11 Summary and future perspectives
SUMMARY

Aims of the thesis
The aims of this thesis were
- 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

The first part focused on diuretic response in acute heart failure, whereas the second part examined several renal biomarkers in both chronic and acute heart failure populations. The principle findings of each chapter are outlined below, and the thesis is concluded with a paragraph on future perspective in which the findings of this thesis are placed in clinical perspective and subsequent research and treatment revenues are discussed.

Part 1: Diuretic response in acute heart failure
The first choice treatment for signs and symptoms of volume overload in patients with acute heart failure is administration of loop diuretics, and these are prescribed to more than 90% of patients admitted with acute heart failure.1,2 Despite the widespread use of loop diuretics over a long period of time, systematic studies investigating the use and response to diuretic treatment in acute heart failure patients have been lacking. After the initiation of loop diuretics several studies showed that most patients with heart failure were relatively diuretic resistant.3-7 However since these initial studies in the 80s, research that systematically investigated diuretic response in heart failure has been scarce. Some retrospective and observational studies have tried to evaluate treatment response using diuretic dose, or weight loss as separate predictors of response to therapy and outcome, with inconsistent findings.8-10 Recently a revival of research focusing on diuretic response in heart failure took place. Independently from each other two groups started studying diuretic response at the same time. Both investigated a diuretic response metric by indexing a measure of decongestion to the administered diuretic dose.11,12 Thus the effect of the diuretic is placed in the context of the dose necessary to achieve this effect. This was a completely novel approach on which the first papers were published in 2014. Both of these papers showed that a poor diuretic response, defined either as weight loss or fluid loss per administered diuretic dose, was associated with worse renal function and poor outcome. After the publication of these papers several questions regarding diuretic response metrics and underlying pathophysiology remained, some of which we proceeded to answer in this thesis.

The first chapter of this thesis, Chapter 1, is a review of the pathophysiology of diuretic resistance in acute heart failure and describes several proposed metrics for the evaluation of diuretic response. Additionally, multiple strategies to overcome diuretic resistance are discussed and clinical recommendations are provided.
The pathophysiology underlying a poor diuretic response is incompletely understood, and is thought to result from a complex interplay between cardiac and renal dysfunction and specific renal adaptation and escape mechanisms. Specific factors that may be involved in the development of diuretic resistance are outlined in figure 1 of this paper. In brief, patients who are resistant to loop diuretics might have reduced absorption of the drug in the intestine, reduced glomerular filtration, or reduced drug availability in the tubules. Additionally, increased proximal or distal sodium reabsorption in the kidney, due to adaptation and neurohormonal activation, may neutralize the effect of loop diuretics.

In this review we also proposed a stepwise treatment approach, including current and novel strategies, to overcoming diuretic resistance. First, a switch to a different loop diuretic, with greater bioavailability or more potency such as torsemide, can be considered. Second, combining two (or more) diuretic classes may improve diuretic response. Third, several other treatment options such as vasodilators, hypertonic saline, ultrafiltration, or novel drugs may be considered in truly diuretic unresponsive acute heart failure patient when the above options have failed. Unfortunately, prospective studies investigating any of these therapies in patients who are truly unresponsive to diuretics are currently lacking.

In Chapter 2 we examined two metrics of diuretic response, namely weight loss after 48 hours per administered diuretic dose, and urine output after 24 hours per administered diuretic dose, in the ASCEND-HF trial, which studied the effect of nesiritide in 7,141 patients with acute heart failure. Early studies on nesiritide, a recombinant B-type natriuretic peptide, showed a beneficial effect on hemodynamics and renal function, however recent studies, including the ASCEND trial, failed to confirm these findings. The aim of this paper was twofold: 1) we aimed to identify determinants and outcome of two metrics of early diuretic response, and 2) establish the effect of nesiritide on diuretic response.

Poor diuretic response, based on weight loss, early after hospital admission for acute heart failure, was associated with low blood pressure, renal impairment, low urine output and an increased risk of death or rehospitalization early after discharge. Diuretic response based on urine output showed similar results in terms of clinical predictors and association with outcome. In this study we specifically focused on early diuretic response, as this provides greater clinical applicability in early identification of a diuretic resistant patients, and possibly earlier administration of alternative treatment strategies. The finding that early assessment of diuretic response provides consistent findings with metrics established over a longer period of time, suggests that clinicians can identify a large number of patients at risk of diuretic resistance shortly after hospitalization. Our analyses also showed that nesiritide has no additive effect on diuretic response, defined by either metric. Based on this there seems to be no place for nesiritide in the treatment of diuretic unresponsive acute heart failure patients.

In Chapter 3 we further attempted to identify diuretic unresponsive patients early during hospitalization for acute heart failure, as early identification may lead to adaptation
of treatment, and ultimately improved outcome. In contrast to the analysis in chapter 2 where we measured early diuretic response, in this study we examined the association of clinical characteristics and biomarkers measured at baseline and after 24 hours with a poor diuretic response after four days. A wide range of clinical characteristics and biomarkers, all addressing different pathophysiological pathways were used to establish both explanatory and predictive models for a poor diuretic response.

We showed that biomarkers associated with diuretic unresponsiveness were markers of atherosclerosis, abnormal renal function and electrolytes. Despite the use of a great number of biomarkers and clinical characteristics, predicting diuretic response at admission was very difficult and biomarkers showed limited additive value. However, if diuretic response is measured after 24 hours, this is a reliable predictor of patients at risk of a poor diuretic response during hospitalization (at 4 days). Therefore, measuring early diuretic response after 24 hours can be used by clinicians to identify patients at risk of diuretic unresponsiveness shortly after admission, and additionally may also be used to design trials studying alternative or additional treatment options in these severely diseased patients.

In the previous chapters we showed that diuretic response is a marker of decongestion, and is associated with poor outcome. However multiple other markers of decongestion have also been studied in heart failure, one of which is hemoconcentration. In Chapter 4 we aimed to study the value of combining two measures of decongestion, hemoconcentration and diuretic response, to better predict patients at low risk for rehospitalization after admission for acute heart failure. We performed our initial analysis in the PROTECT dataset, and consequently confirmed our findings in the EVEREST dataset.

The combination of these two markers of decongestion showed improvement of risk prediction for early rehospitalization after an admission for acute heart failure. In both datasets, patients with both a favorable diuretic response and hemoconcentration had a markedly lower risk of rehospitalization. This may provide clinicians with an easy accessible tool to identify low risk patients that may be used to tailor a patient’s care. High rates of rehospitalization are a great problem after an admission for acute heart failure, and therefore the absence of one of these measures of decongestion may trigger the clinician to re-evaluate his treatment strategy, or decide to discharge a patient if a patient shows both a good diuretic response and hemoconcentration.

Chapter 5 is an editorial about estimated plasma volume, another marker of decongestion. This editorial discusses a paper by Duarte et al. that investigated the value of plasma volume variation at discharge after a hospitalization for acute heart failure and one month after discharge. This study showed that plasma volume provides important prognostic information and may have clinical implications for patient management. In the editorial, we placed these findings in clinical perspective by discussing the frequent flyer phenomenon: patients that are repeatedly rehospitalized quickly after discharge. At the moment it remains difficult to accurately predict which patients are at risk of repeated rehospitalizations. Esti-
mated plasma volume status may be used to assess patients at risk of rehospitalization after discharge, however prospective studies examining the value of estimated plasma volume to assess risk and guide therapy are needed to definitively establish the value of this metric.

**Part 2: Renal biomarkers in heart failure**

Renal function is of great importance in heart failure as it plays a major role in volume and sodium regulation, as well as neurohormonal activation, and is a target for heart failure therapies, such as diuretics and renin-angiotensin-aldosterone-system inhibitors. In addition, impaired renal function is a strong predictor of adverse outcome in heart failure. The interaction between the heart and the kidney is still incompletely understood, and biomarkers may help gain insight in underlying mechanisms and pathways and improve risk stratification. We therefore aimed to study different renal biomarkers in heart failure, assess their prognostic value, their relation with diuretic response, and to investigate whether they provide additional information regarding underlying pathophysiological processes. Some of the biomarkers we studied in this thesis may not actually be ‘renal’ biomarkers. However, interest in these markers originated in nephrology populations, and are as such considered renal biomarkers.

In Chapter 6, we examined the value of serum chloride in acute heart failure. Chloride has an important role in salt sensing and seems to be the main driver in the kidneys ability to sense volume overload. Additionally, chloride plays a role in tubular glomerular feedback, renin release and diuretic targets. Given these observations, we aimed to study the association between (changes in) chloride levels and diuretic responsiveness, decongestion, and mortality in patients with acute heart failure.

In a retrospective analysis of the PROTECT trial we showed that low chloride levels at hospital admission for acute heart failure were strongly associated with several markers of impaired decongestion and poor diuretic response. Interestingly, significant changes in serum chloride were common during the treatment of acute heart failure with approximately half of patients either resolving or developing new hypochloremia. New or persistent hypochloremia 14 days after hospital admission was independently associated with reduced survival, whereas hypochloremia that resolved by day 14 was not.

In Chapter 7, we studied plasma kidney injury molecule (KIM) 1 in both chronic and acute heart failure. Urinary markers of tubular damage, such as KIM-1, have been associated with worsening renal function and poor outcome in patients with heart failure. Whether the same holds true for plasma markers of tubular damage is unknown. We therefore investigated the role and value of plasma KIM-1 in acute and chronic heart failure.

Our analysis showed that plasma KIM-1 was associated with glomerular filtration rate, but not with urinary KIM-1. Additionally, plasma KIM-1 was a modest predictor of outcome. Based on these findings we concluded that these data do not (yet) provide evidence to support the use of plasma KIM-1 as a marker of tubular damage in heart failure patients.
In **Chapter 8**, we examined the value of fibroblast growth factor (FGF) 23 in patients with acute and worsening heart failure. FGF23 is involved in the regulation of sodium homeostasis and is associated with activation of the renin-angiotensin-aldosterone system. Since these mechanisms play an important role in heart failure, we aimed to study the role of FGF23 in patients with acute and worsening heart failure.

We measured FGF23 in 2,399 of the 2,516 patients included in the Biology Study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF) trial. One of the aims of this study was to up-titrate enrolled patients to guideline recommended doses of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs). Our analysis showed that higher levels of FGF23 were associated with more severe heart failure, and poorer renal function. In addition, FGF23 was a strong and independent predictor of adverse clinical outcome, and the highest quintile of FGF23 levels had a six fold increased risk of all-cause mortality, compared to the lowest quintile. Interestingly, patients with higher baseline FGF23 levels less frequently used ACEi or ARBs at baseline, and were less likely to reach guideline recommended target doses after three months of up-titration.

In the final chapter of this thesis, **Chapter 9**, we assessed the value of 24-hour urinary creatinine excretion in patients with chronic heart failure. Plasma creatinine is used to assess renal function; in contrast, urinary excretion of creatinine is an established marker of muscle mass. Interestingly, in patients with chronic heart failure, low body mass has been associated with poor outcome, whereas patients with higher body weight appear to have a lower risk of adverse outcome. This is often referred to as the obesity paradox.

In a small cohort of 120 chronic heart failure patients we showed that patients with a low creatinine excretion rate have smaller body dimensions and more severe heart failure, suggesting this marker identifies patients with muscle wasting or cachexia. Additionally, low urinary creatinine excretion rate was associated with an increased risk of adverse clinical outcome. The clinical application of these findings are limited as 24-hour urine collections are required to assess urinary creatinine excretion rate, and these are rarely obtained in cardiology populations.

**FUTURE PERSPECTIVES**

Over the last decades great advances have been made in the treatment of chronic heart failure. In contrast, for the treatment of acute heart failure many trials investigating novel drugs have failed to show any benefit, and systematic studies investigating the most important and commonly used drug used in this setting, loop diuretics, are lacking. Moreover, acute heart failure poses a great health care problem, both for patients and our health care system, as it is one of the main causes for hospitalization, and is associated with high mortality and readmission rates. One of the topics of this thesis, diuretic response in acute heart
failure, is therefore of great relevance, as inadequate decongestion is considered one of the main causes of high morbidity and rehospitalization rates.

In this thesis we performed several studies to enhance our understanding of diuretic response. We showed that early assessment of diuretic response allows for identification of patients at risk of diuretic unresponsiveness. This finding has clinical relevance for several reasons. Firstly, when confronted with an acute heart failure patient the treating physician is able to make an estimation of the treatment response of this patient by assessing diuretic response only 24 hours after admission using clinically readily available variables. If this response is insufficient, additional treatment strategies can be considered to improve diuretic response. A specific cut-off for an insufficient diuretic response currently does not exist, however it is remarkable that in several different datasets the median diuretic response based on weight loss was -0.4 kilogram per administered diuretic dose. Additional observational studies may however be needed to determine a specific cut-off for an inadequate diuretic response. Secondly, the finding that early diuretic response can be used to identify patients at risk of diuretic unresponsiveness also has value for research purposes, and can be used to design and perform prospective studies investigating diuretic response and alternative treatment options. Currently there is close to no evidence for alternative treatment strategies in diuretic unresponsive patients. Trials incorporating these new metrics to identify diuretic responsive patients should be designed to optimize treatment strategies for these severely diseased patients. Alternative treatment options that should be considered in future trials are, among others, combination diuretic therapy (for instance with metolazone), and hypertonic saline, as these have been suggested to greatly improve decongestion in observational or single center studies.

Using diuretic response metrics to design better trials for these severely diseased patients is a first step, however a better understanding of the underlying mechanisms contributing to diuretic unresponsiveness in acute heart failure patients may also lead to the identification of new targets for therapy. One of the strongest predictors of a poor diuretic response in chapter 3 was chloride, where low chloride levels were associated with a poor response. Despite its common assessment in clinical practice, chloride is often overlooked in the setting of heart failure where sodium has traditionally been considered to be one of the main driving forces. However, in several studies, chloride, and not sodium, showed to have a predominant role in salt sensing mechanisms, as well as tubular glomerular feedback and renin release. Also, recent evidence suggested an association between chloride and the tubular targets for diuretics. Based on this evidence we proceeded to study the value of chloride in acute heart failure in chapter 6, where we showed that low serum chloride is associated with poor decongestion. These two chapters suggest that chloride might be a target for therapy in acute heart failure, for instance by repletion of chloride, or chloride sparing therapies, and further studies specifically focusing on this should be a next step. In a small interventional, proof of concept study in which stable chronic heart failure patients
received lysine chloride suppletion during three days, chloride levels were normalized and the majority of patients experienced findings such as hemoconcentration, weight loss and a reduction in NT-proBNP (submitted). These promising findings suggest that suppletion of chloride indeed leads to increased decongestion, even in stable chronic heart failure patients, and will therefore be an interesting novel research avenue in overcoming diuretic resistance in acute heart failure patients.

One of the few studies investigating diuretic strategies in acute heart failure is the DOSE trial, in which continuous versus bolus use, as well as high versus low dose intravenous loop diuretic use, were compared.\textsuperscript{22} Despite slightly greater diuresis in the high dose group, this study failed to show significant superiority of the bolus or continuous strategy. One of the main reasons for these findings may be that pharmacodynamics, rather than pharmacokinetics in the setting of intravenous treatment of acute heart failure patients, contribute to diuretic unresponsiveness. In ongoing research, we studied the variability in diuretic response, using metrics involving urinary diuretic levels in the urine, to establish true diuretic response at a tubular level. Our results indicated that variability in diuretic response is mainly explained by resistance at the level of the renal tubule rather than factors limiting drug delivery (data not yet published). This study was unfortunately not designed to identify specific parts of the tubule, e.g. proximal sodium absorption, unresponsiveness to the diuretic in the loop of Henle itself, or distal hypertrophy causing excessive sodium reabsorption. Further research aimed at identifying the specific mechanism of tubular unresponsiveness is warranted and future studies should consequently be aimed at identifying new targets instead of trying to improve drug delivery.

Poor renal function is often a complicating factor in the treatment of heart failure patients, as many heart failure therapies, such as renin-angiotensin-aldosterone receptor blockers, and diuretics, have renal effects. The interaction between the heart and kidney has been a popular topic of research since the late 90s, when renal dysfunction in heart failure was first associated with poor outcome. Markers of renal function may help elucidate the underlying processes further. In this thesis we studied the role of FGF23, a phosphaturic hormone that is involved in the regulation of sodium and renin-angiotensin-aldosterone system activation. The results of this study are very promising, as FGF23 is not only a strong prognostic marker, but is also associated with more severe heart failure, and less guideline recommended use of ACEi and ARBs. As such FGF23 may not just be a marker for heart failure severity, but might also turn out to be a target for therapy. This was recently shown in a hemodialysis population, where FGF23 lowering therapy led to a significant reduction in mortality.\textsuperscript{23} Further studies will have to show whether FGF23 also is involved in a poor diuretic response, which may be the case due to its involvement in sodium regulation. If so, this will strengthen the importance of interventional studies aimed at modifying FGF23 levels in heart failure patients.
Finally, rather than just looking at one biomarker or one metric of diuretic response, all of these findings should be placed in the context of the patient, ultimately aiming for an individual patient tailored approach, or “precision medicine” as U.S. president Obama called this in his recent state of the union address. For instance, as mentioned in chapter 4, hemoconcentration in the presence of a good diuretic response is a sign of low risk, whereas hemoconcentration without a good diuretic response, or vice versa, should trigger the clinician to re-evaluate current treatment strategies. Additionally, worsening renal function may not be similarly detrimental in every situation. Even though patients with a poor diuretic response more often have renal dysfunction at baseline, the incidence of worsening of renal function was similar in patients with a poor and a good response. Based on this we suggest that some worsening of renal function, in the presence of a good response to therapy may be necessary, and possibly transient. This was recently referred to as pseudo worsening renal function in the European Heart Journal.13 Also, in patients with a poor response and low chloride, repletion of chloride might be indicated as a treatment option in this specific subgroup, where this may not lead to benefits in patients with a poor response and normal chloride levels. In this era in which multiple tests and biomarkers are easy accessible and available in abundance, in the end it all comes down to the clinician bringing together the pieces of each individual patients puzzle, and initiating and adjusting therapy accordingly. Similarly, in research combining these pieces of the puzzle should lead to trials that enroll the ‘right’ patients, as it is becoming more and more clear that heart failure is a heterogeneous syndrome, and an individualized approach to treatment is required.

The research presented in this thesis has led to a greater understanding of diuretic response and its underlying mechanisms and has shown that easily applicable metrics and markers can be used to identify patients at risk of diuretic resistance. Implementing these findings in the design of prospective trials studying diuretic resistance in acute heart failure will shed more light on alternative treatment strategies for these patients. Ultimately, an enhanced understanding of diuretic response will lead to an improved individualized approach to treating patients with acute heart failure. In this thesis the first strides towards this were taken, and future studies based on our findings will further improve our understanding, increase our knowledge, and enable us to better treat these severely diseased patients.
REFERENCES

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