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CKJ REVIEW

Kidney function changes in acute heart failure: a practical approach to interpretation and management

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ABSTRACT

Worsening kidney function (WKF) is common in patients with acute heart failure (AHF) syndromes. Although WKF has traditionally been associated with worse outcomes on a population level, serum creatinine concentrations vary greatly during episodes of worsening heart failure, with substantial individual heterogeneity in terms of their clinical meaning. Consequently, interpreting such changes within the appropriate clinical context is essential to unravel the pathophysiology of kidney function changes and appropriately interpret their clinical meaning. This article aims to provide a critical overview of WKF in AHF, aiming to provide physicians with some tips and tricks to appropriately interpret kidney function changes in the context of AHF.

LAY SUMMARY

In this article we thoroughly review the literature on a debatable topic in cardiorenal medicine. We aimed to provide physicians with some tips and tricks for interpreting kidney function changes in patients with acute heart failure syndromes.

Keywords: decongestion, diuretic therapy, heart failure, intrarenal venous flow pattern, kidney venous congestion

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INTRODUCTION

Few organs in the body are as intricately linked to each other in their function as the heart and kidneys. Chronic kidney disease (CKD) and heart failure (HF) frequently coexist and share common risk factors [1]. Additionally, the dysfunction of one organ can accelerate the progression of the other. In the acute heart failure (AHF) setting, changes in kidney function are common [2–4]. While some of these changes merely reflect decongestion or a healthy kidney's response to decongestive therapy, others could signify true kidney injury [5]. Distinguishing between the two remains challenging, with crucial management implications. Physicians are often reluctant to prescribe aggressive diuretic therapy in patients with AHF and concomitant kidney impairment and usually withdraw or reduce the dose of diuretics and guideline-directed medical therapy in the presence of an acute increase in serum creatinine, when in reality, some of these patients might benefit from just the opposite. Many clinicians attribute worsening kidney function (WKF) to hypoperfusion, neglecting that, in many cases, it is a proxy of an appropriate response to therapy or, conversely, of an insufficient diuretic intensity [1]. Thus misinterpreting kidney function changes could promote ongoing tubular damage, inappropriate discontinuation or insufficient titration of decongestive or disease-modifying HF therapies [6–8]. The underlying mechanisms of kidney dysfunction in patients with AHF are still not fully understood. The existing literature is difficult to interpret due to different definitions of WKF and the heterogeneity of AHF syndromes.

In the current article, we review the terminology, pathophysiology and prognosis of kidney function changes in this clinical context. Additionally, we provide tips and tricks to interpret kidney function changes in patients with AHF.

EPIDEMIOLOGY

CKD is one of the most prevalent comorbidities in patients with HF, ranging from 20 to 57% in chronic HF and 30 to 67% in AHF registries [2–4]. In the Heart Failure Pilot Survey, CKD was the most prevalent comorbidity in patients with chronic HF (41%) [9]. It was independently related to increased mortality and HF hospitalizations. In addition to prior CKD, changes in kidney function are commonly observed in hospitalized patients with AHF, ranging from 10 to 40% of patients [10, 11]. This wide variability can be attributed, at least partly, to different parameters and cut-off values used to define changes in kidney function (Table 1).

DEFINITIONS

Changes in kidney function in patients with AHF are commonly defined in the literature by the terms 'worsening kidney function' (WKF) and 'acute kidney injury' (AKI). WKF has been broadly defined as an increase in serum creatinine (SCr) ranging from ≥0.3 to 0.5 mg/dl from baseline [10, 12]. However, definitions vary greatly depending on the type of marker used [SCr, cystatin C or estimated glomerular filtration rate (eGFR)] and the degree of change (absolute versus relative). For instance, some investigators use increases in SCr above a threshold (e.g. SCr >1.5 mg/dl) to define WKF [13]. However, these definitions lack universal consensus [6, 14]. In turn, there are three different definitions of AKI: the Risk, Injury, Failure, Loss, End-Stage (RIFLE), Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) criteria [14]. Urine output (UO) is also used as a criterion to define AKI. However, only a small number of studies in AHF have measured UO and evaluated how

Table 1: Definition of changes in kidney function in AHF.

WKF		
eGFR	**Cystatin C**	**Creatinine**
• ≥20% decrease from baseline	• >0.3 mg/dl increase from baseline	• ≥0.3 mg/dl increase from baseline
• ≥25% decrease from baseline		• ≥0.3 mg/dl increase and >25% increase from baseline
• >5% per year decrease from baseline		• ≥0.5 mg/dl increase from baseline
		• ≥1.5 times baseline
		• ≥25% increase + >2.0 mg/dl

AKI		
	Creatinine component	
UO component	KDIGO	AKIN	RIFLE
Grade 1 <0.5 ml/kg/h for 6–12 h	Cr to 1.5–1.9 times baseline over 7 days or absolute increase ≥ 0.3 mg/dl over 48 h	Cr to 1.5–2 times baseline or an absolute increase ≥0.3 mg/dl over 48 h	Cr to ≥1.5 times within 7 days sustained for 24 h
Grade 2 <0.5 ml/kg/h for ≥12 h	Cr ≥2–2.9 times baseline	Cr ≥2–3 times baseline	Cr ≥2 times baseline
Grade 3 <0.3 ml/kg/h for ≥24 h or anuria for ≥12 h	Cr ≥3 times baseline or an increase above ≥4 mg/dl or RRT	Cr ≥3 times baseline or an increase above ≥4 mg/dl (with an absolute increase >0.5 mg/dl) or RRT	Cr ≥3 times baseline or an increase above ≥4 mg/dl (with an absolute increase >0.5 mg/dl) or RRT

Cr: creatinine; RRT: renal replacement therapy.
For AKI criteria, if UO and SCr stage do not correspond to the same stage, patients are classified in the worse stage. Adapted from Mullens *et al.* Evaluation of kidney function throughout the heart failure trajectory—a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:584–603.

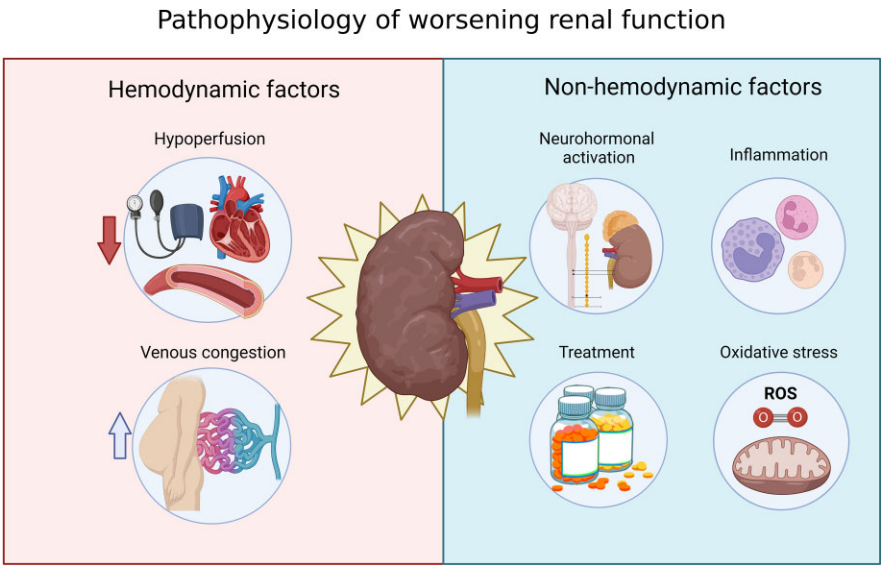

Figure 1: Pathophysiology of worsening kidney function in AHF.

it correlates with SCr or eGFR changes [15]. Furthermore, if a diuretic is being used as the primary treatment, the utility of assessing UO is arguable. As a result, the UO definition of AKI is not routinely used in clinical practice. Table 1 summarises the different criteria used to define WKF and AKI.

PATHOPHYSIOLOGY

Nowadays, AKI is recognized as a syndrome in which one or more mechanisms of kidney damage may be present [16]. The prognosis depends on the underlying cause. Thus a thorough analysis of the pathophysiological mechanisms responsible for kidney function changes during AHF is essential for their correct interpretation. These complex and multifactorial mechanisms include both haemodynamic and non-haemodynamic factors, such as septic AKI or contrast-associated AKI [17, 18]. Fig. 1 summarises the pathophysiology of WKF in AHF.

Haemodynamic factors

Kidney hypoperfusion

Classically, WKF has been attributed to kidney hypoperfusion caused by low cardiac output (CO) or intravascular depletion secondary to diuretic use (deemed the 'pre-renal aetiology') [19]. Reduced CO decreases kidney perfusion, which activates compensatory mechanisms such as the sympathetic nervous system, renin–angiotensin–aldosterone system (RAAS) and vasopressin secretion to preserve eGFR. These mechanisms help to maintain kidney perfusion in the short term by stimulating water and sodium reabsorption, but are deleterious in the long-term, promoting fibrosis, apoptosis and adverse ventricular remodelling. Persistent hypoperfusion could also lead to kidney ischaemia [20].

Several studies have recently challenged this traditional paradigm, demonstrating a lack of correlation between CO and kidney function. Indeed, only a minority of patients with HF with reduced ejection fraction (HFrEF) present hypotension on admission [4, 21]. In fact, most patients have normal or elevated blood pressure and no evidence of hypoperfusion. Also, patients with HF and preserved ejection fraction (HFpEF) have an equal prevalence of WKF compared with HFrEF patients [22, 23]. In a post hoc analysis of the ESCAPE trial, there was no correlation between WKF and cardiac index (CI; cardiac output corrected for the patient's body surface area) [24]. Accordingly, haemodynamic optimization with pulmonary artery catheter-guided therapy did not reduce the incidence of WKF compared with clinical assessment. Along the same line, Mullens *et al.* [25], in a cohort of 145 subjects with AHF, showed that the mean baseline CI was significantly higher in patients who developed WKF (2.0 ± 0.8 versus 1.8 ± 0.4 L/min/m^2). Likewise, Hanberg *et al.* [26] found that a higher CI was paradoxically associated with worse eGFR in a multicentre population of decompensated HF. It is important to note that the kidney microcirculation has autoregulatory properties that maintain eGFR within narrow limits in response to kidney pressure or flow fluctuations [27]. Therefore, high-magnitude blood pressure drops are necessary to surpass this compensatory mechanism. A post hoc analysis of the pre-RELAX-AHF study showed that only large drops in systolic blood pressure (usually >20 mmHg) during the first 48 hours of hospitalization predicted WKF [28]. In summary, current evidence suggests low CO might not be the primary determinant of WKF in patients with AHF.

Kidney venous congestion

Recent studies suggest that an increase in central venous pressure (CVP) has a more pronounced impact on eGFR than a decrease in CO [25, 29]. Early experimental research demonstrated that elevated CVP (>20 mmHg) reduced diuresis in an isolated canine kidney [30]. Similarly, elevated intra-abdominal pressure (IAP; >8 mmHg), found in up to 60% of hospitalized patients with HF, is also associated with greater impairment of kidney function [31]. In turn, a reduction in IAP with different treatments (diuretics, peritoneal dialysis, paracentesis or ultrafiltration) has been shown to improve kidney function [32, 33]. Therefore, many studies support the association between high CVP and WKF, which seems to be superior to the effect of arterial blood pressure, CI or pulmonary capillary wedge pressure to predict WKF. Nonetheless, venous congestion and hypotension may act as complementary mechanisms of WKF. For example, CVP is an independent predictor of WKF, especially when there is low CO

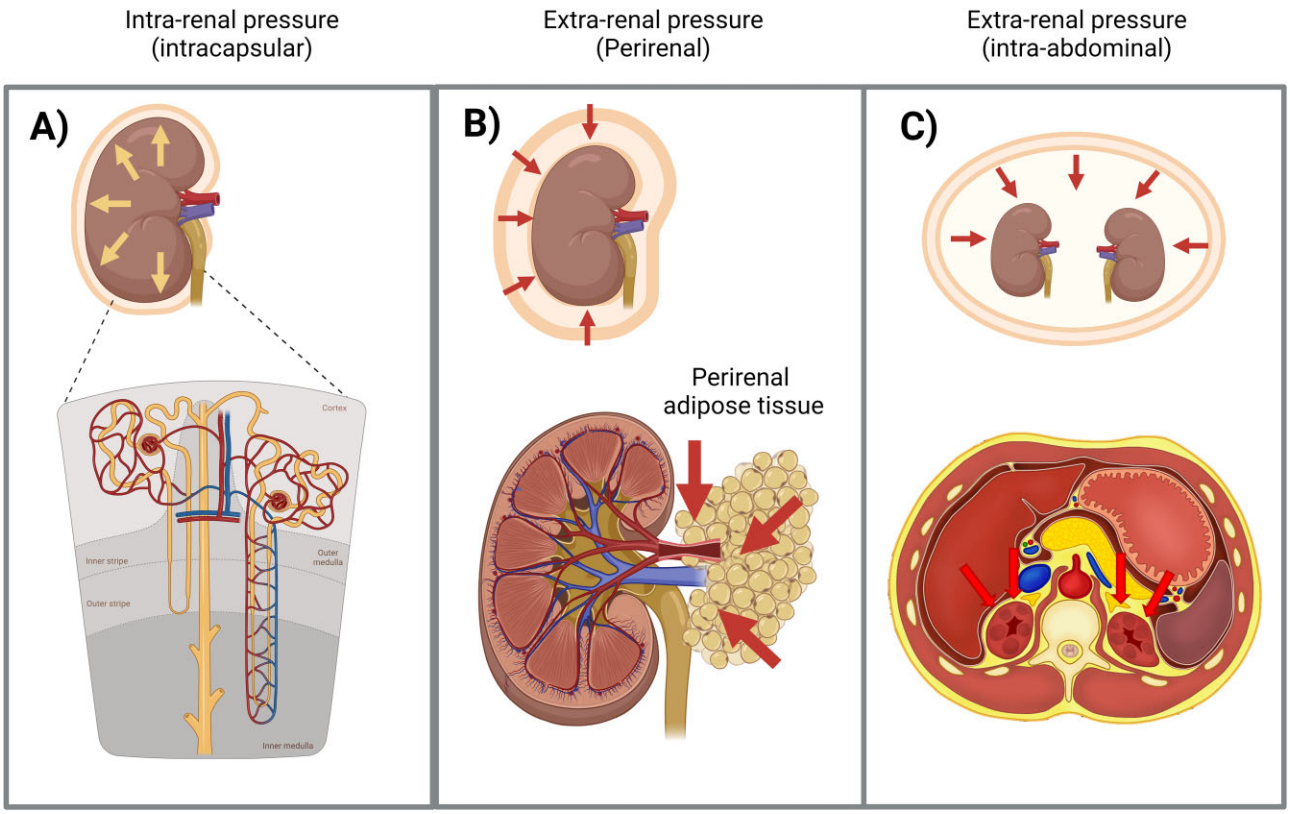

Figure 2: Mechanisms of renal tamponade.

[25, 34]. In an animal model of kidney venous hypertension, only when CO was compromised did eGFR decline [35]. Overall, patients with congestion plus hypoperfusion have worse eGFR and outcomes than patients with either one [36, 37]. These results highlight the importance of preserving adequate perfusion pressure during decongestive therapy.

The exact mechanisms by which increased CVP contributes to WKF are not totally elucidated, but possible explanations include a reduction of the net pressure gradient across the glomerulus, increased intrarenal pressure (intracapsular or interstitial space) causing tubular compression and hypoxia and/or increased extrarenal pressure (perirenal or intra-abdominal space) compressing kidney veins and parenchyma [1]. Boorsma *et al.* [38] recently coined the term 'renal tamponade' to explain the compression of kidney structures that occurs by the combination of increased kidney venous pressure and the inability of the kidneys to expand as they are surrounded by a rigid capsule. The mechanisms of renal tamponade are illustrated in Fig. 2.

These findings support the role of kidney congestion as a novel treatment target, renewing the interest in kidney decapsulation as a potential therapeutic strategy for patients with HF and kidney congestion. This technique is not new and has been used to treat various diseases (kidney abscesses, pre-eclampsia and oliguria) [39]. Studies in animal models of HF or ischaemia-induced AKI have shown promising results [40, 41]. However, to date, there is no evidence in humans with HF.

Contemporary studies have proposed the term 'congestive nephropathy' (CN) as an independent haemodynamic phenotype of kidney dysfunction that could be reversible with decongestion. There is no gold standard for diagnosing CN. Intrarenal venous Doppler (IRD) ultrasonography has emerged as a non-invasive tool to assess intrarenal venous flow (IRVF). A continuous IRVF pattern is associated with low kidney venous pressures. Conversely, a discontinuous IRVF pattern (monophasic or biphasic) indicates elevated venous pressures and thus might identify patients with the CN phenotype [42]. Fig. 3 shows different IRVF patterns in patients with HF. IRD could also help guide decongestive therapy, evaluating treatment response and identifying patients at risk for adverse outcomes [43]. IRVF patterns have shown stronger independent associations with adverse outcomes than invasive haemodynamic measurements [43–45]. A discontinuous IRVF pattern in response to volume expansion is associated with a reduced diuretic response and a worse prognosis [43]. However, confirmation studies evaluating the clinical meaning of IRVF are warranted (e.g. correlating invasive measurements of kidney venous pressure with IRVF). It should be noted that a discontinuous flow pattern is not specific and has also been described in obstructive nephropathy, diabetic nephropathy, pre-eclampsia and tricuspid regurgitation without right-sided HF [46–48]. Lastly, echocardiography has demonstrated its utility in providing non-invasive measurements to identify the pathophysiological mechanisms of WKF in AHF. First, it can estimate the patient's CO and subsequently help to diagnose a hypoperfusion state. Second, it can evaluate systemic venous congestion by estimating haemodynamic parameters such as the CVP, systolic pulmonary artery pressure or pulmonary capillary wedge pressure and by measuring the size and collapsibility of the inferior vena cava [49]. A dilated inferior vena cava (defined as a diameter >2.1 cm) with <50% collapsibility during inspiration estimates a right atrial pressure of 15 mmHg [50, 51].

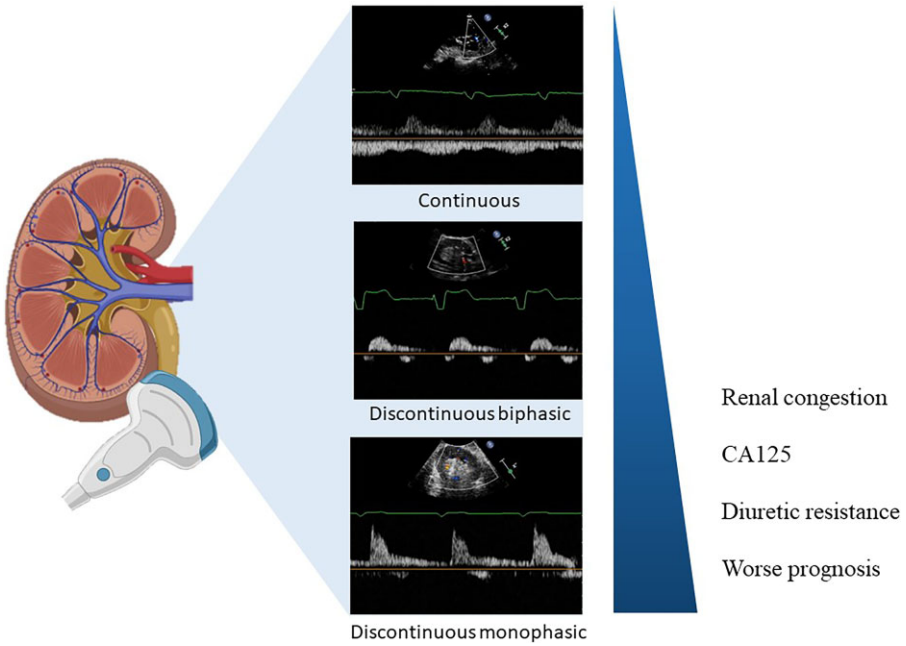

Figure 3: Different intrarenal venous flow patterns in patients with heart failure.

PROGNOSIS

Classically, WKF in the setting of HF has been associated with a longer hospital stay, higher costs and worse outcomes [3]. A meta-analysis of 28 studies of patients with AFH reported that 23% of patients had WKF, which was related to an increased risk of long-term mortality [10]. Nonetheless, the authors point out there was evidence of publication bias, which might overestimate the real relationship between WKF and prognosis. Furthermore, more recent findings have revealed divergent results [52–54]. Applying the same logic, improving kidney function (IKF) and kidney recovery should be expected to translate into better outcomes. However, IKF has also been associated with a greater risk of mortality and HF readmissions [55]. This might be explained by the fact that most of these patients had kidney impairment before hospitalization [56]. Beldhuis *et al*. [57] hypothesized that this paradoxical finding was because previous studies were population-based and did not consider the interindividual differences in kidney function. To prove their hypothesis, Beldhuis *et al*. identified individual trajectories of kidney function during hospitalization and found similar mortality rates, questioning the prognostic importance of kidney function changes in AHF. Overall, these heterogeneous findings could be partially explained by the discrepancy in the diagnostic criteria of WKF, the diversity of underlying mechanisms causing AKI and the complexity of AHF syndromes [58].

TIPS AND TRICKS TO INTERPRET KIDNEY FUNCTION CHANGES IN AHF

Distinguishing true WKF (accompanied by underlying kidney damage) from pseudo-WKF (decongestion, which does not imply tubular damage or a worse prognosis) remains one of the most important challenges physicians face when evaluating patients with AHF. To aid physicians in this task, we propose taking into consideration circumstances/parameters such as the clinical response to therapy and decongestion status, haemodynamic status (wet, dry, pale), baseline kidney function, the magnitude and chronology of kidney function changes, concomitant treatment and kinetics with other biomarkers (Table 2). A proposed algorithm is presented in Fig. 4. This algorithm is an attempt to synthesize all available information on the subject and offer a simplified approach for a complicated problem; however, we hope it will assist medical professionals in their clinical practice.

Baseline fluid overload status

High-dose diuretics are beneficial in patients with total blood volume expansion but can be harmful in patients with mild fluid overload (FO) or those with volume redistribution [59, 60]. In this latter scenario, aggressive diuretic therapy may produce intravascular depletion, leading to kidney hypoperfusion [54]. In contrast, in patients with overt FO, aggressive diuretic therapy may improve organ function (including the kidneys) [61]. In clinical practice, the main challenge remains to identify and optimally define a patient's degree of FO [61, 62]. Núñez *et al*. [63] sought to assess whether SCr changes induced by diuretic therapy differed depending on FO status (as measured by CA125) in AHF. They found that patients with higher CA125 levels (greater FO and higher risk of CN) displayed a decrease in SCr in response to aggressive diuretic therapy, compared with patients with low CA125 values in whom SCr increased. Along the same line, in 1389 patients discharged for AHF, subjects with elevated CA125 and blood urea nitrogen levels (≥24.8 mg/dl) treated with high doses of loop diuretics (≥120 mg/day) had a lower risk of long-term mortality compared with the rest of the population [64]. The property of this biomarker to define the intensity of diuretic therapy was tested in a randomized clinical trial that allocated 160 patients with worsening HF and kidney dysfunction at presentation (mean 33.7 ± 11.3 ml/min/1.73 m^2) to a conventional diuretic strategy (clinically guided) versus CA125-guided therapy (intensive in cases of high CA125 and more conservative

Table 2: Differential diagnosis of worsening kidney function in AHF.

Characteristic	True WKF	Pseudo-WKF
Fluid overload	Mild congestion/fluid redistribution, hypoperfusion	Severe congestion (based on a multiparametric evaluation)
Clinical course and decongestion	Persistent or worsening congestion	Resolution of congestion (multiparametric evaluation)
Baseline renal function and magnitude of changes	Large increase in creatinine or decrease in GFR, especially in subjects with baseline renal dysfunction. Caution if increasing creatinine >50% of baseline or >3 mg/dl and decreasing GFR >10% of baseline if eGFR is <25 ml/min	Small changes in patients with normal or mildly impaired renal function
Onset and time course	≥5 days after admission, persistent	≤4 days after admission, transient
Aetiology	Hypoperfusion, nephrotoxic agents	Venous congestion, diuretic therapy, RAAS inhibitor, ARNI, SGLT2i initiation or up-titration
Prognosis	Worse	Does not necessarily mean a worse prognosis if adequate decongestion is attained

when CA125 was low) [65]. The CA125-guided therapy led to better kidney function at 72 hours and a statistical trend to lower 30-day adverse outcomes. Thus, defining the congestion phenotype of each patient is crucial to choose the intensity of diuretic therapy and interpreting WKF.

Clinical course and decongestion

When evaluating kidney function changes, we recommend considering the patient's clinical context and risk factors for developing AKI (pretest probability) as well as a multiparametric evaluation of decongestion ideally based on clinical assessment (signs and symptoms, weight change, vital signs and urinary output), biomarkers (haematocrit/haemoglobin or natriuretic changes) and imaging techniques such as ultrasonography [66]. WKF in patients with adequate urinary output and clinical improvement does not necessarily portend a worse prognosis [5, 54, 67–73]. Numerous studies have shown that WKF results in a worse prognosis when accompanied by residual congestion [5, 54, 69–73]. For instance, Wettersten *et al.* [69] and McCallum *et al.* [73] demonstrated that WKF during AHF hospitalization was associated with a higher risk of mortality only when N-terminal pro b-type natriuretic peptide (NT-proBNP) levels did not decrease with diuretic therapy. Metra *et al.* [5] also observed that, in the absence of congestion, an increase in serum SCr levels had no prognostic value. Similarly, an analysis of the ESCAPE trial showed that haemoconcentration (a surrogate of decongestion) was associated with WKF and better outcomes [54]. Emmens *et al.* [72] investigated the interaction between diuretic response and WKF on clinical outcomes in patients with AHF using the PROTECT and RELAX-AHF-2 cohorts. They concluded that WKF was associated with a higher risk of cardiovascular death or hospitalization except for patients with a good diuretic response. Comparable results were observed with IKF [70].

In summary, it seems like decongestion, and not changes in kidney function, is the key determinant of prognosis in AHF patients. Indeed, cumulative evidence endorses that surrogates of decongestion such as NT-proBNP, haemoconcentration and weight loss outweigh WKF/IKF as a prognostic parameter [54, 69, 73]. In fact, residual congestion at discharge is one of the main predictors of readmission, and adequate decongestion is often not achieved during hospitalization [74–77]. In a recent post hoc analysis of the DOSE-AHF and CARESS-HF trials, only half of the patients were free from signs of congestion at discharge, and they had lower rates of death and rehospitalization [75].

Baseline kidney function and magnitude of creatinine changes

When interpreting the clinical implications of kidney function changes in the AHF setting, it is essential to consider the patient's baseline kidney function and the magnitude of the change. In a meta-analysis of eight studies with 18 000 patients with HF the odds ratio (OR) was 1.03 (not significant) when the SCr rose by 0.2–0.3 mg/dl or the eGFR decreased by <5–10 ml/min/1.73 m^2. Conversely, the OR rose to 3.22 when the SCr increased >0.5 mg/dl or the eGFR decreased by >15 ml/min/1.73 m^2 [78]. These results suggest that kidney function changes should be viewed as a continuous variable considering the magnitude of changes. This complicates efforts to find a clinically meaningful elevation of SCr to define WKF [12, 58].

Furthermore, the clinical importance of the magnitude of kidney function changes depends on the patient's baseline kidney function. Sánchez-Serna *et al.* [56] found that the presence of WKF at admission was associated with a higher risk of death and HF readmissions, even in the mild stages of AKI. In a study of 705 patients with AHF, the risk of 1-year mortality varied depending on the presence of kidney insufficiency on admission. In patients with impaired kidney function on admission (SCr >1.4 mg/dl), even small increases in SCr levels were independently associated with a greater risk of 1-year mortality. In contrast, in patients with normal or mildly impaired kidney function on admission, only important SCr increases (>1 mg) were related to worse outcomes [79]. Unfortunately, there is no accepted method for establishing baseline kidney function due to the inherent fluctuations in SCr. The Acute Disease Quality Initiative (ADQI) work group suggests that if one or more premorbid SCr values are available, the mean SCr measured 7–365 days before admission is the value that best represents a patient's baseline kidney function [80].

Based on these studies, we postulate that small changes in patients without established kidney failure may represent haemoconcentration rather than kidney damage. In contrast,

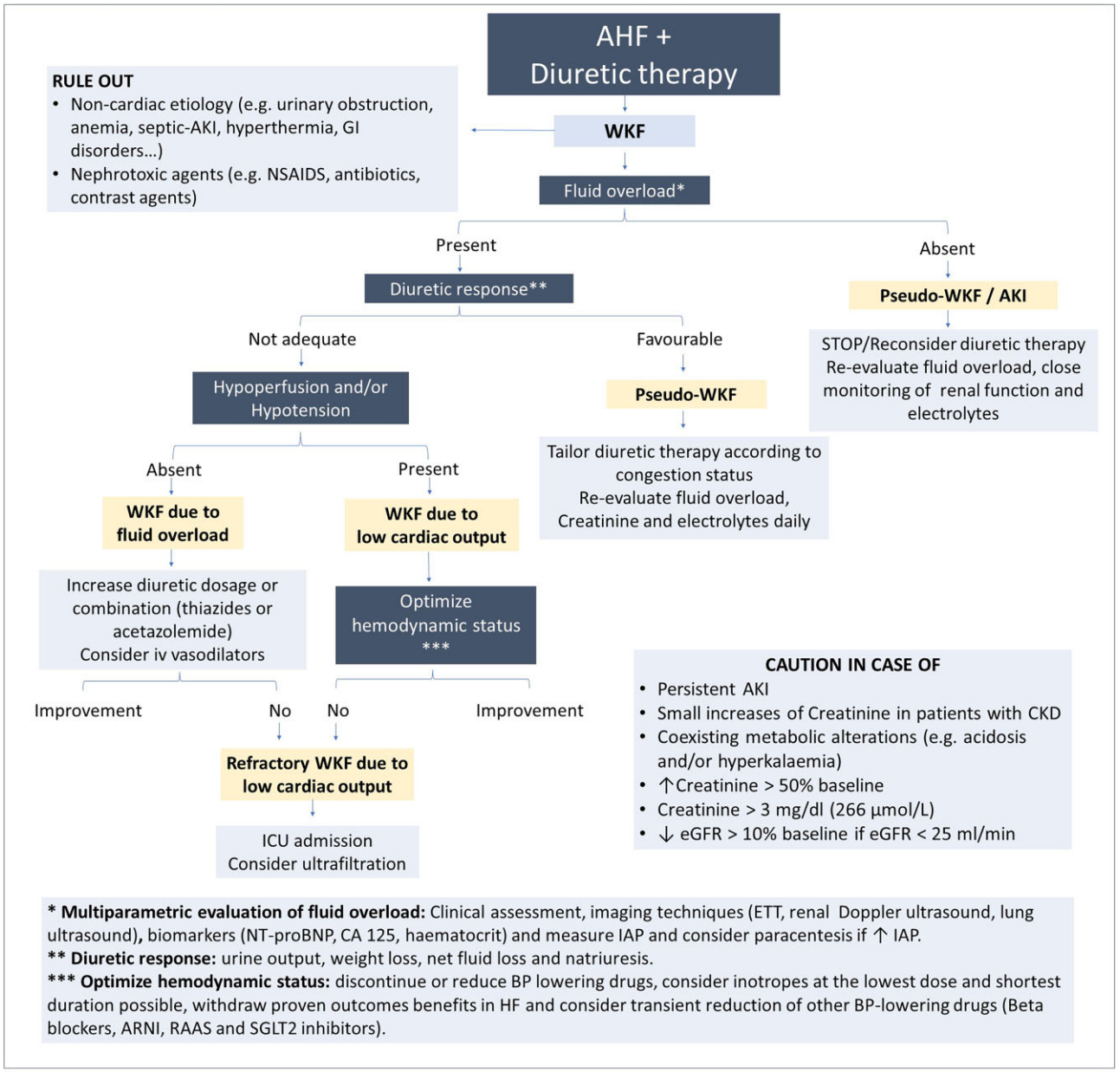

Figure 4: Approach to worsening kidney function in AHF.

extreme changes in SCr, especially when moving in the range of severe kidney dysfunction and/or accompanied by other metabolic alterations (e.g. hyperkalaemia or acidosis) should make physicians suspect true WKF. In light of these findings, the cut-off point for WKF has evolved from an SCr increase ≥0.3 mg/dl [71] to a more demanding definition such as doubling of SCr levels from baseline or a ≥50% sustained decrease in eGFR in the ADVOR trial or sustained reduction of ≥40% in the EMPULSE trial [81, 82].

Onset and time course

In relation to the onset of kidney function changes, Takaya *et al.* [83] reported that late-onset AKI (occurring ≥5 days after hospitalization for AHF) was independently linked to higher mortality and blood urea nitrogen levels, whereas early-onset AKI (≤4 days after admission) was not related to mortality but had higher SCr levels at admission and a greater decrease in body weight. These results suggest different mechanisms may play a role depending on the time course during hospitalization. Acute declines in kidney function are usually the result of haemodynamic alterations present before hospitalization and/or decongestion or initiation/up-titration of neurohumoral blockade. In turn, later changes may be brought on by severe haemodynamic abnormalities, as hinted by a higher blood urea nitrogen level (a surrogate of neurohormonal activation). Timing is also crucial when selecting the baseline kidney function value used to define WKF. Sánchez-Serna *et al.* [56], in an observational, single-centre study of 458 patients hospitalized for AHF, investigated the

occurrence of AKI using two different definitions depending on the SCr value used as baseline: the most recent outpatient measurement prior to admission or the first at admission. The prevalence of AKI almost doubled, from 20.1% to 33.8%, when pre-hospital kidney function was used as a reference. Regardless of the definition, AKI was associated with a longer hospital stay and greater in-hospital mortality. However, only AKI based on pre-hospital kidney function was associated with adverse clinical events after discharge. As for the progression of kidney function changes, transient WKF due to intensive diuretic treatment may not be associated with a worse prognosis, in contrast to persistent WKF [52].

The role of non-traditional diuretic agents

A careful review of the patient's prior medications and those initiated during hospitalization is imperative. Certain nephrotoxic agents can cause WKF [84], and HF patients may be more prone to develop tubular injury after exposure to iodine contrast, antibiotics (e.g. aminoglycosides, vancomycin, etc.) or non-steroidal anti-inflammatory drugs [85–88]. Similar to the increase in SCr that can occur after diuretic therapy, initiation of RAAS inhibitors, angiotensin receptor–neprilysin inhibitors (ARNIs) or sodium–glucose cotransporter-2 inhibitors (SGLT2is) is usually accompanied by an initial and transient decrease in eGFR that is not associated with worse outcomes in the long term. In the EMPA-RESPONSE-AHF trial, the authors found an early decline in eGFR of 8 ml/min/1.73 m^2 within 24 hours of initiation of SGLT2i in AHF patients compared with placebo, which attenuated 30 days after admission. These findings were consistent with a post hoc analysis of the EMPULSE trial, in which empagliflozin caused an initial decrease in eGFR of 2 ml/min/1.73 m^2 at day 15 compared with placebo ($P = .08$), having resolved by day 90 (mean difference 0.9 ml/min/1.73 m^2; $P = .57$) [82]. It is likely that this early decrease in kidney function is followed by a lower slope of eGFR decline and HF re-hospitalizations as observed in chronic HF studies with SGLT2i [89–91]. In the PARADIGM-HF trial, patients treated with sacubitril/valsartan had a slower decline in kidney function despite a greater increase in the urinary albumin:creatinine ratio (UACR) compared with the enalapril group [92]. In the AHF setting of the PIONEER trial, however, there was no difference regarding WKF between the sacubitril/valsartan group and the enalapril group [relative risk 0.93% (95% confidence interval 0.67–1.28)] [93]. These findings suggest that WKF could be a manifestation of the agent's mechanism of action (efferent arteriolar vasoconstriction with RAAS inhibitors or reduced glomerular hyperfiltration with SGLT2i). As a result, the 2021 European HF guidelines consider an increase in SCr of <50% above baseline (as long as it is <3 mg/dl or 266 µmol/L) or a decrease in eGFR of <10% from baseline (as long as eGFR is >25 ml/min/1.73 m^2) as acceptable and expected changes after initiation of RAAS inhibitors, ARNIs or SGLT2is [6].

OTHER RENAL BIOMARKERS

The evolving conceptual model of AKI included searching for new biomarkers to better predict AKI [94, 95]. Although SCr is a criterion for AKI, its reliability is limited because it is both filtered by the glomerulus and secreted by the tubules, and numerous factors influence its values [96]. Also, SCr elevation is a late finding in AKI. SCr concentrations may not change until there is a loss of up to 50% of eGFR and the damage is established [97]. Concepts such as 'renal angina' [98], 'subclinical AKI' [99] and 'acute kidney stress' [100] suggest that tubular injury is already present before SCr increases. In an attempt to overcome the shortcomings of traditional biomarkers, different markers have emerged [101–111]. Neutrophil gelatinase-associated lipocalin (NGAL) is rapidly released (within 2 hours) [101] in response to AKI and was strongly related to adverse outcomes 30 days after discharge in AHF patients in the GALLANT trial [102]. However, these results were not supported by the AKINESIS trial that concluded NGAL was not superior to SCr for predicting WKF, use of kidney replacement therapies and adverse outcomes [103]. Still, two of the most promising biomarkers are urinary insulin-like growth factor-binding protein (IGFBP-7) and tissue inhibitor of metalloproteinase (TIMP-2), which have proven their utility for early detection of AKI even in patients with chronic conditions (diabetes, HF and CKD) [107–109]. TIMP-2 and IGFBP7 are proteins that cause cell-cycle arrest of tubular cells in response to injury, acting as a protective mechanism to allow them to shut down and repair the damage [107]. The US Food and Drug Administration approved the immunoassay test NephroCheck (Astute Medical, San Diego, CA, USA) in 2014 for early detection of moderate–severe AKI in critically ill patients, which measures the urinary concentrations of TIMP-2 and IGFBP7 and combines them into a formula that is the product of their concentrations {[(TIMP-2) × (IGFBP-7)]/1000, in $(ng/ml)^2/1000$)}. A high sensitivity cut-off of 0.3 has been proposed [110]. In critically ill patients, TIMP-2 and IGFBP7 together showed an area under the curve (AUC) of 0.80, which was significantly superior ($P < .002$) to other biomarkers such as NGAL or kidney injury molecule-1 for predicting AKI [108]. With the routine adoption of these biomarkers, the ADQI group suggests a new definition of AKI based on phenotypes regarding functional and damage criteria, in which some patients will have elevated SCr with no increase in damage biomarkers (e.g. initiation of SGLT2i or decongestive therapy) and other patients will have elevated damage biomarkers without increased SCr (acute kidney stress) and a higher risk of developing AKI [111].

Lastly, we must not undermine the utility of older and widely available biomarkers to interpret kidney function changes and guide decongestion, such as haemoconcentration and UACR. As mentioned before, haemoconcentration represents an inexpensive and easily accessible surrogate of decongestion and is associated with lower mortality [112, 113]. A possible goal could be to achieve late and persistent haemoconcentration (>4 days after admission) that probably represents adequate intravascular filling. Nonetheless, haematocrit changes are often small and non-specific [112]. In contrast, albuminuria has recently emerged as a risk marker in HF. Boorsma *et al.* [114] measured UACR in two cohorts of patients from the BIOSTAT-CHF study. Albuminuria was present in 40% of patients and was independently associated with an increased risk of mortality and HF hospitalization ($P < .001$). Moreover, UACR was correlated with biomarkers of congestion [NT-proBNP, biologically active adrenomedullin and CA125 ($P < .0001$)], independent of the EF, even after adjusting for several kidney markers, including NGAL [114].

CONCLUSION

In this review we have debunked two old paradigms. First, the main driver of worsening kidney function in AHF is not hypoperfusion, but venous congestion. Second, worsening kidney function does not necessarily entail a worse prognosis. In order to correctly interpret kidney function changes in AHF, we must consider the patient's clinical context, a multiparametric assessment of initial fluid status and decongestion status. Additionally,

we should account for baseline kidney function, magnitude, timing and duration of changes. Small and transient decreases in kidney function during aggressive diuretic treatment, especially in patients with overt fluid overload (congestive nephropathy phenotype) are not associated with worse prognosis if accompanied by adequate decongestion. Therefore, diuretic therapy and disease-modifying heart failure treatments should not be discontinued in light of minor kidney function changes. Instead, the focus should be centred on achieving decongestion instead of transient changes in kidney function during therapy.

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AUTHORS' CONTRIBUTIONS

L.F.K. and M.L. contributed equally to this work. All authors have participated in the work and have reviewed and agree with the content of the article.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

J.N. is member of the *CKJ* editorial board. The other authors declare no conflicts of interest.

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