Discussion and Future Perspectives
Heart failure (HF) is not only a syndrome characterized by its clinical symptoms, signs and poor prognosis, but also by its high degree of co-morbid organ dysfunction and co-morbidities [1-7]. At least part of the extreme mortality and morbidity of HF has been considered attributable to the existence of these co-morbid conditions [3,8]. Perhaps one of the most important co-morbidities in terms of pathophysiology, prognosis and treatment of HF is the co-existence of renal failure [6,8-15]. Although several terms to address this frequently occurring condition have been proposed, the term ‘cardiorenal syndrome’ is favored by many [16-20]. However, the specific definition of this syndrome still needs consensus. Recent reports have put forward at least five types of the cardiorenal syndrome, differentiating between acute and chronic, as well as cardiorenal and renocardiac, reflecting underlying pathophysiology, although also on these subtypes definitions are still being optimised (Table 1) [18,19].

Several key aspects have been suggested as the cornerstone of this syndrome including: a) the observation that the co-occurrence of heart and renal failure seems to be related to more severe deteriorated prognosis, b) the observation that both entities may worsen each other and c) the presence of pathophysiologic mechanisms relating to each other such as poor hemodynamics, endothelial dysfunction, inflammation and renin-angiotensin system activation [8,17,21-25]. Bongartz et al put forward a model based on Guyton’s model of hemodynamics and fluids control in cardiorenal interaction, introducing ‘cardiorenal connectors’ as specific modifiers of the relationship between hemodynamics and cardiorenal function and failure [17]. However, this model has never been formally tested, and does not include new insights recently observed in the cardiorenal interaction in HF. In the present thesis we have further investigated the contribution of different pathophysiologic determinants of renal failure in patients with heart failure, providing new information on the characteristics and pathophysiology of the cardiorenal syndrome. These and others are listed in Table 2.

**Decreased renal function**

The hallmark of HF is the inability of the heart to preserve cardiac output, resulting in decreased perfusion of peripheral organ systems [24]. However, the most prominent symptoms in HF are not primarily the result of decreased organ perfusion, but consist of the inability of the body to excrete sodium, and secondary water. This is the main cause of the classical symptoms of HF, including dyspnea, peripheral edema, orthopnea, ascites and classical physical signs such as jugular venous distention, rales and weight gain. The reason for excessive salt and water retention is however not primarily related to the cardiac dysfunction itself, but to the co-existing renal failure. The exact mechanism of excessive salt and water retention is in its turn primarily related to decreased glomerular filtration rate (GFR), resulting in the most important question why GFR is reduced in HF.
Hemodynamics: Decreased renal perfusion

In the first part of the 20th century, a great deal of work has been done on the relationship between reduced cardiac function and renal failure, which eventually lead to the discovery of renal autoregulation. In these studies, the main driving force of a reduction in GFR was thought to be attributable to a decrease in renal blood flow (RBF), which was the result of severely increased renal vascular resistance (RVR) as a consequence of increased efferent arteriolar vasoconstriction [26-30]. This concept was re-introduced in the cardiology in the last part of the 20th century when Ljungman et al showed that with decreasing cardiac index, RBF decreased disproportionately fast [25,31]. However, GFR was preserved to some extent by increasing filtration fraction, suggesting increased efferent vasoconstriction. Finally, RBF decreases further, and GFR could no longer be maintained, and dropped along the same line as RBF.

However, with the introduction of angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), this angiotensin II mediated predominantly efferent vasoconstriction is counteracted [32,33]. This has two possible important consequences. First, RBF is increased by decreasing RVR which, after an initial drop in GFR, may preserve GFR over a longer period of time [25]. However, second, it is also possible that by counteracting the GFR preserving mechanism of efferent vasoconstriction a further decline in RBF cannot be counteracted to preserve GFR. Recently, we investigated this last possibility in a cross sectional study, investigating GFR, RBF by radiolabeled tracer techniques in 110 chronic HF patients, who were all on ACEi and/or ARB therapy [34]. We were able to show that with lower RBF values, we could not establish a preservation of GFR as published by Ljungman. Instead, GFR dropped in a similar way compared to RBF, with filtration fraction remaining stable until very low values of RBF are observed [34]. In this last patient group, although filtration fraction decreased, RVR increased, which may suggest afferent arteriolar vasoconstriction in these patients, which we will discuss later. The combination of the findings in HF patients with and without renin angiotensin system (RAS) blocking therapy seem to suggest that a) early GFR preservation with mildly impaired RBF is indeed mainly dependent on efferent

Table 1. Definition of subtypes of the Cardiorenal syndrome

<table>
<thead>
<tr>
<th>Type</th>
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<tbody>
<tr>
<td>Type I</td>
<td>Acute Cardiorenal Syndrome</td>
<td>Acute worsening cardiac function leading to acute renal injury</td>
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<tr>
<td>Type II</td>
<td>Chronic Cardiorenal Syndrome</td>
<td>Chronic reduced cardiac function leading to progressive renal injury</td>
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<tr>
<td>Type III</td>
<td>Acute Renocardiac Syndrome</td>
<td>Acute worsening renal function leading to acute cardiac failure</td>
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<td>Type IV</td>
<td>Chronic Renocardiac Syndrome</td>
<td>Chronic renal failure leading to progressive HF</td>
</tr>
<tr>
<td>Type V</td>
<td>Secondary Cardiorenal Syndrome</td>
<td>Systemic condition causing cardiorenal dysfunction</td>
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Adjusted from Ronco et al.[18,19]
vasoconstriction, that b) the introduction of ACEi and ARB preserves GFR to some extent, but significantly hampers the intrinsic counterregulatory mechanism of the kidney itself to preserve GFR and c) deterioration of GFR with more severe RBF deterioration in the presence of ACEi or ARB may be at least partly attributable to increased afferent vasoconstriction. Together, these observations have consolidated decreased RBF as the most important determinant of GFR in patients with HF, and should be considered as the most important cornerstone of the cardiorenal syndrome.

<table>
<thead>
<tr>
<th>Characteristics of the Cardiorenal Syndrome</th>
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<tr>
<td>Reduced RBF and GFR</td>
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<tr>
<td>Increased Venous Congestion</td>
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<td>Albuminuria</td>
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<td>Tubular Damage</td>
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<td>Worsening Renal Function</td>
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<td>Diuretic Resistance</td>
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<td>Activation of the TGF</td>
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<td>Anemia</td>
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<td>Increased mortality</td>
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</table>

Abbreviations: GFR: glomerular filtration rate, RBF: renal blood flow, TGF: Tubuloglomerular feedback mechanism

Hemodynamics: Increased central venous pressure

In the same experimental studies investigating the effect of reduced RBF in HF, different models were used to initiate decreased renal perfusion pressure. One of these models consisted of increasing renal venous pressure [26,27]. By inducing higher renal venous pressures, the pressure gradient across the glomerulus is decreased when systemic arterial pressure is unchanged, causing a decreased RBF and subsequent decreased GFR. There were however suggestions that increased (central or renal) venous pressure itself may have impact on decreased GFR, independent of the induction of decreased perfusion [26,35,36]. Although these studies could not give a definite answer to whether this was actual the case, more recent studies on this subject showed more convincing results. Higher central venous pressure (CVP) may lead to higher pressures in the encapsulated kidney, causing hypoxia or increase in hydrostatic pressure in Bowman’s capsule, thereby decreasing GFR [37,38]. Other aspects may include an effect of CVP on intrarenal angiotensin II levels, which may have detrimental effect on single nephron GFR [37-39]. Higher CVP may even be linked to proteinuria [40]. We have recently provided more clinical evidence on a direct link between increased CVP and (estimated)
Table 3. Risk factors for development of worsening renal function

<table>
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<tr>
<th>Risk factors for WRF</th>
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<th>Owen</th>
<th>Logeart</th>
<th>Cowie</th>
<th>Jose</th>
<th>Akhter</th>
<th>Metra</th>
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Discussion and future perspectives

GFR in patients with and without HF. In patients with pulmonary hypertension and cardiac dysfunction, a disease very prone to high right sided filling pressures, we showed that in the presence of relatively preserved RBF, higher CVP has no influence on GFR [41]. However, in the presence of reduced RBF, when GFR is already depressed, the presence of higher CVP was associated with further reduced GFR. Importantly, RBF values were similar in those patients with higher and lower GFR, suggesting that CVP had an effect on GFR which was independent of RBF. We further explored this relationship between CVP and estimated GFR in a large cohort of patients with cardiovascular disease and found similar results [42]. Independent of cardiac output, patients with higher CVP levels showed significantly lower estimated GFR levels, compared to those with relatively normal CVP. We are supported on this finding by evidence from other studies, including a substudy of the ESCAPE trial, showing that the single (invasively determined) parameter associated with reduced renal function was in fact right atrial pressure [43]. Furthermore, specific therapy by levosimendan, aimed at lowering CVP showed improvement in renal function [44,45]. Finally, also tricuspid regurgitation, causing increased CVP, was found to be associated with impaired renal function in patients with HF, strengthening the observation of a relationship between CVP and GFR [46]. While invasively determined CVP is probably not feasible in patients with HF, we investigated the relationship between non-invasive signs of venous congestion, and the relationship with renal function and prognosis in patients who participated in the cardiac insufficiency bisoprolol study II (CIBIS-II) study [47]. Signs of congestion were frequently observed in this high risk chronic HF patient population, and patients with more signs of congestion had more severe renal impairment. This was in agreement with our findings of invasively determined CVP. However, also this relationship may also be partly attributable to excessive salt and water retention in response to decreased GFR, although the relationship was even stronger in patients with the relatively highest left ventricular ejection fraction. Finally, we were able to show that, despite the probability that the interobserver variability is very high, signs of venous congestion assessed by physical examination, was a strong, independent predictor of outcome, which increased the risk for all-cause mortality with the presence of more congestive symptoms.

In addition to our findings of the relationship between increased intravasal CVP and GFR, there is also a different pathophysiologic mechanism by which renal venous pressure may rise. This was already shown in the abdominal compartment syndrome, where patients have very high intra-abdominal pressures, which resulted in high renal venous pressures as mechanical complication [48,49]. Indeed, these patients show lower RBF and lower GFR levels. Recently, Mullens et al argued that this situation is not specific to the abdominal compartment syndrome, showing that elevated intra-abdominal pressure in patients with HF may be an important pathophysiologic mechanism of reduced renal function in these patients [50]. In addition, they showed that reducing the intra-abdominal pressure lead to an improvement in renal function, further supporting this hypothesis [51].

In summary, increased CVP of different origins and the presence of congestive symptoms seem to be important pathophysiologic factors in the cardiorenal syndrome, and deserve future attention.
Signs of renal damage: Albuminuric

Increased urinary albumin excretion (UAE) is a strong predictor of cardiovascular events in the general population and in patients with hypertension and diabetes [52-55]. Furthermore, its occurrence in primary renal disease is a predictor of outcome and the first sign of glomerular injury, but is also the main target of therapy in these patients [56]. In addition, numerous reports have showed that the presence of (micro/macro) albuminuria severely increases the risk for the development of HF or risk for HF admissions [53,57-59]. However, in HF itself there is little evidence of the prevalence, pathophysiology and relationship with prognosis of increased UAE, although albuminuria in HF has long been recognized [40]. Van de Wal et al showed that close to one third of patients with HF may have microalbuminuria [60]. Reasons for albuminuria in HF are unclear. In non-HF conditions, albuminuria is considered either as early glomerular injury, or as marker of endothelial dysfunction and leakage [61,62]. Higher blood pressures, and therefore higher hydraulic glomerular pressures have been shown to be correlated to albuminuria in hypertension, but this does not seem to reflect the pathophysiology in HF [63]. On the contrary, lower filtration fraction and the lack of association with higher blood pressures in HF suggest the pathophysiology of albuminuria in HF does not include high hydraulic pressures [34]. Albuminuria may be associated with decreased RBF, which may suggest that albuminuria in HF is related to hypoxic damage [34]. Other mechanisms may also include higher CVP, independent of decreased RBF [40]. And although albuminuria is a strong predictor of events in patient populations other than HF, the relationship between (micro) albuminuria and prognosis in HF is yet to be established.

Worsening renal function

Although the normal course of renal function in HF is yet to be established, studies suggest that up to one third of HF patients experience worsening renal function (WRF) at any point in time [64]. WRF in this regard is defined as an increase in serum creatinine ≥ 26.5 µmol/L (≥ 0.3 mg/dL) with or without a threshold of 25% increase in serum creatinine, roughly corresponding to a decrease in eGFR ≥ 9.0 mL/min/1.73m²[64-66]. In a meta-analysis, WRF was associated with a 60% increase in risk for all cause mortality after > 6 months follow up time, and 30% increase in the risk for HF hospitalization [64]. In addition, patients who already have impaired renal function are at greatest risk for development of WRF. With more severe WRF, we showed a striking increase in the risk for all-cause mortality, rising up to 300% increase when serum creatinine increases > 44.2 µmol/L. Interestingly, only one report assessed the effect of an improvement in serum creatinine (decrease ≥ 26.5 µmol/L), showing favorable outcome in these patients [9]. We investigated the relationship between the occurrence of WRF at different points in time, the relationship with prognosis, and the factors associated with decreasing renal function or WRF in a substudy of the Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) [67]. In our analysis, we showed that WRF during hospitalization, shortly after discharge, or between 6 and 12 months
Discussion and future perspectives

after discharge does not only occur frequently, but is associated with a strong increase in the occurrence of the combined endpoint of mortality and heart failure readmissions. In addition, in a landmark analysis, those patients that did not experience an endpoint in the early follow up phase but still experienced WRF, showed strong decreased survival rates. The pathophysiologic mechanisms behind WRF are not yet clear, but the main studies that have investigated the predictors of WRF are listed in Table 3, including the results from the COACH. This summary shows that next to baseline GFR which is the most important factor, (high dose) diuretics, age, anemia and diabetes are a prominent mediators of the development of WRF [9,65,66,68-76]. This may be true inhospital in patients with acute HF, as well as outhospital in patients with chronic HF. In our secondary analysis, we also have investigated the relationship of different factors and the slope of renal function over time (instead of the occurrence of WRF). The factors involved in renal function changes (decline in GFR) were strikingly similar to those observed in WRF, showing that baseline GFR, age, and co-morbidities (anemia, diabetes, peripheral artery disease, and hypertension) predisposed to a more pronounced GFR decline over time. Prevention and treatment of these factors may possibly prevent the occurrence of either WRF or decreasing GFR, which may eventually lead to improved prognosis in these patients with HF. WRF may be an important aspect in the cardiorenal syndrome, as it may connect the occurrence of tubular damage and decreasing GFR with prognosis and cardiorenal disease progression.

Hemodynamics and renin angiotensin system activity

Hemodynamic derangements seem to be the most important pathophysiologic mechanisms of renal impairment in HF [25,31,34,41]. While decreased GFR relates to impaired prognosis in HF, it is important to know which aspects of the pathophysiology are responsible for the poor survival of these patients, to establish possible targets for therapy. We investigated known and emerging factors associated with prognosis, and the dependency of their prognostic information with GFR [77]. In pathway analysis, we showed that a combination of decreased perfusion, filtration efficacy (Filtration fraction), volume overload, and subsequently hemodilution and anemia, were responsible for the combined effect of decreased GFR on prognosis. This further emphasizes the importance of both reduced perfusion and congestion, not only in the pathophysiology of renal impairment, but also in the effect on clinical outcome.

In additions to pathways that are dependent on GFR, we found that the sole factor associated with cardiovascular outcome, next to reduced renal perfusion, was plasma renin activity (PRA). This was observed, despite (or in spite) the fact that all patients were on either ACEi and/or ARB therapy. Both therapies may increase PRA [78-80], but the effect of elevated PRA in the presence of these agents has so far not been seriously recognized. Only one study, a substudy of the Valsartan Heart Failure Trial (VALHEFT), showed comparable results, showing sustained prognostic effect of elevated PRA, even in the presence of ACEi or beta-blocker therapy [81]. Reasons for this effect are difficult to unravel, since the negative feedback loop of lower angiotensin II levels, and consequently higher renin levels, should be counteracted by
ACE inhibition. However, there is a possibility of ACE-escape, resulting in activation of the angiotensin II response, despite ACEi therapy [82]. In addition, more severe ACEi may result in higher PRA levels, which would indicate that patients with more severe HF, who are more intensively treated with ACEi, have a higher risk for mortality, which is not unlikely. Other reasons may be progressively worsening or renal function, as PRA relates to renal perfusion and cortical hypoxia, which is particularly decreased in HF [23,34]. PRA may also be a more sensitive marker of reduced renal perfusion and renal hypoxia, an effect which may even be greater when RAS inhibition is present. Finally, (pro)renin may have detrimental effects on its own, via an effect through the relatively recent discovery of the (pro)renin-receptor [83,84]. The effect of (pro)renin stimulation may actually be profibrotic, which further supports a link between PRA, renal hypoxia and tubular function [85]. Overall, our finding suggests that treatment with either ACEi or ARB therapy will eventually result in higher PRA levels, which in turn are associated with reduced survival. This may indicate that therapy targeted at decreasing PRA levels may be beneficial on top of ACEi or ARB therapy, as will be discussed later.

Figure 1. Hypothetical vicious circle of decreased glomerular function, tubular damage and albuminuria in heart failure. Abbreviations: GFR: Glomerular filtration rate, NGAL: neutrophil gelatinase associated lipocalin, NAG: n-acetyl-beta-d-glucosaminidase, KIM-1: kidney injury molecule 1. Adapted from Norman et al.[113]
Anemia

The relationship between cardiac and renal failure should not be considered as a simple straight line across which different pathophysiologic mechanism influence each other. There seem to be different mediators involved in this relationship, but these mediators most of the time only have limited effects [17]. There is however one important mediator of the relationship between heart and renal failure, which is anemia. To emphasize it importance, it is often combined with the cardiorenal syndrome, resulting in the cardio-renal-anemia syndrome [86-88]. Although the pathogenesis of anemia in HF is still under debate, it includes erythropoietin (EPO) resistance, iron deficiency, hemodilution and decreased RBF [89-91]. The co-occurrence of renal failure and anemia in HF seems associated with a severely increased mortality risk, which is much higher than could be expected from the presence of either anemia or renal failure alone [92-95]. This might suggest that both entities may indeed worsen each other, with striking effects on outcome. Both renal failure and anemia relate to decreased perfusion and hemodilution, which all individually relate to outcome [77]. The combination of anemia and renal failure may therefore increase the risk of poor outcome via similar pathways, which may increase the strength of these associations with outcome. In addition, the similarities between the pathophysiology of renal failure and anemia may indicate that therapy to improve renal function, which is focused on improvement of these pathophysiologic pathways, may indirectly also improve hemoglobin levels or anemia.

Figure 2. Hypothetical time course of renal impairment and associated pathophysiologic entities in heart failure. Abbreviations: GFR: glomerular filtration rate, RBF: renal blood flow, WRF: worsening renal function. RBF may progressively worsen over time. As a consequence, GFR decreases. WRF may develop and may be associated with tubular damage and albuminuria, both worsening over time. The combination of reduced RBF, GFR, and increased tubular dysfunction and albuminuria will lead to strongly increased mortality.
Signs of renal damage: Tubular damage

In renal disease, not only albuminuria is frequently observed, but also tubular damage (or dysfunction) is prevalent [96-101]. However, in HF, there is exceptionally sparse data on the prevalence and pathophysiologic importance of tubular damage [102,103]. In kidney disease, tubular damage is apparent from histological evaluations of renal biopsies in patients with different etiologies of renal failure, and from increased urinary and/or plasma concentrations of specific tubular marker proteins [97,99,101]. There are a number of specific markers of tubular damage, including beta-2-microglobulin, N-acetyl-beta-D-glucosaminidase (NAG), kidney injury molecule 1 (KIM-1), and neutrophil gelatinase associated lipocalin (NGAL). These markers have been widely described and investigated in both acute and chronic kidney disease [96-101,104-107]. In patients with HF without renal impairment, urinary NAG levels have been shown to be elevated compared to the normal population. In a recent study we showed that urinary NGAL levels are increased in chronic HF patients [108]. In addition, across the severity of eGFR, from HF patients to controls, higher urinary NGAL levels were found in patients with lower eGFR, and higher NT-proBNP levels [108]. In this proof of concept study, NGAL levels remained higher in HF patients compared to controls, even after adjustment for eGFR. This could indicate that tubular dysfunction may progressively worsen, resulting in sustained elevation of urinary NGAL concentrations. In a follow up study, we further explored the prevalence, relationship with renal function and prognosis of different markers of tubular damage in patients with chronic HF [109]. We observed similar results obtained with NGAL for urinary NAG and KIM-1 levels, showing that their levels are increased in patients with chronic HF. However, only urinary NAG related to invasively determined GFR.
and renal perfusion. In addition, urinary NAG, NGAL and KIM-1 levels did not seem to correlate with each other, which would suggest at least some partly different pathophysiology of these markers. Although only NAG was related to renal perfusion, this observation further supports the hypothesis of tubulointerstitial damage occurring when renal (regional) hypoxia develops. In renal disease, tubular damage may arise when high albumin concentrations trigger the tubules to shed these proteins into the urine, but considering the low amount of albumin in HF patients, and the lack of association between urinary NAG, NGAL or KIM-1, a different mechanism may be involved [96,98]. Other studies suggest that also diuretic therapy may initiate renal impairment, possibly also negatively influencing tubular function [76]. Figure 1 shows the hypothetical vicious circle of renal impairment, tubular damage and albuminuria in heart failure. Both decreased perfusion and increased congestion lead to impaired renal function, renal hypoxia, interstitial and tubular damage, albuminuria and subsequently feeds the vicious circle again, to cause sustained renal failure.

The reason why both NGAL and KIM-1 did not correlate to the extent of renal impairment or decreased renal perfusion needs to be investigated further. A reason may be that both markers are more specific for tubular, rather than glomerular damage and dysfunction. Another reason may be that especially NGAL rises quickly in response to tubular damage, but also decrease quickly when the initiating factor has disappeared [110,111]. The striking increase in both urinary NGAL and KIM-1 levels are also observed in patients with acute renal failure, and precedes the rise in serum creatinine by over a day [111,112]. Therefore, these markers may be useful in predicting the occurrence of WRF. This potential of these tubular marker proteins may be useful especially in acute HF, and should be explored in future studies.

In addition to the finding that the concentrations of these tubular marker proteins are elevated in patients with chronic HF, we found that both urinary NAG and KIM-1 levels were predictors of prognosis, independent of GFR. This finding may reflect a different pathophysiological mechanism through which general renal function, or reduced renal perfusion may ultimately lead to increased mortality. Therefore, the role of these tubular markers as a potential target for therapy for reno-protective treatment may be the focus of new studies.

Finally, the role of tubular damage in the progression of renal failure, cardiorenal disease and prognosis should be the focus of new prospective studies in HF. We have hypothesized on the factors involved in the cardiorenal disease progression in Figure 2, showing that with progressively reduced RBF, GFR decreases, with frequent occurring of WRF, increasing tubular dysfunction and albuminuria, which will eventually lead to increased mortality risk.
Table 4. Treatment in the cardiorenal syndrome / HF patients with renal impairment

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ESC Guidelines</th>
<th>AHA/ACC guidelines</th>
<th>Suggestions in literature</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACEi</strong></td>
<td>Creatinine &gt; 2.5 mg/dL contraindication for initiation</td>
<td>Maintain on ACEi as long as possible Cautious initiation when creatinine &gt; 3 mg/dL</td>
<td>ACEI preserves renal function on the long term.[133]</td>
</tr>
<tr>
<td></td>
<td>Creatinine rise after initiation to 3 mg/dL acceptable</td>
<td></td>
<td>Definite survival benefit with GFR &gt; 30 mL/min/1.73 m², possible below 30 mL/min/1.73 m². [124,126]</td>
</tr>
<tr>
<td></td>
<td>Creatinine rise between 3 and 3.5 mg/dL: halve dose</td>
<td></td>
<td>Observational lack of survival benefit in patients with HF, CAD and CrCl &lt; 60mL/min</td>
</tr>
<tr>
<td></td>
<td>Creatinine rise above 3.5 mg/dL: stop ACEi</td>
<td></td>
<td>[123] Start low, careful evaluation renal function</td>
</tr>
<tr>
<td><strong>ARB</strong></td>
<td>Creatinine &gt; 2.5 mg/dL contraindication for initiation</td>
<td>Cautious treatment in patients with severe renal impairment, especially in combination with ACEi or Aldosteron antagonists</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatinine rise after initiation to 3 mg/dL acceptable</td>
<td></td>
<td>Definite survival benefit with GFR &gt; 30 mL/min/1.73 m², possible below 30 mL/min/1.73 m². [122,125]</td>
</tr>
<tr>
<td></td>
<td>Creatinine rise between 3 and 3.5 mg/dL: halve dose</td>
<td></td>
<td>Careful evaluation renal function.</td>
</tr>
<tr>
<td></td>
<td>Creatinine rise above 3.5 mg/dL: stop ARB</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td>Prescribe in patients with renal impairment</td>
<td>Prescribe in patients with renal impairment</td>
<td>Observational survival benefit in patients with HF, CAD and CrCl &lt; 60mL/min [123]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Substudy CIBIS II showed benefit of bisoprolol in CrCl &gt; 30 mL/min/1.73 m² [127]</td>
</tr>
<tr>
<td><strong>Aldosteron Receptor Antagonists</strong></td>
<td>Creatinine &gt; 2.5 mg/dL contraindication for initiation</td>
<td>Prescribe only if: Creatinine &lt; 2.5mg/dL in men Creatinine &lt; 2.0 mg/dL in women</td>
<td>Definite survival benefit with GFR &gt; 60 mL/min/1.73 m², possible between 30 and 60 mL/min/1.73 m² [128]</td>
</tr>
<tr>
<td></td>
<td>Creatinine rise to &gt; 2.5 mg/dL: halve dose</td>
<td></td>
<td>Diuretics increase risk for WRF [68,76]</td>
</tr>
<tr>
<td></td>
<td>Creatinine rise to &gt; 3.5 mg/dL: stop ARA</td>
<td></td>
<td>Diuretics may initiate renal damage</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>WRF with diuretics: check for hypovolemia/dehydration, exclude NSAIDs, withhold ARA, stop concomitant Thiazides, consider reduction ACEi/ARB, consider ultrafiltration</td>
<td>If WRF develops, decrease diuretic dose. If not possible due to congestion: accept WRF to maintain ACEi/ARB.</td>
<td>Higher doses of diuretics needed in patients with renal impairment. [116]</td>
</tr>
<tr>
<td></td>
<td>Loop diuretics preferred when CrCl &lt; 30 mL/min</td>
<td>If refractory to diuretics, consider ultrafiltration</td>
<td>Combine with salt and water restriction, with careful evaluation of renal function. [134]</td>
</tr>
<tr>
<td><strong>Ultrafiltration</strong></td>
<td>Consider when WRF develops, resistance to treatment or treatment withdrawal</td>
<td>Severe renal impairment and/or resistance to treatment</td>
<td>No beneficial effect of ultrafiltration on renal function in UNLOAD. Ultrafiltration may even reduce eGFR in similar fashion as furosemide [141]</td>
</tr>
</tbody>
</table>
Diuretic resistance and tubuloglomerular feedback

Diuretic therapy is an important therapeutic tool to relieve symptoms and signs of congestion in HF, but there is no proof of a randomized clinical trial showing mortality benefit of diuretics over placebo. Instead, diuretic therapy is associated with WRF, and possibly tubular dysfunction, but does improve quality of life in patients with HF [9,68,76,114]. Therefore, it seems diuretic therapy improves signs and symptoms and quality of life, at the expense of deteriorating renal function. There is however another problem with chronic diuretic use, which is termed ‘diuretic resistance’ [115,116]. The mechanism behind diuretic resistance is based on the fact that the distal tubule and collecting ducts will reabsorb more sodium when, because of the promotion of sodium excretion by diuretics, more sodium reaches the distal tubules. Via this way, the netto sodium excretion and therefore, water excretion, is only limited and higher doses of diuretics are necessary to achieve clinical relevant sodium and water excretion [116]. Adding to this problem is the need for loop diuretics to be filtered before they reach the site of action, which is decreased when GFR is reduced [116]. In addition, high distal sodium load will initiate the tubuloglomerular feedback mechanism (TGF). The TGF mechanism protects the kidney from losing too much salt by increasing afferent arteriolar glomerular resistance by the action of adenosine, in response to high sodium levels in the distal tubules [117]. This will result in decreased RBF, and therefore
decreased GFR, which will lead to even more salt and water retention, lower RBF, and lower GFR, eventually feeding a negative vicious circle (Figure 3). Mediation of this mechanism in HF on top of standard HF therapy has been shown to be beneficial for RBF and GFR, and currently trials are underway to determine the effect of an intravenous selective adenosine A1 receptor antagonist (AARA) on clinical outcome in acute decompenated HF patients [118,119]. Interestingly, one small report addressed the effect of AARA on RBF and GFR in chronic HF, showing improvement in both [120]. This further supports our finding that in chronic HF patients on ACEi or ARB therapy, when RBF is very low, GFR is not solely dependent of efferent vasoconstriction, but also on afferent vasoconstriction [34]. This may further emphasize a possible therapeutic role of this new class 'reno-protective' therapies, even in chronic HF.

Table 5. Unconventional, new or device therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Suggestions in literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT</td>
<td>Substudy of MIRACLE trial showed improvement in estimated GFR in patients receiving CRT with reduced baseline GFR [142]</td>
</tr>
<tr>
<td>LVAD</td>
<td>LVAD implantation has been shown to improve CrCl in selected patients, especially those with lowest Cardiac index, diabetics and low BMI. [143]</td>
</tr>
<tr>
<td>Heart Transplantation</td>
<td>ESC guidelines: renal failure (CrCl &lt; 50 mL/min) contraindication for heart transplantation. [1]</td>
</tr>
<tr>
<td>Statins</td>
<td>Observational survival benefit in patients with HF, CAD and CrCl &lt; 60mL/min [123] No significant interaction between treatment effect and eGFR in CORONA [129]</td>
</tr>
<tr>
<td>Adenosine A1 receptor antagonists (Rolofylline)</td>
<td>AARAs improve RBF and GFR in chronic HF [120] AARAs improve CrCl and decreased the need for intravenous diuretics in patients with acute HF [144] AARAs protect against the worsening of renal function with diuretic therapy [118] AARA therapy was associated with improved trichotomous endpoint in the PROTECT II pilot trial.[118]</td>
</tr>
<tr>
<td>Direct renin inhibition (Aliskiren)</td>
<td>Renin inhibition resulted in significant reduction in (NT-pro) BNP and PRA levels in patients with chronic HF. No significant increase in renal dysfunction and/or hyperkalaemia. [145]</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>Levosimendan improves renal function in acute and advanced chronic HF, despite blood pressure lowering. [45,146]</td>
</tr>
<tr>
<td>Vasopressin Antagonists</td>
<td>Tolvaptan showed no improvement in renal function over placebo in the EVEREST trial. No significant interaction between treatment effect and creatinine in EVEREST. [147]</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Low dose dopamine in combination with diuretics may improve renal function in decompensated HF. [148] Dopamine improves RBF in patients with chronic heart failure [149]</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>No short term effect of dobutamine on eGFR in acute HF [45]</td>
</tr>
</tbody>
</table>
Treatment of the cardiorenal syndrome

There is no data on effective and safe treatment of patients who present with the cardiorenal syndrome. In the present thesis, we have put forward pathophysiologic links between cardiac and renal failure, and the relationship with outcome. Therapies in the cardiorenal syndrome should focus on these targets. These include reduced RBF, increased venous congestion, but also anemia, hypertension, tubular dysfunction and sustained RAS-activation. In clinical practice, symptomatic HF therapy is often prescribed, which would normally include RAS-blocking agents, diuretics and beta-blockers [1]. There is however no randomized controlled trial that has evaluated the effectiveness of standard HF care, or specific developed ‘reno-protective’ therapy in patients with combined cardiac and renal failure. Instead, large clinical HF trials have excluded patients with severe renal impairment. Table 4 summarizes key HF therapies as mentioned in the European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines on HF [1,121]. In the recently published guidelines ESC guidelines, increased serum creatinine (above 150 µmol/L (1.7mg/dL)) is acknowledged as a risk factor, but an even higher serum creatinine level (above 220 µmol/L (2.5 mg/dL)) is considered a contra-indication for both ACEi and aldosteron antagonists initiation, while ARBs should only be prescribed in patients with ‘adequate renal function’. When deterioration of renal function occurs, the guidelines suggest halving of ACEi or ARB therapy, even if this occurs after initiation of diuretic therapy. This recommendation however fails to acknowledge that diuretic therapy itself may be the trigger for WRF, although, as discussed, also congestion may predispose to renal failure [9,41,68,121] This is different from the belief in chronic kidney disease in which some decrease in GFR after diuretic therapy is considered favorable. However, considering the low glomerular pressures and low filtration fraction, and the association of diuretic therapy with WRF and secondary outcome, this may not be similar in HF. The AHA guidelines show distinct differences with the ESC guidelines. ACEi and ARB therapy should be continued as long as possible, even if WRF occurs. In agreement with ESC guidelines, beta-blockers should not be withheld, while ultrafiltration may only be indicated in patients who fail to respond to therapy [121]. The last column in table 4 summarizes some findings from observational studies and substudies of clinical trials. Interestingly, ACEi and ARB seem to be effective and safe in patients with mild to moderate renal failure [122-126]. The evidence for aldosteron receptor antagonism seems much less robust in these patients, while beta-blockers show similar results compared to ACEi and ARB [127,128]. Diuretics however have frequently been linked to more severe renal impairment, WRF and patients with renal impairment require higher doses to achieve comparable diuresis [68,76,116,117].

Table 5 shows some unconventional, new or device therapies and their effect in patients with cardiorenal impairment. Levosimendan was shown to improve renal function, an effect which may attributable to its venodilatory effects in combination with the inotropic characteristics of the drug [44,45]. It therefore may be an effective strategy in patients who are congested, but have adequate blood pressures, as levosimendan has been shown to cause some degree of hypotension. Statin therapy seems associated with improved survival in observational studies, irrespective of renal function, but the CORONA and GISSI-HF trial failed to provide evidence
of survival benefit of rosuvastatin over placebo, showing no interaction between eGFR and treatment in the CORONA [129,130]. As discussed, new AARAs may counteract the TGF mechanism, which is currently being studied in the PROTECT-II studies, which particularly focuses on patients with cardiac failure and moderate to severe renal failure (creatinine clearance 20-80 mL/min) [118]. A new study, the DIURETICS-HF, is underway to establish the effect of diuretics withdrawal on clinical outcome in patients with chronic HF, which may show interesting results with regards to renal function [131]. If diuretic therapy is considered, this should always be combined with a low sodium diet, as it limits the possibility of the kidney to bypass the diuretic action of the drug by initiating vigorous salt and water retention in the distal tubulus [132]. Furthermore, dietary sodium restriction itself, especially when GFR is relatively preserved, may help reduce congestion via similar mechanisms, thereby decreasing the likelihood of renal failure as a consequence of venous congestion. As discussed earlier, we found that despite ACEi or ARB therapy, PRA was a strong predictor of outcome, suggesting that further blockade of the RAS (other than combining ACEi and ARBs) could be beneficial in patients with chronic HF.

Currently, a large number of trials with a direct renin inhibitor, aliskiren, is being conducted, and has so far resulted in the completion of one chronic HF study. The Aliskiren Observation of heart Failure Treatment trial (ALOFT), showed that with the addition of aliskiren, a significant reduction in (NT-pro)BNP and PRA levels could be achieved, without increasing the incidence of renal dysfunction and hyperkalaemia [145]. This has prompted the planning and design of a large double blind, placebo controlled trial with aliskiren in chronic HF, the Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE), which will evaluate the effect of aliskiren on clinical outcome. Furthermore, a small safety and renal efficacy study on aliskiren in patients with chronic HF in combination with renal dysfunction (eGFR 30-60mL/min/1.73m²), the effect of Additive Renin Inhibition with Aliskiren on renal blood flow and Neurohormonal Activation in patients with Chronic Heart Failure and Renal Dysfunction (ARIANA-CHF-RD) study, is underway to investigate the effect of aliskiren on RBF, when added to standard HF therapy. Finally, while decreased RBF as a result of decreased cardiac output is the main determinant of decreased GFR, improvement of cardiac function may be an indirect way to improve GFR. A method to establish this may be cardiac resynchronization therapy, which was recently shown to improve estimated GFR in a substudy of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial. Although these new therapies shed some new light on therapeutic potentials in patients with HF and renal impairment, solid evidence based medicine in the cardiorenal syndrome is still lacking.

In the present thesis we have investigated and discussed the cornerstones of the cardiorenal syndrome in HF. We have provided evidence on new pathophysiologic links; we have described new potential targets for therapy, and discussed promising pharmacological new therapies. However, the pathophysiology and treatment of the cardiorenal syndrome should be the focus of experimental and mechanistic studies as well as large randomized trials to eventually improve prognosis in this high mortality patient group.
Discussion and future perspectives

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Discussion and future perspectives


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Discussion and future perspectives


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