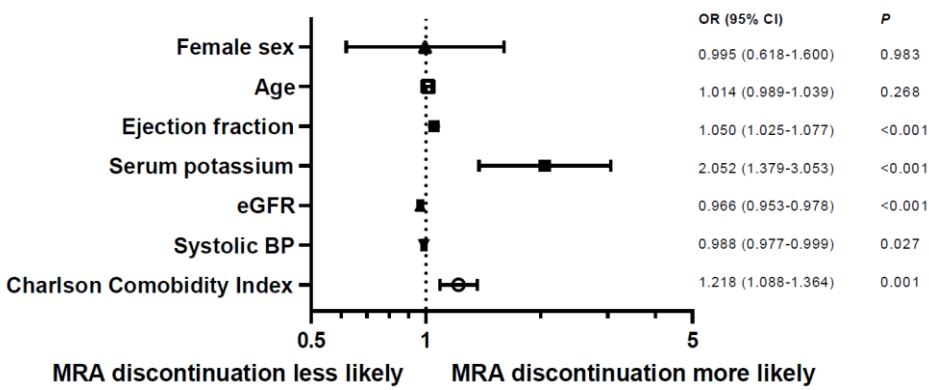


*Figure 19. Multivariable logistic regression of factors associated with MRA discontinuation including all patients (n=572). OR = odds ratio, CI = confidence interval, eGFR = estimated glomerular filtration rate, BP = blood pressure, MRA = mineralocorticoid receptor antagonist.*

When patients with guideline-directed relative contraindication of MRAs were excluded (eGFR <30 ml/min/1.73 m² or S-potassium >5.5 mmol/L), the independent predictors of MRA discontinuation that remained were higher LVEF and CCI-index (p<0.001) and elevated S-potassium (p=0.045). Lower eGFR was no longer significant (p>0.05).

Patients were followed by a mean of 2 years and 3 months. There was a total of 184 deaths, 123 (41%) in the discontinued MRA group and 61 (22%) in the continued MRA group. Patients that discontinued MRAs had a lower probability of survival (log-rank p<0.001). When adjusting for covariates, MRA discontinuation still increased the risk of all-cause mortality (HR 1.48; 95% CI, 1.07-2.05 p=0.019).

## Paper IV

Since renal dysfunction was the most common reason to discontinue MRA treatment, we wanted to further explore the consequences when MRAs are used by patients with both heart failure and renal dysfunction. Among 1137 patients with LVEF ≤40%, approximately half (48%) of all patients had moderately impaired renal function. Of these patients, 416 were included in the final analysis depending on if they had MRAs at index and follow-up (On MRA) or if they had never had MRAs (No MRA) (Figure 20).

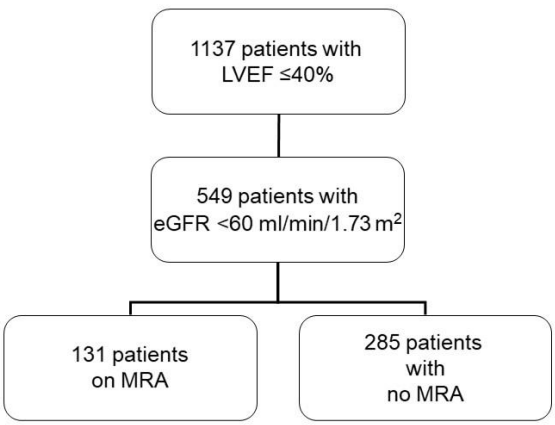


*Figure 20. Flowchart of patient distribution in paper IV.*

Median follow-up time between the two S-creatinine values was about 2 years. The No MRA group was followed 5 months longer than the On MRA group (p=0.048). Most patients had moderately impaired renal function, although more patients in the No MRAs group had severe impaired renal function. The On MRA group were younger, had a lower LVEF, and a higher index eGFR (p<0.001). Patients were equally distributed by sex, comorbidities, heart rate, blood pressure, and BMI, and there was no difference in treatment with ACEIs/ARBs or BBs (p>0.05). However, more patients in the On MRA group had treatment with loop diuretics (p=0.001) (Table 12).

*Table 12. Characteristics of patients included in Paper IV depending on MRA treatment.*

| Characteristic | On MRAs (n=131) | No MRAs (n=285) | *P* |
|---|---|---|---|
| **Females, n (%)** | 47 (36) | 101 (35) | 0.931 |
| **Age, y** | 77 ± (9) | 82 ± (9) | <0.001 |
| **EF, %** | 33 ± (9) | 35 ± (9) | 0.025 |
| **Follow-up time, days (median (IQR))** | 649 (740) | 799 (678) | 0.046 |
| **Inclusion 2010-01-01, n (%)** | 22 (17) | 71 (25) | 0.065 |
| **NT-proBNP (ng/L) (median (IQR))** | 3140 (1338-8224) | 3120 (1280-7448) | 0.683 |
| **P-haemoglobin, mmol/L** | 133 ± (20) | 128 ± (17) | 0.003 |
| **P-Sodium, mmol/L** | 140 ± (3) | 140 ± (3) | 0.344 |
| **P-Potassium, mmol/L** | 4.3 ± (0.4) | 4.3 ± (0.5) | 0.448 |
| **Index eGFR, ml/min/1.73m²** | 48 ± (9) | 41 ± (13) | <0.001 |
| **eGFR 30-59 ml/min/1.73 m², n (%)** | 127 (97) | 225 (79) | <0.001 |
| **eGFR 15-29 ml/min/1.73 m², n (%)** | 2 (2) | 51 (18) | <0.001 |
| **eGFR <15 ml/min/1.73 m², n (%)** | 2 (2) | 8 (3) | 0.273 |
| **Medications, n (%)** | | | |
| **ACEI/ARB** | 111 (85) | 229 (80) | 0.283 |
| **Beta-blocker** | 114 (87) | 226 (79) | 0.058 |
| **Loop diuretic** | 106 (92) | 189 (77) | 0.001 |
| **Thiazide diuretic** | 4 (6) | 14 (8) | 0.483 |

*MRA = mineralocorticoid receptor antagonist; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; EF = ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease. Values are means and standard deviation (SD), number (%), or median (interquartile range (IQR)) when appropriate. P values are from the X2, Student t test, Mann Whitney U-Test or Fishers exact test as appropriate*

There were 128 patients (32%) who had WRF during follow-up, with no difference between the On MRA group and the No MRA group (n=32 (25%) vs. n=83 (30%), p=0.293). WRF was more common with a longer follow-up time. Mean eGFR declined at a similar rate in both groups. Predictors of WRF were higher systolic blood pressure and previous hospitalization for heart failure. Of note, MRA use was not an independent predictor (Table 13).

*Table 13. Factors associated with Worsening Renal Function.*

| Factor | OR (95% CI) | *p* |
|---|---|---|
| **MRA treatment** | 0.81 (0.48-1.35) | 0.421 |
| **Age** | 1.02 (1.00-1.05) | 0.100 |
| **Female Sex** | 0.65 (0.41-1.03) | 0.069 |
| **eGFR index** | 1.01 (0.99-1.03) | 0.285 |
| **Diabetes** | 1.11 (0.67-1.84) | 0.673 |
| **SBT at index** | 1.01 (1.00-1.03) | <0.015 |
| **Hospitalization for HF** | 2.13 (1.34-3.39) | <0.001 |

*OR = odds ratio; CI = confidence interval; MRA = mineralocorticoid receptor antagonists; eGFR = estimated Glomerular Filtration Rate; SBT = systolic blood pressure; HF = heart failure. Worsening renal function is defined as a decline in eGFR >20% between the index and follow-up. The OR and 95% CI are adjusted logistic regressions.*

There were 221 deaths (53%), 45 (34%) in the On MRA group and 176 (62%) in the No MRA group. Patients on MRAs had a higher probability of survival, log rank p<0.001. However, the use of MRAs at index and follow-up did not have an impact on the adjusted risk of all-cause mortality (HR 0.93; 95% CI, 0.66-1.32 p=0.685). WRF was associated with increased adjusted risk of all-cause mortality (HR 1.43; 95% CI, 1.07-1.89 p=0.014) and higher index eGFR lowered the risk of all-cause mortality (HR 0.97; 95% CI 0.96-0.98; p<0.001). When only including patients with WRF, MRAs did not increase the risk of adjusted all-cause mortality.

# Discussion

## Pattern of MRA use

In Paper I, 45% of the patients with HFrEF were prescribed and maintained on MRAs. Considering the 10% without MRA treatment and no clear contraindications, together with some of the patients listed in the contraindication group with only moderate renal impairment, we estimated that about 60% of the patients with HFrEF would tolerate MRA treatment in the long-term. These results are in line with registry studies from Europe and the United States where MRA treatment varied between 33-42% (53, 110, 111, 113-115). However, it is not possible to fully compare the results from a registry study to a real-world observational study, due to possible differences in the quality of the collected data, variance in recruitment, inclusion criteria and the risk of selection bias (128). In a study similar to ours, where electronic health record was used to identify a cohort of patients with chronic HFrEF, 54% of all eligible patients received MRAs and about half of the patients had 50% or less of the target dose (129).

In Paper III, we found that 52% of all patients initiated on MRA during follow-up discontinued treatment. MRAs were reinitiated in almost half of these patients, but 43% re-discontinued treatment. MRA discontinuation was more common in our heart failure population compared to a study from the Swedish heart failure registry that included patients with LVEF <30% where only one-third of the patients discontinued MRAs, and an observational cohort study on patients with HFrEF from Sweden, United Kingdom and the United States where the discontinuation rate was 40% (113, 117). Further, in a retrospective observational study based on electronic medical records including patients with HFrEF admitted to a hospital between 2011-2013, the discontinuation rate was 33% by a median follow-up of 3 years (130). The higher discontinuation rate in our study compared to other studies is likely due to differences in inclusion criteria, methodology, and in follow-up time.

## Why are patients with HFrEF not treated with MRAs?

### *Renal impairment*

In Paper I, the main contraindications for non-prescription of MRAs were renal dysfunction, hyperkalemia and hypotension. Similar reasons for non-prescription of MRAs in eligible patients with HFrEF were found in the previously mentioned electronic health record based study (129). Of those with renal dysfunction as a contraindication to MRAs, 51 patients only had mild-moderate

renal impairment and no other contraindication. With the exception of six patients, all patients with hyperkalemia had renal impairment. This means that three out of four of all patients with hyperkalemia also had renal dysfunction as a reason for non-prescription of MRAs. Since patients with both moderately impaired renal function and mild to moderate hyperkalemia require more surveillance and laboratory monitoring, these results may imply that patients at a higher risk of developing serious hyperkalemia or WRF are denied treatment. Our findings are in line with a study from the Swedish Heart Failure Registry where moderately impaired renal function (eGFR <60 ml/min/1.73 $m^2$) was one of the independent factors for non-use of MRAs (53).

In Paper III, we found that one of the most common reason for discontinuing MRAs was renal dysfunction but 42% of patients only had moderately impaired renal function at discontinuation. Despite that some of those patients also were listed with hyperkalemia as a contraindication, only three patients had S-potassium >5.5 mmol/L. In addition, decreased eGFR was an independent predictor of MRA discontinuation when adjusting for other clinically relevant factors. These results are consistent with the previously mentioned multinational observational cohort study and with data from the CHAMP-HF where patients with CKD were found to have a higher discontinuation rate for all guideline-directed medical therapies for heart failure including MRAs, compared to patients without CKD (117, 131).

Due to these results, we wanted to investigate the outcome for MRA treatment in patients with at least moderately impaired renal function and HFrEF. In our HFrEF population, 48% had at least moderately impaired renal function (eGFR <60 ml/min/1.73 $m^2$), which is consistent with previously reported rates of moderately impaired renal function in patients with HFrEF (52, 100). A consideration with the RAAS-I treatment in patients with moderately impaired renal function is increased risk of WRF, which is associated with increased mortality in patients with HFrEF (52, 94, 132). In Paper IV where we only included patients with HFrEF and impaired renal function, the group with MRA treatment, compared to the group without MRA treatment, had no increased frequency of WRF and no difference in decline in eGFR during the follow-up time of 2 years. In post-hoc analysis of the landmark MRA trials, MRAs were shown to increase the risk of WRF but the overall benefit of MRAs was present despite development of WRF (95-97). In Paper IV, MRA treatment did not have an impact on survival when adjusting for covariates while WRF increased the risk of all-cause mortality. In comparing our study to the post-hoc analysis of the landmark MRA trials, we had a smaller population but with a higher mean age, larger number of comorbidities and an overall higher background rate of WRF, which might explain why we failed to see a difference by MRA treatment on WRF or survival. Furthermore, we only had follow-up values from one point in time,

which might have caused us to miss cases where S-creatinine was increased between follow-ups and a total of 12 patients was loss during follow-up. On the other hand, another possible explanation is that there was no actual difference in WRF or survival depending on MRA treatment in the relatively short time of follow-up.

***Hyperkalemia***

In Paper III, one-fourth of the patients discontinued MRAs due to hyperkalemia, but only one-third had at least moderate hyperkalemia (S-potassium >5.5 mmol/L). Of these, 3 % had serious hyperkalemia (S-potassium >6.0 mmol/L) that compares with an incidence of 1.5%-5% in the landmark MRA trials (38-40). Half of the patients with elevated S-potassium also had renal dysfunction as a reason for discontinuation. Increased levels of S-potassium and decreased eGFR were independent predictors of MRA discontinuation in our study, after adjusting for age, sex, blood pressure, ejection fraction and CCI. Discontinuation of MRAs due do the combination of lower kidney function and hyperkalemia has been seen elsewhere (93, 133). Moderate hyperkalemia in combination with higher age and renal dysfunction is associated with increased risk of serious hyperkalemia (133). In a Swedish observational study including patients initiated on MRAs between 2007-2010 with a median time on treatment of 12 months, 11% of the heart failure patients that discontinued MRAs had at least one event of moderate hyperkalemia (S-potassium >5.5 mmol/L) (93). Further, results from a Danish population-based cohort study that included patients with first-time hospitalization for heart failure between 2000-2012, showed that the risk of hyperkalemia (S-potassium >5.0 mmol/L) was 25% during the first year and 32% 3 years after heart failure diagnosis with an association between hyperkalemia, decreasing eGFR values and use of spironolactone (134).

When all patient with guideline-directed contraindications were excluded, reduced renal function was no longer an independent predictor of MRA discontinuation but increased S-potassium remained as an independent predictor. We made the interpretation that slightly elevated S-potassium levels are more decisive for MRA discontinuation in clinical practice than decreased eGFR. Dyskalaemia in heart failure is a complex issue and the relationship between s-potassium levels and adverse outcomes appears to be U-shaped where both low S-potassium levels and high S-potassium levels are associated with adverse outcomes (135, 136). Hypokalaemia (S-potassium <3.5 mmol/L) has a 1-year incidence of 20% in heart failure and are associated with excess morbidity and mortality in patients with heart failure including the risk of life-threatening ventricular arrhythmias (137). Hyperkalemia (S-potassium >5.5 mmol/L) is also associated with life-threatening arrhythmias and deaths (134, 138). In the previously mentioned study from Denmark, patients with heart failure and

hyperkalemia, compared with matched patients with heart failure without hyperkalemia, had an increased adjusted 6-month risk of mortality (134). A subject of debate is whether the association between hyperkalemia and increased mortality in heart failure is due to the discontinuation of RAAS-I or the hyperkalemia itself. In a subgroup analysis of the BIOSTAT-CHF, hypo- and hyperkalemia at baseline and changes in S-potassium levels during uptitration of ACEIs/ARBs were not associated with worse outcome, but higher S-potassium at baseline was an independent predictor of lower ACEIs/ARBs use (139). In a study from the previously mentioned ESC-HF-LT registry, both hypokalaemia and hyperkalemia were associated with adverse outcomes, but after adjusting for discontinuation of RAAS-I, hyperkalemia was no longer associated with all-cause mortality but RAAS-I discontinuation was strongly associated with increased all-cause mortality (140). These results are in line with the results from Paper III where we showed that MRA discontinuation increased the adjusted risk of all-cause mortality but not S-potassium levels. These findings may imply that hyperkalemia can impact clinical outcomes directly but is also a risk factor for underuse and discontinuation of RAAS-I which in turn increases the risk of adverse outcomes.

In conclusion, by scrutinizing the medical records of patients with HFrEF, we showed that renal dysfunction and mild to moderate hyperkalemia are major contributing factors to the underuse of MRAs. Physicians seem to be more cautious about mild to moderate hyperkalemia than to moderate renal impairment when it comes to discontinuing MRAs, and our results imply that the combination of moderate renal dysfunction and mild hyperkalemia increases the risk of MRA discontinuation.

***Blood pressure***

Another common cause of non-prescription and discontinuation of MRAs was low blood pressure and orthostatic hypotension. In the RALES trial, there was no difference in blood pressure between the groups, and in the EMPHASIS-HF and EPHASUS trial, blood pressure decreased more in the MRA group compared to placebo but with small changes (38-40). Nevertheless, in our study, we found that low blood pressure and orthostatic hypotension were common limiting factors for MRA treatment in clinical practice. Hypotension in heart failure depends on dynamically changing clinical variables, whereas the interpretation of the cause of the low blood pressure depends on the clinical context, for example, acute or chronic settings. In our study, we included a mixture of patients hospitalized for heart failure as well as ambulatory patients. Hence, the clinical context of MRA discontinuation or non-prescription due to hypotension could vary substantially. The reasons for low blood pressure in ambulatory heart failure patients can range from reduced stroke volume due to impaired LVEF, hypovolemia due to diuretics,

and treatment related vasodilation (141). In addition, there is no strong consensus regarding how to define severe hypotension. In the majority of the clinical trials on medical treatment in HFrEF, it was the clinical judgement rather than a pre-defined blood pressure threshold that was used to characterize hypotension. In a review of management of low blood pressure in ambulatory patients with HFrEF, it was stated that MRAs exert the least hypotensive effect of all guideline-directed medical therapy (i.e., ACEIs, ARBs, BBs, ARNI, SGLT2), while exhibiting advantageous effects on mortality (141). Hence, it was recommended that dose reduction or discontinuation of MRAs should be considered as a last resort in cases with hypotension. In patients with acute heart failure, low blood pressure (systolic blood pressure <90 mmHg) was associated with increased mortality (142). In the Meta-Analysis Global Group in Chronic (MAGGIC) Heart failure Risk Score, lower systolic blood pressure was a significant independent predictor of mortality in patients with HFrEF (143). However, it is not possible to determine if this correlation between low systolic blood pressure and outcome represents an actual causation. There is an absence of real-life data on the clinical outcomes of low blood pressure in elderly ambulatory patients with chronic heart failure with a representative comorbidity burden. Despite this, hypotension is a common dilemma in clinical practice with no present management recommendation (3). However, it has been suggested that there are many steps to perform that include confirming the linkage between symptoms of suggestive hypotension and measured low blood pressure, adjusting the dose of loop diuretics, and other HFrEF treatments (ACEIs/ARBs, BBs, ARNI), before decreasing or, as a last step, discontinuing MRA treatment (141).

***Gap between guidelines and clinical challenges***

In Paper I, the 10% of the patients without MRAs and no clear contraindication had less hospitalization for heart failure and only one-third had a follow-up at the cardiology clinic. Further, these patients had a higher age, less treatment with ACEIs/ARBs and BBs, higher LVEF, less use of CRT and higher systolic blood pressure compared to patients with MRAs; these results are similar to the previously mentioned study from the Swedish Heart Failure Registry. We concluded that these patients might have a more inactive heart failure and therefore went unnoticed. Hence, it seems like these patients with heart failure may often be overlooked, which implies that we need better methods for identifying patients in need for treatment. In cases of non-prescription, 29 patients had normalized LVEF as a reason for non-prescription. It is likely that these patients no longer had indication for MRAs after initiation of RAAS-I and BBs, which is correct according to the former guidelines (12). However, it is doubtful if MRAs should be discontinued due to improved LVEF. In the Therapy withdrawal in Recovered Dilated cardiomyopathy—Heart Failure (TRED-HF) trial, withdrawal of RAAS-I, BBs and MRAs in asymptomatic patients with

improvement from LVEF 40% to over 50% resulted in a substantial reduction of LVEF and worsening symptoms within 8 weeks from withdrawal (144). This study suggests that improvement of LVEF under medical treatment rather reflects remission than recovery. In the recent consensus document for definition and classification of heart failure, a new class of heart failure was suggested – heart failure with improved EF, where it is recommended that these patients should not be classified as HFmrEF or HFpEF since discontinuation of guideline-directed medical therapy in this group of patient leads to poor outcome (1).

The lower use of ACEIs/ARBs and BBs could be a partial explanation as to why patients did not receive treatment with MRAs. Further, we showed that patients without MRAs received a lower percentage of target dose of ACEIs/ARBs and BBs, compared to patients on MRAs. When Paper I was conducted, guidelines stated that patients should reach target dose or maximum tolerated doses of ACEIs/ARBs and BBs before initiating MRAs (12, 13). These guidelines were unclear as to whether to prioritize dose increasement before adding another drug to the list (3, 12, 13). In a subgroup analysis of the EMPHASIS-HF study, there was still a survival benefit with MRAs despite not receiving maximum doses of ACEIs/ARBs and/or BBs (145). However, if the patient experience side effects such as WRF, hypotension or hyperkalemia, the guidelines do not clearly express which medicines to dose-adjust or discontinue; this could cause uncertainty for the treating physician in how to deal with these common side effects.

It seems like inadequate means of follow-up further contribute to the underuse of MRAs. Several observational studies in real-world settings have reported a low adherence to guideline-directed follow-up and laboratory monitoring after MRA initiation (99, 144). In a mix-method study with clinicians at a medical centre in United States, barriers to MRA use were identified from three general sources (146). These sources were patient-based barriers (concerns for risks of drug interaction due to polypharmacy, adverse effects in fragile patients with other comorbidities, non-adherence to regular follow-up, risk of WRF and hyperkalemia), provider-based barriers (unclear provider roles and responsibilities, coordination, follow-up gaps in transition of care giver, lack of familiarity or experience with MRAs amongst non-cardiologists), and system-based barriers (system overload, time constrains, lack of systematic follow-up). This study strengthens our results in paper III where we saw that MRA discontinuation according to guidelines were more commonly performed by cardiologists compared to non-cardiologists, especially when MRAs were discontinued due to elevated S-potassium.

In conclusion, our findings imply that the clinicians have to weigh the risk and benefits of initiating and continuing MRA treatment on an individual basis and

that the frailest patients at risk for WRF or worsening hyperkalemia are denied treatment due to uncertainties about safe use due to inadequate follow-up.

## Accurate estimation of renal function in patients with heart failure

In paper II, we evaluated eight different S-creatinine-based equations for eGFR in the wide range of patients with heart failure, including HFrEF, HFmrEF and HFpEF. Of the exclusively S-creatinine based equations, none of the equations met all criteria of accuracy, precision and a non-significant McNemar test. This result was consistent within subgroup analyses based on LVEF. All exclusively S-creatinine based equations overestimated eGFR compared to mGFR. LM-rev showed the highest precision, lowest mean difference, and highest accuracy of the exclusively S-creatinine-based equations. We argue that this could be due to that the LM-rev equation was developed on a Swedish population with an age (mean 66 years) and mGFR (mean value 55 ml/min/1.73 $m^2$) that were more similar to the demographic characteristics of our study group compared to, for example, CKD-EPI in which patients had a lower age (mean 47 years) and a higher mGFR (mean 68 ml/min/1.73 $m^2$) (119, 124). In our study, CG-IW showed nearly as good values in agreement with the LM-rev. The use of ideal weight instead of actual weight seems more suitable in patients with heart failure since fluid retention is a source of falsely high actual weight (147). CKD-EPI is a commonly used equation but showed very low accuracy and a substantial overestimation in our study.

The MDRD equation also required analysis of S-albumin and S-urea and the BIS1 equation only included patients 70 years or older, which is why only about half of the study populations were included in those equations. The MDRD equation was the only equation to meet all criteria of accuracy, precision, and a non-significant McNemar test. Further, it showed a low bias and was the only equation to slightly underestimate eGFR. An important consideration is that the mean value of eGFR was 28 ml/min/1.73 $m^2$ since S-albumin and S-urea were mainly available in patients with at least moderately impaired renal function. It is possible that the use of S-albumin and S-urea corrected for falsely low S-creatinine in these patients. However, the results from the MDRD equations are less generalizable due to the highly selected and low number of patients.

To our knowledge, LM-rev, BIS1, the full age spectrum equation (FAS) and the simplified MDRD corrected for IDMS (sMDRD-IDMS) have not been previously externally validated in patients with heart failure (100, 148-151). The agreement of CKD-EPI, MDRD and the Cockcroft-Gault's actual weight (CG-AW) was previously compared in a study based on patients in the Swedish heart failure registry; the results showed considerable disagreement between the three

equations in up to 50% of the patients and that the choice of an equation had a major impact on which patients were categorized to a level of renal function where medication dose adjustment was recommended (100). In another study on 45 patients with heart failure referred for heart failure transplantation, $^{51}$Cr-EDTA was compared with MDRD, simplified MDRD and CG-AW and CG-IW (148). CG-AW systematically overestimated eGFR while the use of CG-IW completely abolished the bias observed in the CG-AW equation. MDRD had the lowest bias, mean difference and highest precision. These results are in general consistent with the results from our study despite considering the lower age and severity of heart failure of the study population compared to ours. However, the patients in the study had a similar mGFR to the patients in our study, and mGFR was measured with the same method, which might explain the comparable results. In another study, 120 patients with chronic heart failure and LVEF $\leq$45% underwent 125I-iothalamate clearance measurement between 2003 and 2010 (150). mGFR was compared with eGFR estimated by sMDRD, CKD-EPI, CG and two cystatin C-based equations. In line with the results from our study, both CKD-EPI and sMDRD overestimated eGFR at lower levels of mGFR. Of the creatinine-based equations, CKD-EPI outperformed sMDRD and CG, as CG had the worst performance among the creatinine-based equations. However, the cystatin C-based equation had lower bias and greater accuracy and precision than all creatinine-based equations.

In our study, the McNemar test was significant for all exclusively creatinine-based equations, which implies that a significant number of patients were falsely categorized into eGFR over 30 ml/min/1.73 m$^2$ when the mGFR showed an actual value under 30 ml/min/1.73 m$^2$. This finding suggests that the choice of equation has an impact on dose initiation and dose adjustment since the RAAS-I treatment in heart failure requires eGFR $\geq$30 ml/min/1.73 m$^2$ for dose initiation and lower eGFR values should entail dose adjustments or discontinuation of treatment (3). Major clinical trials on medical treatment for heart failure have used a wide range of different equations for eGFR as well as fixed cut-off S-creatinine levels (38-40, 107, 152). Considering the results of our study and previous studies, the choice of equation for estimating renal function has clinical implications in the medical treatment for patients with heart failure, especially in patients with moderately impaired renal function since their renal function is closer to these cut-off levels (100, 150).

In conclusion, none of the exclusively creatinine-based equations were accurate in predicting mGFR in Paper II. An important consideration is that mGFR was only available in patients where a clinical decision had been made to measure GFR. Only 3% of the total heart failure population was included; however, the study group showed similar characteristics as the whole heart failure population except for a lower mean age, higher median S-creatinine, and higher frequency of

diabetes. The mean mGFR of 42 ml/min/1.73 $m^2$ limits the generalization to patients with both heart failure and at least moderately impaired renal function. Further, in a selected group of patients with heart failure and moderately to severely impaired renal function, MDRD showed accurate values, which have been proved previously (148). Since muscle mass is the most important determinant of creatinine generation, it is possible that the overestimation of eGFR in patients with heart failure is caused by low S-creatinine levels due to cardiac cachexia and sarcopenia, which was previously demonstrated with a prevalence of 20% in patients with chronic heart failure (153). A drawback of our study was that Cystatin C was only available in eight patients, which is why no further analysis with Cystatin C-based equations was possible. Cystatin C based equations, instead of S-creatinine-based equations, were previously proved to estimate GFR more accurately in patients with heart failure since Cystatin C has been thought to be less affected by muscle mass than S-creatinine (150). In a recent study comparing CKD-EPI equations based either on Cystatin C or S-creatinine with measured creatinine clearance in patients with decompensated heart failure, Cystatin-C based eGFR indeed was unbiased compared to S-creatinine based eGFR, but there were no differences in accuracy and precision (154). Of note, Cystatin C and S-creatinine were both associated with muscle mass although the magnitude of the association with Cystatin C was lower than with S-creatinine. This strengthens the argument that directed measurements of GFR or at least confirmatory test by Cystatin C-based or Cystatin C and S-creatinine based eGFR should be performed in clinical situations where highly accurate GFR is needed (59).

## Methodological considerations

An important question is whether the patients in the heart failure population can be considered a community-based heart failure population. By including all patients with heart failure that lived within the primary catchment area of Umeå University Hospital, Sweden, our attempt was to gather an unselected community-based heart failure population. However, to confirm reliability, we only included patients that were diagnosed with heart failure at the Heart Centre or Department of Internal Medicine. In Paper I, we consistently used the term community-based heart failure population. In papers II-IV, we excluded the term community-based since we realized that not including patients in primary care might have led to that we missed a number of patients with heart failure. To our current knowledge, it is not possible to find out the exact number of patients that were only treated within the primary care between 2010 and 2018. We are planning to perform a study to investigate the primary care heart failure population in further detail. Nevertheless, in 2016, the heart failure prevalence in our population was 2.3%, which is in line with epidemiological data from 2015

from Uppsala and Västerbotten in Sweden, that showed a heart failure prevalence of 2.2% (5).

This thesis is based entirely on medical records reviews. Due to the retrospective observational study design, it is not possible to establish a cause-effect relationships, however, we could still compare differences between groups (155). Therefore, in cases where no difference was found between groups, there was an inherent risk of a type II error. However, we would not have been able to increase the sample size since we used all medical information at our disposal. Since this is a single-centre population, it limits the external validity and generalizability. Nevertheless, it seems like our heart failure population resemblances previously described real-world patients with heart failure. The mean age of our total heart failure population was 81 years and 75 years for patients with HFrEF, whereas the mean age of the registry studies were 65-73 years. Of the patients with HFrEF in our database, 31% were females that compares to 24%-29% in the registry studies (53, 112, 114).

An important consideration with medical record-based research is that the data abstractors must code the medical records accurately and consistently. We used a standardized abstraction form that provided information in detail on how to gather and code each variable. Furthermore, the validity assessment showed a high agreement with the collected data. Since we were restricted to data that already was documented, some data were missing; for example, information on NYHA class was not available.

An important notation is that the guidelines for MRA treatment in patients with HFrEF have not changed over the past decade. MRAs are recommended in all patients with chronic HFrEF with NYHA II-IV and LVEF $\leq$35% in ESC guidelines from 2012 and 2016 (3, 12, 156). In the ACCF/AHA guidelines for the management of heart failure from 2013, MRAs are recommended in all Stage C (structural heart disease and symptoms of heart failure) patients with HFrEF with NYHA II-IV and LVEF $\leq$35%, or after an acute myocardial infarction in patients with LVEF $\leq$40% (13). The Swedish National board of Health and Welfare recommend MRAs in all patients with NYHA II-IV and LVEF $\leq$35%, and recommend Eplerenone to patients with HFrEF (LVEF $\leq$40%) after myocardial infarction (157). We chose to set the inclusion of LVEF at $\leq$40% since a portion of the patients with HFrEF are recommended MRAs at LVEF $\leq$40%. For the group with no clear contraindication to MRAs in Paper I, we were not able to further analyse which of the 28 patients with LVEF 36-40% would have met the specific criteria of heart failure post myocardial infarction. However, 14 of these 28 patients (50%) with LVEF 36-40% had a history of coronary artery disease, although, we could not determine time-relationships between the events due to the study design.

At our centre, it was common that patients started on MRAs before a new echocardiography was performed. To follow ESC guidelines from 2016 and 2012 correctly, a new echocardiography and clinical evaluation should be done after up titration of RAAS-I and BBs and before initiating MRA treatment (12, 156). It is possible that this practice may have led us to overestimate the number of patients eligible for MRAs. We did not assess the inappropriate use of MRAs, but a previous study has described infrequent rates of inappropriate use; in an observational analysis of patients from Get With The Guidelines-Heart failure quality improvement registry from 2005-2007, only 3% of the patients receiving a MRA met at least one criteria for inappropriate use (110).

In Paper III, we used direct content analysis (125). In contrast to conventional content analysis, which is designed to be used when existing theory or research is limited, direct content analysis is used to validate or extend existing theory or prior research. We presented our results by frequency of codes. Of note, codes that were similar were put together into one new code before presenting the results. Renal dysfunction and hyperkalemia could be identify either by texts or lab results and were given different codes depending on the method. Comparative statistics between the two codes of renal dysfunction and hyperkalemia showed no differences depending on which method was used. The drawbacks of predefined codes are the risk of mainly finding evidence that supports the already existing theory; this we tried to avoid by being open to define new codes during the reading process. However, it is unavoidable not to be biased when looking for reasons for discontinuations since all researchers were aware of prior research and guidelines in the field; this is another reason why we used direct content analysis where the bias is informed. In Paper I, the codes were defined after the medical records were read and text passages were highlighted, which is a method more similar to conventional content analysis. Further, in Paper I, the Cockcroft-Gault equation was used to calculate creatinine clearance; this is one of the most commonly used equations and was used in the EPHESUS trial (40, 63, 120). However, in Paper II, we showed that the revised Lund-Malmö (LM-rev) equations were the most accurate to be used in patients with heart failure, which is why we used the LM-rev equation to calculate eGFR in Papers III-IV.

## Future perspectives

Since renal dysfunction and hyperkalemia are the most common causes of underuse of MRAs, the use of potassium-lowering agents may allow further use of MRAs and other RAAS-Is. Although there are several treatment strategies for acute hyperkalemia, until recently, sodium polystyrene sulfonate in addition to reduced doses of RAAS-I, dietary potassium restriction and the administration of loop diuretics have been the only available options to reduce the risk of chronic hyperkalemia (158). Sodium polystyrene sulfonate has several side effects that

include gastrointestinal toxicity. Novel potassium binders have been approved to mitigate the risk of hyperkalemia. Patiromer and sodium zirconium cyclosilicate binds potassium in the gastrointestinal tract in exchange with calcium or hydrogen and sodium, respectively, and are better tolerated than sodium polystyrene sulfonate. In The Evaluation of RLY5016 in Heart failure patients (PEARL-HF) trial that included patients with heart failure and CKD with a history of hyperkalemia or discontinuation of RAAS-I, patiromer compared to placebo lowered potassium levels, reduced the development of hyperkalemia and caused more patients to tolerate maximum doses of spironolactone (159). In patients with hyperkalemia at baseline, sodium zirconium cyclosilicate has proved to cause a significant reduction in S-potassium at 48 hours in patients with hyperkalemia and to maintain normokalaemia during 12 days of maintenance therapy (160). Further, other trials in people with diabetes and kidney disease have shown that patiromer reduced hyperkalemia and resulted in a higher number remaining on spironolactone when used in patients with CKD and hypertension (161, 162). The Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASI Medications for the Treatment of Heart Failure (DIAMOND) is ongoing and is testing the impact on clinical outcomes of a strategy with patiromer administration versus placebo in patients with HFrEF who have hyperkalemia on RAAS-I or history of hyperkalemia with subsequent reduction or discontinuation of RAAS-I (3, 158). In conclusion, increased utilization of potassium sparing agents is likely to increase the use of ACEIs/ARBs and MRAs in heart failure patients with impaired renal function (158). Today, the recently updated ESC guidelines for heart failure recommend use of potassium lower agents in patients with chronic or recurrent hyperkalemia on RAAS-I therapy (3).

A suggested new treatment for cardiorenal disease is nonsteroidal MRAs. Compared to steroidal MRAs (i.e., spironolactone and eplerenone), which concentrates preferably to the kidney, the nonsteroidal MRAs was shown to have a more balanced distribution between the heart and kidney (74). Nonsteroidal MRAs, in particular finerenone, were suggested to have a higher potency than eplerenone and better selectivity for MR than spironolactone. Finerenone has another mechanism of action than steroid MRAs; it has been suggested to offer a more pronounced anti-fibrotic efficacy in animal models. In addition, it has no active metabolites compared to spironolactone and has a shorter half-life. These properties have been suggested as beneficial in patients with kidney failure, partly due to more potent anti-inflammatory and anti-fibrotic effects on the kidney as well as less effect on S-potassium and a more rapidly recovery from hyperkalemia than steroidal MRAs. In the Phase II ARTS programme, the safety of finerenone compared to placebo or spironolactone in patients with HFrEF and mild to moderate CKD was evaluated and the results showed that the mean increase in S-potassium and decreases of eGFR and systolic blood pressure were smaller in

the finerenone group compared to the spironolactone group. WRF was reported in 38% of the patients receiving spironolactone but the frequency of WRF in the finerenone group were comparable to placebo (163). In the Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease (FIDELIO-DKD) trial, the composite primary outcome of kidney failure (defined as >40% decrease in eGFR) or death from renal causes was assessed in patients with CKD and type 2 diabetes, and showed a lower risk of the primary outcome in the finerenone group (HR 0.82; 95% CI 0.73-0.93; p=0.001) (164). The Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes (FIGARO-DKD) trial that included patients with CKD (eGFR 25-90 ml/min/1.73 $m^2$) and type 2 diabetes treated with RAASIs, showed a reduced risk of the primary outcome of a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke or hospitalization for heart failure (HR 0.87; 95% CI 0.76-0.98; p=0.03) where the benefit was driven by reduced incidence of hospitalization for heart failure (HR 0.71; 95% CI 0.56-0.90), despite the exclusion of patients with symptomatic HFrEF at baseline (165). Further, in the ongoing FINEARTS-HF study, the effect of finerenone compared to placebo is being evaluated in patients with heart failure and LVEF >40%, with the composite primary outcome of number of cardiovascular deaths and heart failure events. In conclusion, the role of nonsteroid MRAs in heart failure is yet to be established, but previous trials exert promising results in the particular subgroup of patients with heart failure and CKD who have a higher risk of side effects including hyperkalemia on steroid MRAs.

Both nonsteroid MRAs as well as novel potassium binders might be an improvement for the medical treatment of the subgroup of patients with heart failure and reduced renal function that suffer an increased risk of potentially serious side effects such as hyperkalemia and WRF. Nevertheless, improved medical treatment in this subgroup might not be comparable to closing the gap between the existing guideline-directed treatment with steroid MRAs. In a previous systematic review, studies were reviewed on implementation interventions to improve guideline-directed medical therapy in heart failure. Electronic medical system intervention was associated with significant improvements in the prescription of heart failure medicines, followed by the use of clinical pathways and multifaceted intervention (166). Clinical multidisciplinary teams with clear predefined responsibilities were effective for optimizing dose titration to target dose. However, very few studies have shown results in clinical outcomes. It was suggested that more studies on implementation interventions are needed that not only examine the process outcomes, but also the clinical outcomes.

In conclusion, regardless of the results of large RCTs, the clinical outcomes for heart failure treatment depends on the prescription of appropriate medications,

the patient's adherence to these medications, and the follow-up care. Therefore, more research is needed on how to optimize the implementation of MRAs in clinical-practice and how to improve the follow-up care in order to optimize treatment and clinical outcome in this fragile group of patients.

# Conclusions

Based on data from medical records, we studied a real-world population of patients with heart failure. The included patients with heart failure had a high mean age and an abundant number of comorbidities that included hypertension, CKD, coronary artery disease and diabetes. Hence, this real-world heart failure population is a fragile group of elderly patients with a life-threatening clinical syndrome, caused by a heterogeneous variety of diseases. We estimated that about 60% of the patients with HFrEF would tolerate MRA treatment in the long-term, but only about 45% of the patients with HFrEF in our population were prescribed and maintained on MRAs. About half of all patients discontinued MRA and we found that the most common reasons were renal dysfunction and hyperkalemia, although a majority of those did not have guideline-directed contraindications. Elderly patients without hospitalization for heart failure and without follow-up at a cardiology clinic were more often without MRA treatment. We suggest that the risk of inadequate means of follow-up restrains optimal use of MRAs, especially in patients with moderately impaired renal function and or mild hyperkalemia that require frequent and regular laboratory monitoring to assure the safe use of MRA.

Nearly half of all patients with HFrEF had at least moderately impaired renal function; however, the use of MRAs did not increase the risk of WRF and about one-third of all patients developed WRF independent of treatment with MRAs. With a mean follow up of just over 2 years, our results imply that MRA discontinuation increases the adjusted risk of all-cause mortality. Estimating renal function by eGFR is an important factor in the management of the medical treatment in heart failure. We found that none of the exclusively creatinine-based methods were accurate in predicting eGFR in our heart failure population. This suggests that more accurate methods are needed for determining eGFR in patients with heart failure as this can have an impact on the risk of not receiving optimal medical therapy.

Our findings provide explanations to the gap between guideline-directed use of MRAs and real-world practice. More research is needed on implementation intervention in order to improve the prescription of appropriate medications, the patient's adherence to these medications, and the follow-up care in patients with heart failure.

# Acknowledgements

Jag vill ta tillfället i akt att tacka alla de personer som gjort den här avhandlingen möjlig:

**Krister Lindmark**, huvudhandledare, som gett mig förtroendet att ge mig av på den här resan. Tack för din vägledning, kunskap och positiva förhållningssätt som gjort avhandlingen möjlig. Jag uppskattar din uppmuntran, tillgänglighet och lösningsorientering.

**Helena Norberg**, bihandledare, för att du hjälpt mig att navigera rätt på min forskarutbildningsresa. Ditt stöd, noggranna granskningar och bidrag till arbetet har varit helt avgörande.

**Ellinor Bergdahl** och **Fredrik Valham**, bihandledare, för era kloka kommentarer, bidrag och kritiska granskningar av manuskripten.

Mina medförfattare, **Andreas Jonsson**, **Ida Viklund**, **Gustav Wessberg** och **Adrian Söderström**, för ert bidrag kring studieupplägg, diskussion av resultat och för ert arbete med insamling och sammanställning av journaldata.

**Robert Lundqvist**, statistiker vid Region Norrbotten, för att du på ditt pedagogiska sätt gett mig fördjupad förståelse kring statistiska frågor och praktiskt handhavande av statistikverktyg. Jag uppskattar ditt reflekterande förhållningssätt och våra vetenskapliga diskussioner.

**Ulrika Viklund,** forskningssjuksköterska, för ditt utförliga arbete med att samla in all journaldata till databasen men också för trevligt resesällskap.

Till **”sommarstudenterna”** som ytterligare bidragit till insamling av journaldata.

**Region Norrbotten**, som gett mig medel och forskningstid. Särskilt tack till **Malin Bergenstråle**, AT-samordnare, för ditt tålamod med mina ständiga schemaändringar och din problemlösningsförmåga.

**Ylva Stenberg**, doktorandkollega, för alla skratt längst vägen och trevligt arbetssällskap.

Till **”De löpande tikarna”** för ett svagt deltagande i ett motionslopp för många år sedan men ett desto starkare band och stöttning av varandra på vår väg genom livet och karriären sedan dess.

Slutligen ett stort tack till min familj. Mina föräldrar, **Lena** och **Lasse**, för att ni gett mig modet att våga mig ut på okända vägar i livet. Er hjälp då vardagen inte riktigt har gått ihop har varit ovärderlig. Till mina svärföräldrar, **Solveig** och **Urban**, för all er stöttning och hjälp de senaste händelserika åren.

Till min man, **Viktor**. Vi har en total oförmåga att inte göra allting tillsammans och jag skulle inte vilja ha det på något annat sätt. Tack för ditt tålamod, förståelse, stöd, uppmuntran och kärlek.

Till mina barn, **Axel** och **Nils**, som precis börjat era egna resor ut i livet. Ni ger mening till mödan på vår färd.

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