1 Introduction and aims
INTRODUCTION

Over the last years, the prevalence of heart failure has been slowly increasing due to improved treatment of chronic heart failure and its underlying causes and an aging population. The mortality and morbidity associated with heart failure however remain higher than most forms of cancer, and especially after a hospitalization for acute heart failure, up to 40% of patients has either died or is rehospitalized within 6 months.1,2 The period after discharge for an acute heart failure hospitalization is an extremely vulnerable phase and the risk for early death or heart failure readmission is extremely high in this period. Despite recent advances in our ability to predict risk of mortality in heart failure, this is not the case for heart failure rehospitalization and the underlying cause of high readmission rates is still incompletely understood. This is a great problem, which places a major strain on our health care system.3 One of the commonly suggested causes of these high rehospitalization rates is incomplete decongestion at discharge after an admission for acute heart failure. The main reason for an acute heart failure hospitalization is signs or symptoms of congestion for which the first choice treatment is administration of loop diuretics. These aim to establish a negative fluid balance, and thus alleviate signs and symptoms associated with fluid overload. Diuretics have been used in acute heart failure for many years, even though large randomized studies are lacking. Several small studies and case reports after the introduction of loop diuretics showed that the absorption of loop diuretics in heart failure patients was delayed.4-7 Additionally, the dose response curve is thought to be shifted downwards and to the right, meaning that the maximal response that can be obtained is diminished.8 Based on these findings heart failure patients are considered relatively diuretic resistant, and a poor response to diuretics frequently occurs during hospitalization for heart failure.9,10 The exact incidence of diuretic resistance is currently unknown due to the lack of consensus on a definition. Recently a definition for diuretic response during hospitalization for acute heart failure was proposed, in which weight loss was indexed to diuretic dosing.11 This study showed that a poor diuretic response was associated with less symptom relief and poor short-term outcome. Additionally, a poor diuretic response was more common in patients with impaired renal function. As a consequence of this landmark study, in the first part of this thesis we aimed to study different diuretic response and decongestion metrics in acute heart failure patients.

Diuretic resistance is frequently found in patients with underlying renal disease and it is well known that in patients with concomitant renal insufficiency higher doses of loop diuretic are required to deliver normal amounts of diuretic into the urine.8 Renal function is of great importance in heart failure, and the interaction between heart failure and renal dysfunction has been studied extensively over the past decades.12 The kidneys play a dominant role in maintaining sodium and fluid balance, and in a situation of heart failure, the body attempts to do so by activating several compensatory mechanisms. Renal dysfunction
and worsening renal function are common in heart failure, and associated with a poor prognosis, both in chronic and acute settings. Not only markers of glomerular dysfunction and worsening of these over time, but also markers of tubular dysfunction have been shown to be associated with poor outcome in heart failure patients. Consequently, other renal biomarkers may also be of interest in heart failure patients as these may help gain greater insight in the underlying pathophysiology and improve risk stratification. For instance, renal markers associated with poor diuretic response may help identify patients at risk, or prove to be a target for therapy. In the second part of this thesis we therefore aimed to study renal biomarkers in heart failure patients.

AIM OF THE THESIS

The primary aims of this thesis are:

- To examine different definitions of diuretic response, the prevalence of a poor diuretic response, and gain insight in underlying pathophysiological processes
- To study different renal biomarkers in heart failure, assess prognostic value, and provide additional information regarding underlying pathophysiological processes

Part 1 focuses on diuretic response in acute heart failure. Loop diuretics are the treatment of first choice for the management of fluid status in patients with acute heart failure. However, despite this therapy, a large number of patients do not reach euvolemia, which is a great and complicating problem that is associated with high mortality and rehospitalization rates. The reasons for a poor diuretic response are manifold, and are thought to result from the complex interaction between the cardiac and renal dysfunction, and specific renal adaptation and neurohormonal adaptation and escape mechanisms. Chapter 1 reviews the pathophysiological background of diuretic resistance, evaluation and definition of diuretic response, as well as current and future strategies to improve diuretic response in patients with acute heart failure. Chapter 2 examines the association between two diuretic response metrics with clinical characteristics and outcome in a retrospective analysis of the ASCEND-HF trial, a randomized controlled trial with neutral results that examined the effects of nesiritide in patients with acute heart failure. Chapter 3 sets out to identify clinical characteristics and biomarkers associated with a poor diuretic response in a retrospective analysis of the PROTECT trial, a randomized controlled trial with neutral results that examined the effects of rolofylline in patients with acute heart failure. Chapter 4 studies the combination of two measures of decongestion, hemoconcentration and diuretic response, in assessing low risk of heart failure rehospitalization after an admission for acute heart failure. Chapter 5 is an editorial on the importance of estimating decongestion in order to prevent readmission for heart failure after a hospitalization for acute heart failure.
Part 2 examines several renal markers in chronic and acute heart failure. Cardiac function and renal function are closely intertwined and studying renal biomarkers in heart failure may provide insight in underlying pathophysiological processes, improve risk stratification and may identify potential targets for therapy. Chapter 6 examines the associations between (changes in) serum chloride, diuretic responsiveness, decongestion, and mortality in acute heart failure patients. Chapter 7 presents the results of plasma kidney injury molecule 1 in both patients with chronic and acute heart failure and investigates associations with renal function and clinical outcome. Chapter 8 examines the value of fibroblast growth factor 23 in patients with acute and worsening heart failure and investigates associations with outcome and guideline recommended therapy. Chapter 9 studies the value of twenty-four hour urinary creatinine excretion in chronic heart failure patients and investigates associations with clinical characteristics and outcome.

Finally, the findings and relevance of this thesis, as well as future perspectives pertaining to this, are discussed in the Summary and future perspectives.
REFERENCES

1. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847.


Part 1
Diuretic response in acute heart failure