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# The role of the kidney in acute and chronic heart failure

Gaetano Ruocco[1,2] · Alberto Palazzuoli[1] · Jozine M. ter Maaten[3]

## Abstract

Renal dysfunction affects approximately 30 to 50% of heart failure (HF) patients. The unfavourable relationship between heart and kidney dysfunction contributes to worse outcomes through several mechanisms such as inflammation, oxidative stress, impaired hydrosaline homeostasis, and diuretic resistance. Renal dysfunction not only carries important prognostic value both in acute and in chronic HF, but also is a potential precipitating factor after the first diagnosis. Because renal dysfunction encompasses different etiologies, a better understanding of its definition, incidence, and pathophysiology provides additional information. Although old and novel available biomarkers for the detection of renal dysfunction have been recently proposed, there is no general consensus regarding the terminology and definition of renal dysfunction in HF. Due to some specific pathophysiological mechanisms, renal impairment seems to be different on an individual patient level and, recognizing it in acute and chronic settings, could be useful to optimize decongestive treatment. For these reasons, in this review, we aim to describe and evaluate different phenotypes of renal dysfunction in acute and chronic HF and the possible management in these settings.

## Key messages

• Chronic kidney dysfunction and worsening renal function are highly prevalent in acute heart failure and chronic heart failure and associated with poor outcomes.
• This association is modified by the context in which it occurs, i.e. worsening renal function in the context of adequate decongestion in acute heart failure, or worsening renal function after initiation of neurohormonal blockers in chronic heart failure.
• Future research should be aimed at elucidating the mechanisms involved in these differenct contexts, as well as alternative treatment approaches in the case of true worsening renal function.

**Keywords** Renal dysfunction · Worsening renal function · Acute heart failure · Chronic heart failure · Pathophysiology · Outcome

## Abbreviations

| | |
|---|---|
| ACEi | Angiotensin-converting enzyme inhibitors |
| AHF | Acute heart failure |
| AVP | Arginine vasopressin |
| BUN | Blood urea nitrogen |
| CHF | Chronic heart failure |
| CKD | Chronic kidney disease |
| eGFR | Estimated glomerular filtration rate |
| HF | Heart failure |
| HFmrEF | Heart failure with a mid-range ejection fraction |
| HFpEF | Heart failure with a preserved ejection fraction |
| HFrEF | Heart failure with a reduced ejection fraction |
| MRA | Mineralocorticoid receptor antagonist |
| NGAL | Neutrophil gelatinase–associated lipocalin |
| RAAS | Renin-angiotensin-aldosterone system |
| RBF | Renal blood flow |
| sCr | Serum creatinine |
| WRF | Worsening renal function |

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## Introduction

Renal dysfunction affects approximately 30 to 50% of heart failure (HF) patients. Although there are several differences among acute and chronic conditions of both the heart and the kidney, renal impairment in heart failure is related to poor

prognosis in all [1–3]. This unfavourable relationship between heart and kidney dysfunction contributes to worse outcomes through several mechanisms such as inflammation, oxidative stress, impaired hydrosaline homeostasis, and diuretic resistance. Following from this intricate pathophysiology, the evaluation of renal dysfunction in acute and chronic HF deserves a better understanding in terms of definition, incidence, pathophysiology, and outcome [4, 5]. In patients with acute heart failure (AHF), it is possible to distinguish between two phenotypes of renal impairment: patients with baseline renal dysfunction, defined as chronic kidney disease (CKD), and patients who develop worsening renal function (WRF) during hospitalization. Both CKD and WRF are related to adverse outcome, but the underlying pathophysiological mechanisms are distinctly different. Together with renal dysfunction, there are several factors that contribute to worse outcomes in AHF patients such as electrolyte unbalances. Indeed, a recent meta-analysis performed by Savarese et al. showed that lower estimated glomerular filtration rate (eGFR) was related to the occurrence of dyskalaemia and in particular to hyperkalaemia, which is also associated with poor prognosis in the context of renal dysfunction in HF [6]. Similarly, a sub-analysis of the BEST trial demonstrated that both hypochloraemia and hyponatraemia were related to a poor prognosis [7]. Recently, several authors tried to re-define renal impairment in AHF taking into account the underlying aetiology and pathophysiology. In chronic heart failure (CHF), the presence of renal dysfunction is generally defined as reduction in eGFR where a cutoff value < 60 ml/min/1.73 m$^2$ is used to identify patients with CKD. This condition affects about 50% of patients with CHF and is associated with an increased risk of mortality. Similar to patients with AHF, CHF patients can develop WRF during ambulatory follow-up; this WRF is related to poor prognosis depending on the underlying mechanisms, i.e. kidney function deterioration due to diuretic resistance or in contrast due to up-titration of neurohormonal blockers [5, 8, 9]. In this review, we aim to describe and evaluate different phenotypes of renal dysfunction in acute and chronic HF and the possible therapeutic strategies in these settings.

# Acute heart failure

## Pathophysiology of acute renal impairment in AHF

The pathophysiological view of renal impairment during acute decompensation of HF includes systolic and diastolic cardiac dysfunction leading to reduced renal blood flow (RBF) and increased renal venous congestion. The consequences of these haemodynamic processes are a reduction in renal perfusion and increased neurohormonal activation which lead to acute renal impairment (Fig. 1) [10, 11].

### Haemodynamic derangements

Patients with AHF usually have low cardiac output which causes a reduction in renal perfusion or RBF. As the kidneys receive about 20–25% of cardiac output, its reduction triggers the renal baroreceptor system and subsequent kidney autoregulation through adjustment of vasoconstriction of efferent arterioles in response to renal artery pressure which is mediated by the renin-angiotensin-aldosterone system (RAAS). However, this autoregulation remains within certain limits. Persistent low RBF causes renal tubular hypoxia and subsequent acute tubular necrosis with tubulointerstitial injury. This is followed by neurohormonal activation that attempts to restore RBF through sympathetic overdrive and additional RAAS activation [8, 12, 13]. Together with this forward renal failure due to renal hypoperfusion, venous congestion has an additional important detrimental haemodynamic effect. In HF patients, during acute decompensation, left ventricular filling pressures are increased leading to pulmonary circulation overload and subsequent pulmonary congestion, resulting in increased right atrial pressures and central venous pressure [14, 15]. Elevated central venous pressure delays the outflow pressure of the blood flow through the kidney causing renal venous hypertension. This further reduces RBF because of increased efferent pressures, decreased transrenal perfusion pressure, increased intraglomerular hydrostatic pressure, increased intratubular pressure, and reduced net filtration pressure. The increase in central venous pressure additionally results in high intra-abdominal pressures that contribute to decreased renal perfusion and elevated hydrostatic and intratubular pressure through the reduction of abdominal compliance [8, 9, 16, 17]. The increase in intra-abdominal pressures has been shown to be strongly related to renal impairment in AHF [18]. Following from this, in AHF patients refractory to treatment, the mechanical removal of fluids through paracentesis or ultrafiltration is related to the reduction of intra-abdominal pressures which leads to improvement in renal function [19].

### Neurohormonal overdrive

Continuous renal hypoperfusion and renal venous hypertension lead to the disruption of renal autoregulation mechanisms. As a consequence of this, there is an increase in sympathetic activity, RAAS activation, and increased arginine vasopressin (AVP) release [20]. Systemic and renal vasoconstriction represent the detrimental effects of this state, as in the setting of reduced cardiac output, this further reduces RBF and glomerular filtration rate. Moreover, sympathetic stimulation causes increased peritubular capillary oncotic pressures and reduced peritubular capillary hydrostatic pressure with consequent increases in sodium resorption in the proximal tubule. Together with increased sympathetic activity,

**Fig. 1** Common and different pathways of HFrEF and HFpEF developing RD. AHF, acute heart failure; AVP, arginine vasopressin; CKD, chronic kidney disease; CVP, central venous pressure; HFpEF, heart failure with a preserved ejection fraction; HFrEF, heart failure with a reduced ejection fraction; RAAS, renin-angiotensin-aldosterone system; RBF, renal blood flow; RV, right ventricle; SNS, sympathetic nervous system; WRF, worsening renal function
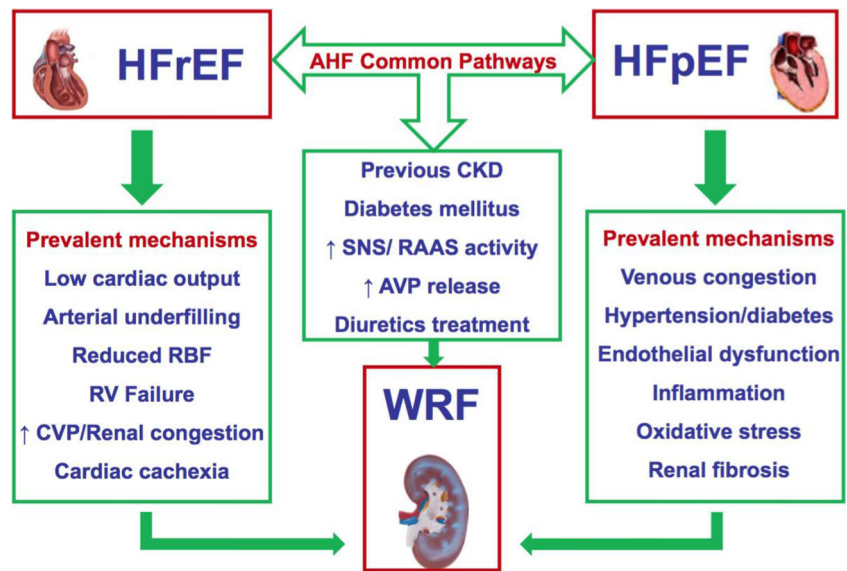


there are several hormonal mechanisms that contribute to worsening renal function in AHF. Indeed, reduced cardiac output and subsequent reduced RBF give rise to increased juxtaglomerular renin release which activates angiotensin II [20–22]. Angiotensin II plays a pivotal role in vasoconstriction stimulation through the direct action on renal arterioles and through a synergistic play with the sympathetic nervous system. Angiotensin II additionally contributes to reduced excretion of sodium and water with direct effects on the tubule and through the stimulation of both adrenal and pituitary glands, resulting in increased levels of aldosterone and AVP, furthermore contributing to sodium and water reabsorption. This ultimately results in a vicious circle which further contributes to worsening renal function and worsening symptoms in AHF patients. Indeed, the increase in sodium and water reabsorption leads to intravascular volume overload, subsequently contributing to a downward spiral of congestion and heart failure [17]. The final effect is a reduction in glomerular filtration rate and subsequent reduced urine output. Nevertheless, these pathophysiological mechanisms include several different aspects which vary for each patient in relation to inflammatory/oxidative stress, anaemic status, and nutritional and body composition factors.

## Clinical meaning of renal biomarkers in AHF

The incidence of renal impairment in AHF patients ranges from 20 to 40% [23]. It is well known that CKD, defined as eGFR < 60 ml/min/1.73 m$^2$, is associated with a poor prognosis in AHF, and the prognostic value of this comorbidity increases progressively with the reduction of eGFR [24]. Although CKD is a well-recognized risk factor of adverse outcomes and several registries have documented its prognostic impact, we cannot make the same observation for acute renal dysfunction in AHF. Many studies demonstrated that acute renal impairment, in the setting of acute heart failure, was associated with a higher rate of re-hospitalization and mortality. There is however a lack of consensus on a definition of renal impairment in the setting of AHF. The most commonly used definition of worsening renal function (WRF) is an increase of serum creatinine levels during hospitalization (≥ 0.3 mg/dl), and this has consistently been shown to be associated with a poor prognosis in multiple studies [25–31]. One of the main limitations of this definition is related to the use of creatinine as the only marker of renal dysfunction. Serum creatinine (sCr) is primarily a marker of glomerular filtration and therefore does not recognize renal tubular injury in the absence of a significant reduction in GFR. Its increase only occurs after almost half of the kidney function is lost which may be days after the renal insult has occurred. Slow kinetics are the equivalent of low application in the dynamic of the acute setting [32]. Different studies added eGFR to the WRF definition based on serum creatinine. This combined definition has been shown to provide additional prognostic value [2, 33–36]. However, also eGFR shows some limitations. It would be ideal to measure true GFR in the acute setting; however as this is not feasible, eGFR formulas are used. Limitations of these are for instance the use of body mass and age of patients, leading to bias. Indeed, due to the relation between serum creatinine and muscle mass variability, a new formula for eGFR was proposed. In particular, a new renal biomarker, serum cystatin C, was able to predict adverse events in AHF [37]. Moreover, serum cystatin C was not influenced by body mass and reflects glomerular impairment of the kidney. For this reason, CKD-EPI formulas based on serum creatinine and serum cystatin C might be the most accurate to predict real glomerular filtration rate in HF patients as well as obese patients [38, 39].

WRF in the acute phase of HF results from reduced RBF, venous renal hypertension, and congestion of the kidney. This pathological condition plays a pivotal role in the alteration of tubular function. SCr and eGFR are not accurate in recognizing tubular changes in acute renal dysfunction [9]. For this reason, beyond creatinine, many studies have focused on blood urea nitrogen (BUN) in the assessment of WRF. The main difference between sCr and BUN is the reabsorption of BUN at the tubular level. Both AVP and RAAS mediate urea transport together with sodium reabsorption and volume status. As such, BUN represents a renal mirror of neurohormonal overdrive in AHF. This condition is amplified by arterial underfilling and overdiuresis due to overtreatment [40]. Therefore, BUN measurement during hospitalization could inform about WRF aetiology and provide more accurate prognostic information in comparison with creatinine and eGFR [2, 41–43]. Some authors studied the ratio between BUN and sCr (BUN/sCr), which revealed a linear association with poor outcome in AHF. This ratio could be viewed as a complete (glomerular/tubular and neurohormonal) renal marker able to recognize acute WRF in AHF with additional prognostic power (Table 1) [44–46].

Finally, new specific markers of glomerular (albuminuria) or tubular damage (neutrophil gelatinase–associated lipocalin [NGAL], N-acetyl-beta-D-glucosaminidase [NAG], kidney injury molecule-1 [KIM-1]) have been studied, demonstrating their prognostic value. However, no specific data are currently available about these in terms of acute WRF in the setting of AHF [47, 48]. Maisel et al. studied the value of plasma NGAL in patients hospitalized for AHF in predicting WRF. This study showed that NGAL was not superior to creatinine for the prediction of WRF or adverse in-hospital outcomes [49]. Therefore, despite ongoing scientific interests in renal biomarkers, it is not yet possible to replace traditional renal function measurements (sCr, BUN, eGFR) with new renal biomarkers. Additionally, the previously discussed tubular markers have initially been studied in nephrological settings and have only been compared with histopathological-proven tubular injury in this setting. This has never been done in subjects with heart failure, and therefore, the extent of true tubular damage remains unclear.

## Differential value of WRF depending on the setting

Recently, it has also been hypothesized that the value of WRF might depend on the context in which it occurs. For instance, a slight decrease in renal function might be beneficial in the setting of good decongestive response in patients with AHF. Therefore, three subtypes of WRF are proposed:

- Pseudo WRF—due to congestion (also at the levels of the kidney) and subsequent efficient decongestive treatment. Several studies showed that during decompensation, HF patients undergoing decongestive treatment developed WRF. In this setting, HF patients who developed WRF together

**Table 1** Studies including the BUN/creatinine ratio in AHF

| First author (study) | Renal dysfunction definition | Marker | Prognostic impact |
|---|---|---|---|
| Ather et al. [30] | WRF was defined as > 20% reduction in eGFR from admission to discharge and increased BUN at discharge. | eGFR ΔBUN | Development of WRF (defined as reduction in eGFR) during AHF treatment was not associated with mortality. ΔBUN was associated with 1-year mortality. |
| Klein et al. (OPTIME-CHF) [2] | Increase of ≥ 25% in BUN or decrease of ≥ 25% in eGFR during hospitalization. | eGFR BUN | An increase of > 10 mg/dl in BUN during hospitalization was associated with a worse 60-day survival rate: BUN (per each 5-mg/dl increase) had a hazard ratio of 1.08 (95% CI, 1.01 to 1.16). |
| Palazzuoli et al. [35] | WRF: the in-hospital rise in serum creatinine ≥ 0.3 mg/dl or estimated glomerular filtration rate (GFR) reduction ≥20%. BUN increase was defined as a rise in BUN ≥ 20% during admission. | Creatinine eGFR BUN | BUN increase ≥ 20% during hospitalization for AHF predicts a poor outcome independently from renal function deterioration and decongestion. WRF predicts adverse outcome only if BUN increases substantially or clinical congestion persists. |
| Ruocco et al. [36] | BUN increase at discharge ≥ 20% with respect to baseline. | BUN | BUN increase of more than 20% was associated with poor outcome, independently of the persistence of congestion signs. |
| Matsue Y et al. [38] | Higher BUN/sCr ratio than age-specific and sex-specific normal values of the BUN/sCr ratio. | BUN/sCr | In patients with AHF, BUN/creatinine higher than age-specific and sex-specific normal range is associated with worse prognosis independently from both creatinine and BUN. |
| Brisco et al. [39] | IRF: the improvement in eGFR ≥ 20%; WRF: a ≥ 20% deterioration in eGFR | eGFR BUN/sCr | An elevated admission BUN/Cr identifies decompensated patients with heart failure likely to experience IRF with treatment. However, this improvement seems to be largely transient, and RD, in the setting of an elevated BUN/Cr, remains strongly associated with death. |
| Testani et al. [40] | RD: eGFR ≥ 60 ml/min/1.73 m² | eGFR BUN/sCr | In the setting of acute decompensated HF, the combined use of BNP and BUN/Creat stratifies patients with renal dysfunction into groups with significantly different clinical phenotypes and prognosis. |

AHF, acute heart failure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; IRF, improved renal function; sCr, serum creatinine; WRF, worsening renal function; RD, renal dysfunction

with efficient decongestion at discharge did not have a poor prognosis and the in-hospital creatinine increase did not persist after discharge. The pathophysiological meaning of this situation might be found in the congestive aetiology of WRF and the discharge resolution of it. These patients were usually sufficiently perfused and they show a good response to decongestive treatment [50, 51]. This subtype is recognizable by haemoconcentration and osmolarity reduction during decongestive therapy. Therefore, it is often related with significant clinical decongestion and it permits a diuretic titration after infusional period.

- True WRF—which is related to both congestion and hypoperfusion that persists in the post-discharge period. Following previous findings, patients with residual congestion at discharge usually demonstrated a sustained creatinine increase also in the post-discharge period. In this setting, WRF is due to both increased renal venous pressure and reduced arterial perfusion. This subtype of WRF usually persists after discharge influencing diuretic treatment response and electrolyte unbalance after discharge. Oral loop diuretic doses after the acute phase cannot be reduced and often a combination with another diuretic class is mandatory to achieve efficient diuresis [36, 52–55]. A recent post hoc analysis of the PROTECT trial demonstrated the prognostic value of WRF in patients experiencing residual congestion [56]. This subtype is related to neurohormonal overdrive, and it is often associated with poor diuretic response needing additional loop diuretic amount or ultrafiltration therapy. A true WRF is also associated with BUN increase, sodium avidity from the tubule, and more interstitial fluid accumulation

- WRF occurring during CKD—which is mainly related to reduced cortical blood flow and chronic glomerulosclerosis with reduced cortical wall. This subtype is much more prevalent in older subjects with a high atherosclerotic burden, in uncontrolled diabetes, and in patients with a history of severe hypertension. WRF in these patients could reflect a real eGFR deterioration due to more severe illness, and decreased renal perfusion at cortical site. A recent study of Nunez et al. showed that patients with baseline CKD and associated WRF during hospitalization were more prone to adverse events in comparison with patients without baseline CKD. Current data have been summarized in a meta-analysis by Damman et al. [24]. For these reasons, this subtype of acute renal impairment should be considered the most detrimental in terms of prognosis [57] (Fig. 2).

The above proposed classification is an attempt to distinguish the more dangerous forms from neutral subtypes. Accordingly, a recent post hoc analysis describing temporal occurrence of WRF demonstrated similar clinical characteristics and prognostic impact in all WRF typologies [56].

Interestingly, patients experiencing an improvement of renal function during diuretic therapy showed a worsened outcome. It has been hypothesized that this paradoxical situation could reflect the discontinuation/down-titration of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE-Is/ARBs) and beta-blockers, and/or right ventricular dysfunction leading to increased central venous pressure [58]. All these data confirm the need for a better understanding of the "real impact" of different WRF subtypes in relation to the pre-existing kidney status, haemodynamic condition, and congestion profile. In this framework, the main goal should be effective decongestion together with continuation of neuro-hormonal blockade in order to counteract rennin angiotensin activity in the nephron [59, 60].

## Treatment strategies in AHF patients developing WRF

The cornerstone of AHF treatment is diuretic therapy with the aim to reduce symptoms through the reduction of pulmonary and systemic congestion. The most frequently used diuretic class in AHF is loop diuretics that increase diuresis and reduce left ventricular filling pressures and consequent symptoms. However, these agents have several side effects such as hypokalaemia, hyponatraemia, and renal impairment. Moreover, administration of loop diuretics might also result in some adaptive effects in the kidney: at the glomerulus by a reduction of RBF, at the proximal tubules by increasing sodium resorption, and at the collecting duct by increasing aldosterone activity. Following from this, loop diuretics increase neurohormonal activity and sympathetic nervous system activity [59, 60]. It has been suggested that all these features (combined) lead to WRF. Among the different studies regarding loop diuretics, there is consensus that higher doses of loop diuretics more frequently lead to WRF and are associated with poor outcomes; however, this might be confounded by indication. A recent meta-analysis of randomized controlled trials studying the effect of loop diuretics did not show any differences between continuous and intermittent administrations in terms of all-cause mortality [61–63].

Because of lacking evidence about the time, the dosage, and the modality of administration of diuretics in AHF patients, several authors introduced a new concept regarding diuretic therapy: the diuretic response. Indeed, recognizing patients who are resistant to diuretic therapy is useful in terms of treatment adjustment and prognosis. Therefore, several formulas were explored including weight loss or urine output per administered loop diuretic dose, this way taking into account the dose of loop diuretic required to obtain the achieved effect. All these studies demonstrated that poor diuretic response was associated with more advanced heart failure, renal impairment, diabetes, atherosclerotic disease, in-hospital worsening heart failure, residual congestion, and poor outcomes. Early recognition of this condition should improve in-hospital
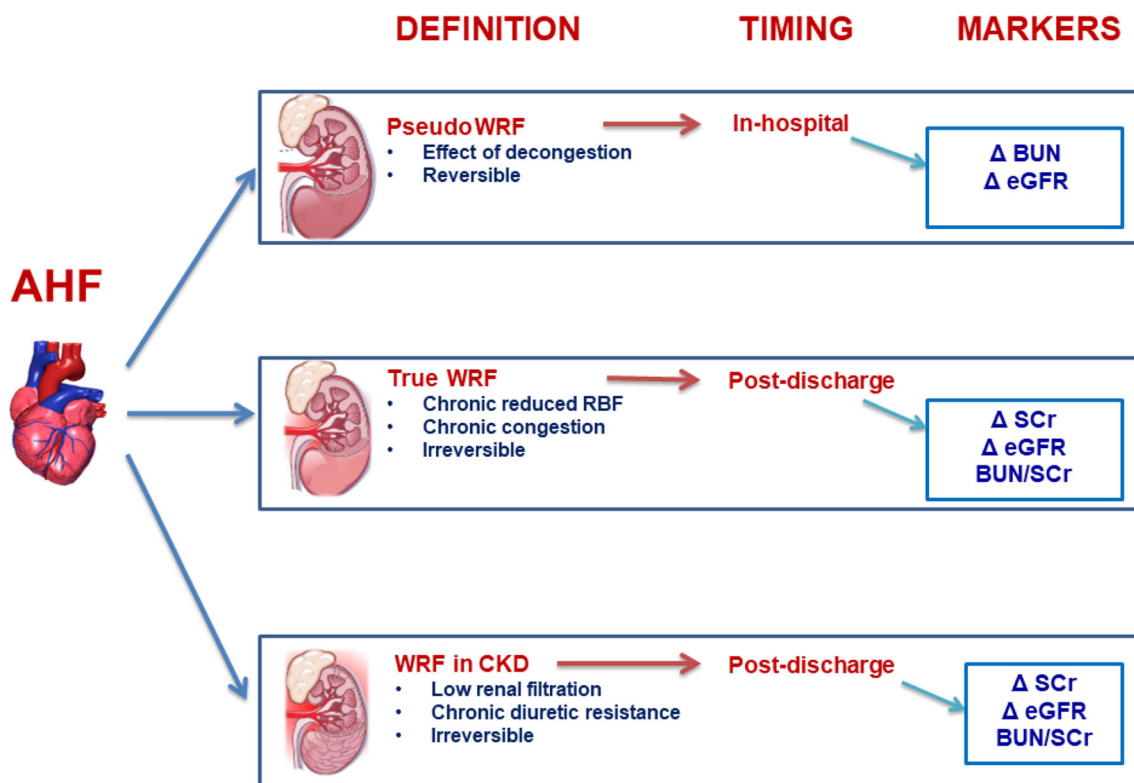
**Fig. 2** Classification of WRF in AHF. AHF, acute heart failure; BUN, blood urea nitrogen; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; sCr, serum creatinine; WRF, worsening renal function

patients' management, and reduce WRF incidence and improve outcomes. Based on this, currently several trials are underway to improve diuretic response, and study alternative treatment options [64–66]. An approach that is currently employed is for instance, combination diuretic therapy. A possible treatment avoiding diuretic resistance and related side effects is the addition of the carbonic anhydrase inhibitor "acetazolamide." This drug works at proximal tubule where the main amount of sodium reabsorption occurs. Acetazolamide inhibits sodium reabsorption and reduces renin production and subsequent neurohormonal activation through the delivery of chloride to the macula densa cells. The ADVOR trial will investigate the combination of acetazolamide and loop diuretics in relation to decongestion in AHF with volume overload [67].

In AHF patients, in case of inadequate diuresis, guidelines recommend to increase loop diuretic dose or to add a thiazide diuretic. Among thiazide diuretics, there were no differences in terms of outcome and side effects between oral metolazone and intravenous chlorothiazide. However, several authors have recently demonstrated that in the acute setting, HF patients receiving metolazone were more prone to electrolyte unbalances, WRF, and adverse event occurrence with respect to patients taking high doses of loop diuretics. Taken together, sequential nephron blockade strategy is associated with higher rates of WRF and adverse events [68, 69].

Moreover, several authors studied the effect of mineralocorticoid receptor antagonists in AHF patients. In the ALARM-HF trial, mineralocorticoid receptor antagonist use in the acute setting reduced in-hospital mortality [70]. Similarly, Verbrugge et al. showed that in 80 AHF patients with a high risk of renal dysfunction, treatment with spironolactone was safe and increased natriuresis [71]. However, recent findings from ATHENA HF demonstrated that spironolactone did not improve decongestion in AHF independently from renal dysfunction. Therefore, despite the observation that in-hospital use of this drug appeared to be safe in HF patients with moderate renal dysfunction, there is limited applicability for the addition of mineralocorticoid receptor antagonists to increase diuretic response [72].

The above-described observations suggest that during decongestive therapy titration, several factors should be considered: (1) diuretic response which is an independent prognostic factor in AHF; (2) combined therapy (MRA; thiazide) to obtain a greater diuresis and subsequent decongestion; (3) ACE-Is/ARBs and beta-blocker therapy should be continued to sustain neurohormonal blockade if tolerated; (4) baseline CKD and WRF incidence during the treatment, of which the adverse effects depend on the context; (5) diuretic side effects such as electrolyte imbalances. A good balance among these factors might be the only possible solution to improve prognosis related to AHF treatment.

# The kidney in chronic heart failure

## Pathophysiology of kidney dysfunction in chronic heart failure

In chronic heart failure (HF), several processes influence kidney function and can contribute to the development of concomitant renal dysfunction. In brief, decreased cardiac output, predominantly due to heart failure with a reduced ejection fraction (HFrEF), results in decreased organ perfusion. In patients with heart failure with a preserved ejection fraction (HFpEF), elevated filling pressures are the main haemodynamic feature and decreased systolic filling will result in inadequate stroke volume reserved, ultimately causing a decreased cardiac output. A reduction of cardiac output in patients with chronic HF has been shown to result in a decrease in renal blood flow [73, 74]. The kidney is generally able to sustain these changes due to its autoregulatory function. In HF patients, however, this autoregulatory function is (partly) blocked by medications [75]. Additionally, in response to a diminished cardiac output, the kidney promotes mechanisms that result in water and sodium retention, ultimately causing (subclinical) congestion, which in turn causes further kidney dysfunction. Both in experimental settings and in patients with either chronic or acute HF, an increase in central venous pressures or abdominal pressure was associated with an increased risk of worsening renal function [13, 18, 76, 77]. An increased venous pressure leads to increased renal (interstitial) pressure, which in turn causes tubular collapse and minimal pressure gradients over the glomerulus diminishing passive filtration. Furthermore, neurohormonal activation in chronic HF patients (brought on by the reduction in cardiac output, as well as by increased venous pressures) mediates the effect of heart failure on renal dysfunction. For instance, angiotensin II causes afferent and efferent vasoconstriction, directly influences estimated glomerular filtration rate, and promotes sodium retention in the proximal tubule, and renal fibrosis. Additionally, adenosine further reduces renal blood flow and activates tubuloglomerular feedback, resulting in a reduction in glomerular filtration rate. In HF, the kidneys are furthermore prone to tubulointerstitial damage due to reduced tissue perfusion and hypoxemia.

## The kidney in heart failure with a preserved ejection fraction

Traditionally, most research has focused on the effect of HFrEF on kidney function, rather than the effects of HFpEF on kidney function. Interestingly, albuminuria was recently identified as a risk factor for new-onset HFpEF, and HFpEF is common in patients with chronic kidney disease (CKD) [78]. Several hypotheses therefor exist regarding the directionality of the relation between heart failure with a preserved ejection fraction and renal dysfunction [79]. Through consequences of HFpEF such as elevated filling pressures, autonomic dysfunction, and low nitric oxide levels, HFpEF might contribute to the development of kidney dysfunction (Fig. 1). CKD itself however might cause HFpEF through microvascular dysfunction, uremic toxins, and RAAS activation. Finally, common underlying mechanisms, such as inflammation and endothelial dysfunction, might drive the development of both renal dysfunction and kidney disease [80].

## Kidney dysfunction and prognosis

Traditionally, the severity of kidney dysfunction is defined based on the estimated glomerular filtration rate (GFR), where an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 $m^2$ is most commonly defined as CKD.

In a large meta-analysis, the prevalence of CKD in patients with chronic HF was 42%. The presence of CKD was significantly associated with an increased risk of mortality (OR 2.36 [2.08–2.47], $P < 0.001$) [24]. Furthermore, in both HFrEF and HFpEF, the presence of CKD was associated with an increased risk of all-cause mortality (OR 2.00 [1.81–2.21], $P < - 0.001$ for HFrEF; and 3.22 [2.66–4.90], $P < 0.001$ for HFpEF). Similarly worsening renal function, usually defined as an increased in serum creatinine $\geq 0.3$ mg/dl, is associated with poor outcome both in HFrEF and in HFpEF [24]. An exception to this is the occurrence of WRF after the initiation of angiotensin-converting enzyme inhibitors (ACEi), which is not associated with worse outcomes.

## Biomarkers of kidney dysfunction in chronic heart failure

GFR, i.e. the rate at which substances are filtered by the kidney, is the most frequently used method to assess renal function. Serum creatinine is used to calculate eGFR, yet due to some active tubular secretion, this provides a slightly imperfect (over)estimation of GFR. In systolic CHF, the Chronic Kidney Epidemiology Collaboration (CKD-EPI) most accurately estimates measured GFR compared with the simplified Modification of Diet in Renal Disease (sMDRD) [81]. Another marker that is commonly assessed in association with renal function is blood urea nitrogen (BUN), which is determined by glomerular filtration, tubular reabsorption, and neurohormonal activation. The BUN/creatinine ratio might aid in distinguishing between pre-renal and intrinsic renal diseases; in pre-renal problems, significant neurohormonal activation causes a disproportional reabsorption of BUN in comparison to creatinine [40]. Both BUN and the BUN/creatinine ratio identify HF patients with an increased risk of adverse outcomes. Albuminuria in HF is thought to be the consequence of endothelial dysfunction, inflammation, podocyte damage, disrupted tubular reabsorption, and congestion, and has been

shown to provide additional information on top of eGFR or the BUN/creatinine ratio [82, 83]. Tubular damage markers, such as neutrophil gelatinase–associated lipocalin (NGAL), $N$-acetyl-β-D-glucosaminidase (NAG), and kidney injury molecule 1 (KIM-1), have all been shown to be increased in HF patients compared with controls, and are associated with poor outcome [84, 85]. Both NAG and KIM-1 have been found to be susceptible to diuretic-induced volume changes, suggesting that these markers could be used to monitor response to diuretic treatment or haemodynamic changes [86]. At the present, there is however no clinical applicability in HF of these markers yet. Finally, a novel cardiorenal connector might be proenkephalin (PENK), which a is an endogenous opioid peptide that exerts both cardiovascular and renal effects. PENK levels are elevated in HF populations in comparison with healthy controls, and are strongly associated with worsening renal function and outcome [87, 88]. Further studies are needed to provide more insight in the exact value of PENK in HF.

Recently, urinary sodium, as assessed in spot urinary samples, has regained interest in HF patients. In a single-centre study of HF outpatients, spot urinary sodium was assessed weekly [89]. This study showed that patients who developed AHF experienced a drop in urinary spot sodium concentration the week before hospital admission for AHF. Outpatient assessment of spot urinary sodium might therefore be a readily, applicable marker to guide or initiate treatment and prevent hospital admissions for AHF.

## Treatment of patients with chronic heart failure and kidney dysfunction

The 2016 ESC HF guidelines recommend treatment with ACEi and beta-blockers for symptomatic HFrEF patients [90]. Addition of mineralocorticoid receptor antagonist (MRA) is recommended for patients who remain symptomatic. All of these medications potentially influence renal function or expose HF patients with renal dysfunction at a greater risk of adverse events, such as hyperkalaemia. Additionally, data on the effect of these medications is limited in HF patients with severe renal dysfunction, as these patients have been excluded from randomized controlled trials. Therefore, HF patients with concomitant renal dysfunction are less likely to receive guideline-recommended therapies, even though this is not always justified.

Retrospective analyses in small subgroups of HF patients with renal impairment showed that treatment with an ACEi led to an equal relative risk reduction compared with HF patients with normal renal function [91]. Given that the risk of poor outcome is greater in HF patients with renal impairment, the absolute risk benefit of ACEi might be even higher in this subgroup. Caution should be observed with regard to renal function and electrolytes, as treatment with an ACEi, specifically in patients with renal dysfunction, may cause worsening renal function or hyperkalaemia. An initial moderate increase in creatinine shortly after introduction of an ACEi is however expected; this is not associated with poor outcome.

**Table 2** Novel data on guideline-recommended therapies and renal function in chronic heart failure

| Author (study) | Population | Renal function | Conclusions |
|---|---|---|---|
| Ferreira et al. (EMPHASIS-HF) [82] | 2737 patients with systolic heart failure (NYHA class II), and a recent hospitalization for heart failure, or elevated natriuretic peptide levels, randomized to eplerenone or placebo | Eplerenone doses were stratified according to renal function <br>• 25 mg/day in patients with eGFR 30–49 ml/min/1.73 m$^2$ <br>• 50 mg/day in patients with eGFR ≥ 50 ml/min/1.73 m$^2$ | Effectiveness of eplerenone was not influenced by renal function. <br>Patients with impaired renal function were more likely to experience adverse events. |
| Damman et al. (PARADIGM-HF) [83] | 8399 patients with heart failure with a reduced ejection fraction randomized to sacubitril/valsartan or enalapril | CKD was defined as an eGFR < 60 ml/min/1.73 m$^2$ <br>Pre-specified renal endpoint, time-to-first occurrence of any of: <br>1) A 50% decline in eGFR from baseline <br>2) 30–60 ml/min/1.73 m$^2$ decline in eGFR from baseline <br>3) Reaching end-stage renal disease | Compared with enalapril, administration of sacubitril/valsartan led to a slower decline in eGFR and was associated with improved outcomes, also in patients with CKD. <br>There was no difference in the occurrence of the pre-specified endpoint. Treatment with sacubitril/valsartan was however associated with a slight increase in urinary albumin-to-creatinine ratio. |
| Voors et al. (PARAMOUNT) [88] | 301 patients with heart failure with a preserved ejection fraction, history of signs and symptoms of heart failure, elevated natriuretic peptides, and diuretic use, randomized to sacubitril/valsartan or valsartan | Worsening renal function was defined as an increase in serum creatinine > 0.3 mg/dl and/or 25% increase between two time points. | Treatment with sacubitril/valsartan was associated with preservation of eGFR compared with valsartan therapy. It was however associated with an increase in urinary albumin creatinine ratio. |

*CKD*, chronic kidney disease; *eGFR*, estimated glomerular filtration rate; *NYHA class*, New York Heart Association class

Several large subgroup analyses from randomized clinical trials showed clear mortality and morbidity benefit associated beta-blocker treatment in HF patients with renal dysfunction. Interestingly, the relative risk reduction associated with beta-blocker use might even be greater in HFrEF patients with CKD [92].

Initially MRAs were considered contra-indicated in patients with renal dysfunction due to the risk of hyperkalaemia. However, the beneficial effect of both spironolactone and eplerenone on outcomes in HF patients was extended to those with renal dysfunction [93, 94]. A recently published secondary analysis of the Eplerenone in Mild Patients Hospitalized and Survival study in Heart Failure (EMPHASIS-HF) studied the beneficial and adverse effects of eplerenone use across renal function. Even though patients with an eGFR < 50 were assigned lower target doses of eplerenone (i.e. 25 mg versus 50 mg), despite a comparable beneficial effect on outcome, adverse events were more frequent in patients with a baseline eGFR < 50 (Table 2) [95]. Patients with renal dysfunction should be monitored closely after initiation of a MRA, as hyperkalaemia might develop resulting in life-threatening tachycardias.

A novel medication that was added to the 2016 ESC HF guidelines is sacubitril/valsartan. Initiation of sacubitril/valsartan is recommended as a replacement for ACEi in symptomatic HF patients on optimal guideline-recommended medical treatment. In a retrospective analysis of the prospective comparison of ARNI with ACE inhibition to determine impact on global mortality and morbidity in heart failure (PARADIGM-HF) trial, sacubitril/valsartan led to a slower rate of eGFR decline compared with enalapril [96]. The relative risk reduction associated with sacubitril/valsartan was similar in patients with and without renal dysfunction (Table 2). For all of these medications (ACEi, beta-blocker, MRA, sacubitril/valsartan), no data is available regarding their use in patients with severe renal dysfunction (CKD stages 4–5).

Limited data is available on the effect of renal dysfunction on the response to cardiac resynchronization therapy (CRT) as these patients are often also excluded from these trials. The available data suggest that patients with renal dysfunction show less reverse remodelling in response to CRT implantation, yet this is still associated with improved outcomes and should therefore be considered [97, 98].

Finally, loop diuretics are recommended in HF patients with signs and symptoms of congestion. In patients with renal dysfunction, the dose/response curve of diuretics is shifted rightward and upwards, meaning that higher doses of diuretics are recommended to achieve similar effects [99]. This is discussed in more detail in the previous section on treatment of acute HF patients with renal dysfunction. It should be noted that down-titration of loop diuretics might be feasible in up to 60% of patients to facilitate up-titration of guideline-recommended therapies [100].

## Conclusions

Both in acute and in chronic heart failure, renal dysfunction and worsening renal function are highly prevalent and associated with poor outcomes. This association might however be modified by the context in which it occurs. Worsening renal function in the context of adequate decongestion in acute heart failure, or worsening renal function after initiation of neuro-hormonal blockers in chronic heart failure could have neutral consequences. Oppositely, WRF occurring during scarce decongestion, poor diuretic response, and previous CKD is associated with adverse outcome, and it deserves a specific management that is still to be elucidated.

## Compliance with ethical standards

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