Nephrol Dial Transplant, 2024, **0**, 1–9
https://doi.org/10.1093/ndt/gfae146
Advance access publication date: 29 June 2024

REVIEW

Acute kidney injury in acute heart failure–when to worry and when not to worry?

Debasish Banerjee [1,2], Mahrukh Ayesha Ali [1,2], Angela Yee-Moon Wang [3] and Vivekanand Jha [4,5,6]

[1]Renal and Transplantation Unit, St George's University Hospitals NHS Foundation Trust, London, UK
[2]Molecular and Clinical Sciences Research Institute, St George's, University of London, London, UK
[3]Duke-National University of Singapore, Academic Medical Center, Singapore General Hospital, Singapore
[4]Faculty of Medicine, School of Public Health, Imperial College London, London, UK
[5]The George Institute of Global Health, Delhi, India
[6]Prasanna School of Public Health, Manipal Academy of Higher Education, Manipal, India
Correspondence to: Debasish Banerjee; E-mail: debasish.banerjee@stgeorges.nhs.uk

ABSTRACT

Acute kidney injury is common in patients with acute decompensated heart failure. It is more common in patients with acute heart failure who suffer from chronic kidney disease. Worsening renal function is often defined as a rise in serum creatinine of more than 0.3 mg/dL (26.5 µmol/L) which, by definition, is acute kidney injury (AKI) stage 1. Perhaps the term AKI is more appropriate than worsening renal function as it is used universally by nephrologists, internists and other medical practitioners. In health, the heart and the kidney support each other to maintain the body's homeostasis. In disease, the heart and the kidney can adversely affect each other's function, causing further clinical deterioration. In patients presenting with acute heart failure and fluid overload, therapy with diuretics for decongestion often causes a rise in serum creatinine and AKI. However, in the longer term the decongestion improves survival and prevents hospital admissions despite rising serum creatinine and AKI. It is important to realize that renal venous congestion due to increased right-sided heart pressures in acute heart failure is a major cause of kidney dysfunction and hence decongestion therapy improves kidney function in the longer term. This review provides a perspective on the acceptable AKI with decongestion therapy, which is associated with improved survival, as opposed to AKI due to tubular injury related to sepsis or nephrotoxic drugs, which is associated with poor survival.

Keywords: acute heart failure, acute kidney injury, decongestion, diuretic therapy, fluid overload

INTRODUCTION

Heart failure was described as an epidemic 25 years ago and remains a major clinical challenge today. The global prevalence of heart failure is an estimated 64.34 million cases, although there is a dearth of data from developing countries. Globally, this leads to 9.91 million years lost due to disability and consequent economic burden with conservative estimate of $346.17 billion. In the UK, there are 200 000 new diagnosis of heart failure each year, with prevalence of about 1 million. The condition remains underdiagnosed, with an estimated 385 000 undiagnosed heart failure cases consequently remaining untreated [1].

The kidney is an amazing organ with secretory, metabolic and endocrine functions. It is highly vascular and receives up to 25% of the cardiac output, and the renal plasma flow is close to 625 mL/min [2]. The kidney autoregulates the flow of blood elegantly, the glomerular filtration pressure and glomerular filtration rate (GFR) are maintained by regulating the blood flow, using the vascular tone of the afferent and efferent arteries, to the glomerulus [3].

Worsening renal function, more commonly referred to as acute kidney injury (AKI) is defined as deterioration of kidney function associated with the rise in serum creatinine of 26 µmol/L (or 0.3 mg/dL) [4, 5] or 50% from baseline; or a drop in urine output. The risk factors of AKI are increasing age, diabetes, presence of ischaemic heart disease, chronic kidney disease (CKD) and heart failure. The causes of AKI are sepsis, urine infection, glomerulonephritis, urine obstruction, interstitial nephritis and tubular toxicity due to drugs; and haemodynamic insults from drugs including diuretics. It is important to distinguish between non-haemodynamic and haemodynamic insults, as we will discuss further [4, 5].

Acute decompensated heart failure is defined as a rapid onset clinical syndrome with signs and symptoms of fluid overload and pulmonary congestion including oedema, raised jugular venous pressure, bilateral chest crepitations, S3 gallop sound, breathlessness, weight gain, requiring urgent or emergent decongestion therapy, often hospital admission [6–8]. The risk factors for acute heart failure are age, presence of diabetes, hypertension, tachyarrhythmias, ischaemic heart disease, chronic obstructive pulmonary disease and CKD. The precipitating factors are accelerated hypertension, dietary salt and fluid non-compliance, cardiac arrhythmias, infection, non-adherence to heart failure drugs and AKI [7–9].

The heart and the kidney support each other in a healthy state to maintain the body's homeostasis including blood pressure, salt and water balance. In disease states, they can adversely affect each other's function causing clinical deterioration and decompensation. When acute heart failure precipitates AKI it is also called cardiorenal syndrome type 1. When AKI precipitates acute heart failure it is called cardiorenal syndrome type 3 [9, 10].

Received: July 2, 2023; Editorial decision: May 17, 2024

The AKI that happens with acute heart failure may be linked to temporary haemodynamic changes such as low renal artery blood flow and poor renal venous return, which are potentially reversible. In contrast, co-existing AKI due to other reasons for example sepsis and nephrotoxic drugs (or prolonged, severe haemodynamic insult) may be irreversible and associated with poor prognosis. Many studies have tried to distinguish the two by measuring tubular injury biomarkers [11–13]. Rademaker *et al.* investigated the renal manifestations of acute decompensated heart failure (ADHF) in an ovine model, and observed significant haemodynamic changes and activation of neurohormonal factors with marked decline in renal function, reduced urine output and creatinine clearance. Even after recovery from ADHF at 25 days, the creatinine clearance remained impaired, with renal biopsies taken during ADHF and after recovery showing extensive parenchymal change including prominent mesangial cells, early acute tubular injury and interstitial fibrosis. Transcriptomic analysis showed altered gene expression during the acute decompensated phase, indicating that the inflammatory processes driven by interleukin-1β suppress the protective endothelial nitric oxide synthase, whereas post-recovery the altered gene expression switches on the renal protective pathways, and dampens the pro-inflammatory pathways limiting fibrotic injury [14].

Understanding the mechanism of impact of acute heart failure on AKI and vice versa is essential for clinical decisions in managing multimorbid, often elderly, unwell patients admitted with acute congestive heart failure.

THE KIDNEY–HEART INTERACTION

Many patients with heart failure have concomitant CKD, increasing susceptibility to AKI with acute heart failure. Indeed, CKD is deemed to be the most prognostically important comorbid condition, being more predictive of mortality in patients with chronic heart failure than the underlying cardiac ejection fraction [8–10]. In addition, comorbid conditions including hypertension, diabetes, use of diuretic medications and increasing age are associated with development of AKI in acute heart failure [8–10]. Acute heart failure can cause AKI by kidney hypoperfusion, activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous systems causing a reduction in GFR, which then stimulates the arginine vasopressin secretion and fluid retention, leading to a vicious cycle of venous congestion and hypoperfusion, a pro-inflammatory state with resultant oxidative stress [15–17]. ADHF is characterized by sodium avidity and fluid retention due to increased neurohormonal activity. With co-existing CKD, the renal derangements caused impaired natriuresis even before clinical signs of heart failure appear [18].

AKI itself can precipitate acute heart failure due to an inability to excrete salt and water leading to volume overload, activation of the renin–angiotensin system and sympathetic nervous systems, increasing cardiac afterload, and generation of reactive oxygen species, inflammation and endothelial dysfunction [15–17]. In a registry study of 31 245 patients with AKI matched with 146 941 non-AKI patients followed up for 365 days, AKI was associated with an increased risk of heart failure [adjusted hazard ratio 1.44 (95% CI 1.33–1.56)] [19].

MANAGEMENT OF WORSENING RENAL FUNCTION IN ADHF

Clinical assessment

A careful assessment to determine volume status and degree of fluid overload is essential, with special attention paid to ruling out other complicating features such as sepsis, drug toxicities which independently affect kidney function, as well as identifying underlying comorbid conditions including CKD. Deterioration of kidney function on background of pre-existing CKD is associated with poorer prognosis in terms of mortality and morbidity as shown by Zhou *et al.* [20]. Careful bedside evaluation to look for signs of pulmonary and peripheral oedema and elevated right heart pressures is important. Raised jugular venous pressure, a third heart sound and positive abdomino-jugular test along with lung signs when positive indicate elevated right heart pressures and compromised cardiac performance. An jugular venous distention was highly sensitive (81%) and specific (80%), with a predictive accuracy of 81% for raised pulmonary wedge pressure (≥18 mmHg). Lower limb oedema is another sensitive indicator but is less specific as can be due to other comorbidities associated with leg oedema [21, 22].

Pertinent blood tests including biomarkers of decompensated heart failure—pro-brain natriuretic peptide (BNP) and troponin—may be useful [23]. Along with monitoring urine output and daily fasting weights, imaging techniques like ECHO and point-of-care ultrasound assessment of fluid status are useful tools for assessment and towards developing a personalized treatment approach for each patient [23, 24]. There are several radiological methods of volume assessment including chest X-ray, inferior vena cava ultrasound, renal venous Dopplers, lung ultrasound, carotid artery ultrasound, heart echocardiogram, heart magnetic resonance imaging and bioimpedance analysis. Some radiological markers are shown to be beneficial in assessing volume status, e.g bioimpedance analysis, but randomized trial evidence of their utility in guiding decongestion is limited. The ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial failed to show any mortality benefit or reduction in hospitalizations with use of invasive monitoring, however in certain complex clinical situations right-sided catheterization may be considered, particularly in intensive care setting—for example difficult to diurese patients where a more nuanced approach to address subclinical congestion while avoiding intravascular depletion are required. It can help identify complicating factors such as pulmonary hypertension [25].

Venous congestion

The impact of renal venous congestion on AKI during acute heart failure admission was very elegantly demonstrated in a study with 145 consecutive heart failure patients admitted for intensive therapy with central venous pressure monitoring. In this study the mean (± standard deviation) age of the patients was 57 ± 14 years, ejection fraction was 20 ± 8% and serum creatinine was 1.7 ± 0.9 mg/dL. It was noted that patients with AKI, defined as a rising serum creatinine of >0.3 mg/dL, compared with patients without AKI, had higher baseline serum creatinine (1.9 ± 0.9 versus 1.5 ± 0.8 mg/dL); similar doses of furosemide, systemic arterial blood pressure (111 ± 21 versus 108 ± 15 mmHg), pulmonary capillary wedge pressure (25 ± 7 versus 24 ± 7 cm); higher cardiac index (2.0 ± 0.8 vs 1.8 ± 0.4 L/m^2); but higher central venous pressure (18 ± 7 vs 12 ± 6 cm). The risk of AKI increased

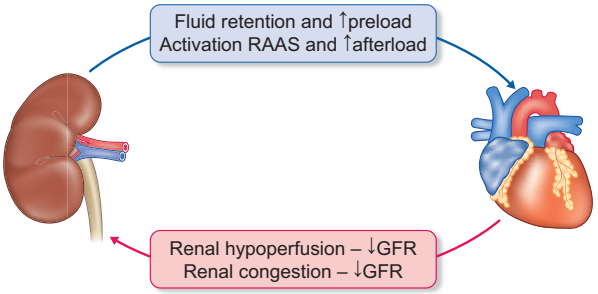

Figure 1: The adverse impact of kidney failure and heart failure on each other.

with increasing central venous pressure, with 75% of patients developing AKI when the central venous pressure was more than 24 cm. Increasing central venous pressure and not decreasing systolic blood pressure were associated with AKI. Baseline elevated central venous pressure and not baseline cardiac index predicted the development of AKI [26]. Thus, central venous congestion was largely responsible for AKI in these patients with ADHF.

The term congestive nephropathy is used to describe the pattern of renal impairment due to reduced renal venous outflow and rising renal interstitial pressure, which may be potentially reversible [27–29]. Renal venous congestion triggers hormone activation leading to increased renal sodium resorption, leading to volume overload, increased intra-abdominal pressure and eventually right ventricular stress. Thus, reduced renal perfusion along with increased vascular congestion and hence increased central venous pressure leads to worsening renal function in decompensated heart failure. In addition, Boorsma *et al.* proposed the concept of 'renal tamponade', the compression of renal structures due to the confines of the renal capsule linking the two. In animal models of heart failure and acute renal ischaemia, removal of the renal capsule has been shown to be effective is improving the compression related injury [30] (Fig. 1).

Multiple studies indicate that it is venous congestion rather than reduced cardiac output that drives the detrimental interplay of above factors leading to development of cardiorenal syndrome. Hence adequate decongestion is the mainstay of management, but this is complicated by the risk of worsening renal function with diuretic use due to reduced intraglomerular pressure and consequent increased neurohormonal activity [31–33].

DECONGESTION THERAPY

Decongestion options include use of oral or intravenous diuretics or ultrafiltration (UF). Proper diagnosis and ongoing assessment of congestion helps with escalation of diuretic therapy and if diuretic therapy fails it may indicate an AKI not related to congestion, or there might be true diuretic resistance in which case UF may be an option.

Importance of achieving adequate decongestion

A study with 599 patients admitted with acute heart failure in a large European institution over a period of 1 year and followed for 797 ± 619 days demonstrated the benefits of diuretic therapy with adequate decongestion in terms of mortality and readmissions to hospital, despite the presence or absence of AKI and rising creatinine compared with patients who did not achieve decongestion. This study included 34% of the patients with diabetes, 36% with atrial fibrillation, 35% with CKD and mean ejection fraction of 33%. The overall post-discharge mortality or combined mortality with acute heart failure readmission rates were 13% and 43%, respectively. Patients who had worsening of their kidney function and achieved adequate decongestion were no different from the patients who achieved decongestion and did not develop worsening of their kidney function, adjusted hazard ratio for mortality 1.2 [95% confidence interval (CI) 0.9 to 1.6, $P = .11$]. Having baseline CKD was a predictor of poor outcome, and AKI was a predictor of poor prognosis in patients where adequate decongestion was not achieved [33] (Table 1).

In an analysis of 336 patients from the ESCAPE trial, with mean age 56 ± 13 years, 34% diabetic patients and mean ejection fraction 19%, the patients who achieved adequate decongestion had better survival than the patients who did not achieve adequate decongestion with diuretic therapy, despite worsening of their kidney function compared with the patient who did not achieve decongestion [25, 34].

In another analysis of the ESCAPE trial of 433 patients the baseline serum creatinine was a predictor of time to death or death and readmission [hazard ratios 1.2 (95% CI 1.1 to 1.3, $P < .0001$) and 1.14 (95% CI 1.1 to 1.2, $P < .0001$)], whereas a rise in serum creatinine of 0.3 mg/dL was not associated with shorter time to death or time to death and readmission [hazard ratio of 1.3 (95% CI 0.8 to 2.1, $P = .27$) and 1.26 (95% CI 0.9 to 1.6, $P = .9$)] [35].

In a urinary biomarker substudy [NAG (N-acetyl-b-D-glucosaminidase), NGAL (neutrophil gelatinase-associated lipocalin), KIM-1 (kidney injury molecule-1)] of 105 patients from the Cardiorenal Rescue Study in Acute Decompensated Heart Failure Trial (CARRESS-HF) acute heart failure patients with AKI were randomized to pharmacological therapy or fixed rate UF arm. It was observed that the severity of pre-existing AKI was not associated with baseline renal tubular injury biomarkers ($r = 0.14$; $P = .17$). Intensive volume removal was associated with worsening serum creatinine in 53% of patients and was associated with worsening in renal tubular injury biomarkers (odds ratio 12.6, $P = .004$) which was in turn associated with higher incidence of haemoconcentration (odds ratio 3.1, $P = .015$), and interestingly, better recovery of serum creatinine at 60 days compared with group with no increase in tubular injury markers($P = .01$). This suggested that provided decongestion is achieved, the transient AKI during the course of treating acute heart failure is acceptable [13].

In another interesting study of 1643 patients with acute heart failure, aged 70–79 years, 34% diabetics, 755 patients (46%) developed AKI, defined as ≥26.5 μmol/L rise in creatinine within 48 h or an increase ≥1.5 from baseline within the prior 7 days, out of which 310 (19% of total, 41% of AKI) were community acquired and 445 (27% of total, 59% of AKI) were hospital acquired. The community-acquired AKI patients had higher brain natriuretic peptide, troponin T, creatinine rise and intensive care admissions. The community-acquired AKI patients had lower systolic blood pressure 102 mmHg (95–120) than hospital-acquired AKI patients 126 mmHg (100–143). The NGAL was higher in patients with community-acquired AKI. The community-acquired AKI patients suffered higher mortality compared with hospital acquired AKI patients. This study perhaps indicates the patients with community-acquired AKI had a mixture of AKI due to haemodynamic insult and/or tubular toxic causes, in higher proportion than the patients with hospital-acquired AKI, hence associated with the poorer outcome [36].

In a multinational cohort of 736 acute heart failure patients requiring admission for intravenous diuretic therapy, BNP and

Table 1: Impact of AKI with and without decongestion on mortality, and associated weight loss, diuretic dose and BNP at discharge.

Patient groups according to AKI and congestion at discharge	Univariate HR (95% CI) for mortality	Multivariate HR (95% CI) for mortality	Weight loss (kg), furosemide dose (mg), BNP at discharge[a]
No AKI and no congestion	1	1	2.5 ± 3.3, 71 ± 113, 1951 (860–4458)
AKI but no congestion	1.24 (0.7–2.0)	1.2 (0.9–1.6)	3.4 ± 3.7, 124 ± 151, 1951 (1218–4012)
Congestion yet no AKI	1.95 (0.8–5.0)	1.5 (0.8–2.6)	1.9 ± 3.2, 142 ± 161, 2760 (1056–5476)
Both congestion and AKI	5.35 (3.0–9.0)*	2.1 (1.4–3.3)*	2.8 ± 4.3, 230 ± 202, 2386 (1576–16152)

[a]Mean ± standard deviation or median (IQR).
There was no difference in mortality between AKI and no-AKI if there was no congestion at discharge. Total 599 patients, mean age 69 ± 10 years, diabetes mellitus 35%, CKD 35%, EF 33%, mortality 13%, readmission 43%, over 671 days (261–1275).
*$P < .005$ [33].
HR: hazard ratio; EF: ejection fraction.

urinary NGAL was measured serially at admission, after 4 h, on Days 1, 2 and 3, and at discharge. The mean baseline serum creatinine was 1.2 mg/dL (0.94–1.6). 53% of the patients achieved adequate decrease in BNP defined as more than 30% from the baseline value. These patients were younger with less CKD. In-hospital mortality was 3%, 1-year mortality was 18% and readmission was 19%. The 1-year mortality was not associated with admissions urinary NGAL [adjusted hazard ratio 1.02 (95% CI 0.93 to 1.12, $P = .63$)], but associated with the BNP decrease [adjusted hazard ratio 0.55 (95% CI 0.37 to 0.82, $P = .003$)]. The peak urinary NGAL or the discharge urinary NGAL were not related to 1-year mortality. This study demonstrated that 1-year mortality was higher in acute heart failure patients with AKI if there was no decongestion achieved at discharge. It also showed that the transient tubular damage during diuretic therapy was not associated with an increased risk of 1-year mortality in patients who achieved adequate decongestion [36, 37].

The ROSE-AHF (Renal Optimization Strategies Evaluation—Acute Heart failure) trial provided an experimental model for investigating worsening renal function [defined as ≥20% decrease in estimated GFR (eGFR)] during aggressive diuretic therapy for decompensated heart failure as the trial protocol stipulated use of high-dose loop diuretics. Ahmad *et al*. observed that in 283 patients on the ROSE-AHF trial who received a median dose of 560 mg IV furosemide [interquartile range (IQR) 300–815 mg], inducing a urine output of 8425 mL (IQR 6341–10, 528 mL) over the 72-h intervention period, worsening renal function occurred in 21.2% of population and was not associated with rise in renal tubular injury biomarkers (NGAL, NAG or KIM-1). In fact, increases in NGAL, NAG and KIM-1 were associated with improved survival [31, 38].

Pharmacological decongection therapy

Loop diuretics such as furosemide, bumetanide and torsemide acting at the level of loop of Henle by inhibiting the sodium, potassium, chloride cotransporter remain the mainstay of pharmacological therapy for ADHF, administered orally or intravenously [39, 40]. Felker *et al*. investigated the difference between intermittent and continuous administration of intravenous loop diuretics as well as comparing high-dose versus low-dose diuretics in ADHF in a randomized controlled trial of 308 patients. It was concluded that there was no difference in the global assesment of symptoms and renal function across the two groups, nor was a change noted with high-dose versus low-dose diuretic use. The use of high-dose diuretics was associated with more effective diuresis but with a transient worsening of renal function [39–41].

ULTRAFILTRATION FOR DECONGESTION

The use of ultrafiltration (UF) for decongestion in setting of ADHF remains a subject of some debate. A number of randomized controlled trials including UNLOAD (The Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure), CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) and AVOID-HF (Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure) tried to answer this question, comparing patients randomized to UF arm with patients receiving intravenous diuretics [42]. UNLOAD showed that the UF arm had better decongestion with more net fluid weight loss compared with diuretic group, without detriment to renal function or blood pressure. In addition, the UF arm also had less hospital readmissions (up to 53% reduction), less duration of readmission hospital stay and less non-scheduled heart failure–related attendances in the 90-day follow-up period [43].

The CARRESS-HF trial, in contrast, showed that UF was perhaps inferior to diuretic therapy due to the worsening of renal function (0.23 mg/dL increase in serum creatinine for UF compared with 0.04 mg/dL decrease for pharmacological therapy), with similar fluid weight loss across the two groups. There was no difference observed in rehospitalization and mortality across the two groups, despite the creatinine rise in the UF arm [44]. Later 'per-protocol' analysis of the trial data showed that UF was in fact associated with improved decongestion with higher net fluid losses compared with pharmacological therapy group. It was felt that therapy was prematurely stopped across both groups for concerns regarding worsening renal function, although more recent data show that a transient worsening of renal function during the decongestion therapy is associated with better outcomes due to more effective decongestion [42]. The AVOID-HF suffered from slow recruitment but did show fewer hospital readmissions in the UF group [42, 45]. A meta-analysis of seven randomized controlled trials investigating the role of UF in management of ADHF determined that UF was associated with more effective decongestion with better net fluid loss, as well as reduced heart failure–related rehospitalizations, with no difference in change in kidney function or adverse events compared with the pharmacological treatment group [42]. A number of important considerations need to be taken into account when planning UF in context of ADHF however, including establishing timely access, use of anticoagulation, early initiation of UF rather than later when presented with diuretic resistance, and a more patient-tailored approach. The current data do not reflect a difference in response to UF in heart failure with reduced ejection fraction compared with heart failure with preserved ejection fraction [42–45].

Table 2: Recent studies of diuretic therapy with efficacy, outcome and kidney side effects.

Study	Population and eGFR	Intervention	Urine output	Weight loss (kg)	Outcomes	AKI/renal events (%)
Dauw *Circ HF* 2024, ENACT HF51	401 AHF, eGFR 49 (32–74)	Urine Na monitoring vs usual care	5.7 (5.4–6.1) vs 4.3 (4.1–4.7) L at 2 days	3.6 ± 2.5 vs 3.4 ± 2.7 kg at 2 days	LOS 5.8 (5.2–6.6) vs 7 (6.4–7.7) days	Renal events 6.1% vs 7%
Yeoh *EHJ* 2023, DapaResist52	61 AHF, eGFR 41 (32–54)	Dapa10 mg v metolazone 5–10 mg/day		2.6 ± 1.8 vs 3.2 ± 1.8 kg at 3 days		AKI 47% vs 50%
Trullas *EHJ* 2023, CLOROTIC53	230 AHF, eGFR 43 (34–58)	HCTZ 25–100 mg/day vs placebo		2.3 (1.2–3.9) vs 1.5 (0–3.2) at 3 days		AKI 46% vs 17%
Biegus *EHJ* 2023, EMPULSE54	530 AHF, eGFR 50 (36–65)	Empagliflozin 10 mg vs placebo		3.2 ± 0.3 vs 1.2 ± 0.3 kg at Day 15		AKI 7.7% vs 12.1%
Mentz *JAMA* 2023, TransformHF55	2859 HHF eGFR, 59 ± 25	Torsemide vs furosemide			No mortality difference	
Mullens NEJM 2023, ADVOR50	519 AHF, eGFR 39 (29–52)	Acetazolamide vs placebo 500 mg/day	4.6 ± 1.7 vs 4.7 ± 1.8 L at 2 days		Better decongest in eGFR <39	Renal events 2.7% vs 0.8%
Ter Maaten Nat Med 2023 PUSH-HF56	310 AHF, eGFR 54 (35–72)	Urine Na monitoring vs usual care	6.2 ± 3.0 vs 5.7 ± 2.8 L at 3 days	4 (6.1–2.2) vs 3 (4.9–0.7) kg 3 days	No HHF + mortality difference	Renal events 1% both groups

The study year and names are mentioned. The baseline eGFR in median with IQR or mean with standard deviation and in mL/min/1.73 m^2, EMPULSE study followed patients for 90 days, TANSFORM-HF followed patients for 12 months, most study durations are short, urine output and weight loss is over 2–3 days.
AHF: acute heart failure Na: sodium; HHF: hospitalization for heart failure; LOS: length of stay; HCTZ: hydrochlorothiazide.

When to worry about diuretic resistance and its management

Diuretic resistance, defined by Krämer *et al.* as a clinical state characterized by loss of diuretic response before the treatment goal of relief from fluid overload has been achieved [42, 46]. It poses a significant clinical challenge and can be multifactorial, such asinadequate diuretic doses, poor medication adherence, pre-existing CKD, use of medications such as non-steroidal anti-inflammatory drugs, methyldopa, propranolol and minoxidil, haemodynamic factors such as hypotension and reduced renal blood flow, and pharmacokinetic factors such as impaired absorption from gut due to gut oedema, poor secretion of diuretic into the tubular lumen and poor transport of drug in hypoalbuminemic state all can lead to diuretic resistance. The 'braking phenomenon' involving haemodynamic and neurohormonal aspect can also contribute to diuretic resistance by activation of sympathetic nervous system and RAAS due to reduced extracellular fluid volume from ongoing diuresis and increased urinary sodium due to diuretic use sensed by macula densa leading to tubuloglomerular feedback activation—this leads to increased tubular sodium resorption [42, 46, 47]. Prolonged use of loop diuretics can lead of hypertrophy and hyperplasia of distal convoluted tubule, collecting tubule and collecting duct, leading to increased tubular sodium resorption—this nephron remodelling is another mechanism contributing to diuretic resistence [42, 46, 47].

Management of diuretic resistance hence must be multifaceted, including restriction of dietary sodium to 2–3 g/day [48]. Water restriction <1.5 L/day may be useful particularly in patients with dilutional hyponatraemia. The so called 3Ttrial was a randomized, double-blind trial comparing the use of combination diuretic therapies in setting of ADHF and diuretic resistance in 60 patients. Patients were randomized to either oral metolazone, intravenous chlorthiazide or tolvaptan, with all three groups receiving high-dose intravenous furosemide as well; the primary outcome assessed was weight loss at 48 h. While all three interventions led to improved weight loss at 48 h, the cost difference between the therapies (intravenous chlorthiazide and tolvaptan being quite expensive) has lead to adoption of a metolazone-first strategy [49]. A randomized control trial of 519 patients showed that addition of intravenous acetazolamide to standard intravenous loop diuretic therapy led to more effective decongestion compared with placebo, with similar incidence of worsening renal function, hypotension, hypokalemia and adverse events across both groups [50]. Where available in clinical practice UF may be used. Hence diuretic therapy involving agents acting at different parts of the kidney nephron, e.g carbonic anhydrase inhibitor or sodium–glucose co-transporter (SGLT) inhibitor for proximal tubule, thiazide or mineralocorticoid inhibitor for distal tubule, together with loop diuretics, may help overcome diuretic resistance.

KNOWLEDGE GAPS AND FUTURE RESEARCH

The recently conducted studies report variable rates of AKI depending on the baseline CKD, diuretic dose, diuretic response, duration of follow-up and investigator reporting (Table 2). The renal event rates/AKI vary from as low as 1% up to 47% [50–56]. With empagliflozin compared with metolazone, in 530 patients with median eGFR around 50 mL/min, in the EMPLUSE study the AKI incidence of 7.7% was not associated with adverse outcomes when followed for 90 days [54]. A study of successful natriuresis guided diuretic therapy of 310 patients, with median GFR of 54 mL/min the kidney events were low (1%) [56].

We know from the available evidence that with significant decongestion and rising creatinine, less than 50% from baseline, or stage 1 AKI does not have adverse clinical effects during management of ADHF. Whereas in the absence of decongestion, AKI

Table 3: Traffic light system for management of *de novo* AKI in patients with ADHF.

AKI with no worries	May need closer monitoring	AKI with worries
AKI 1with decongestion and no UTI, Sepsis, Raised CRP	*AKI 1 and no decongestion* *AKI 1 with sepsis,UTI, CRP>100* *AKI2/3 with decongestion*	*AKI2/3 and no decongestion* *AKI2/3 sepsis, UTI, CRP>100*

See text for further explanation.
UTI: urinary tract infection; CRP: C-reactive protein.

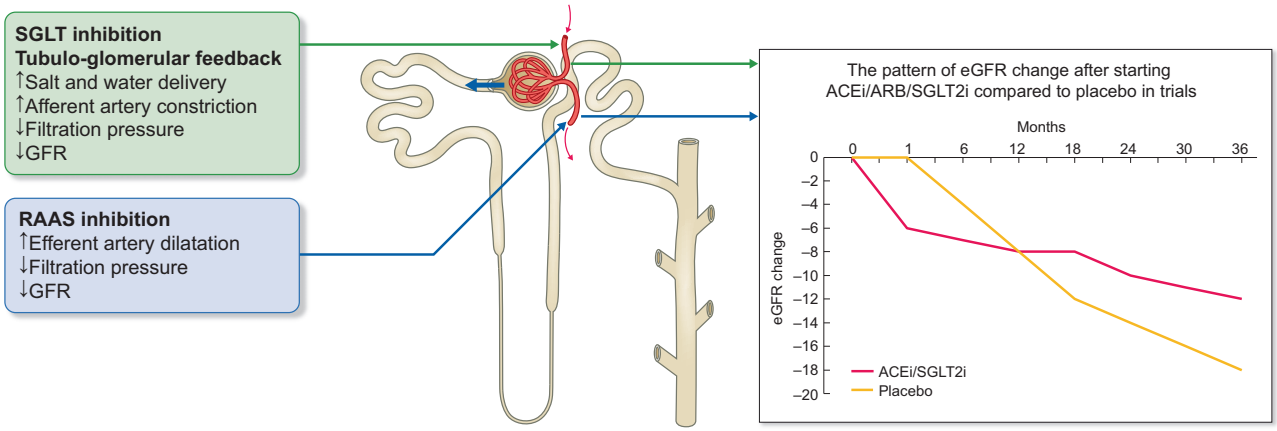

Figure 2: Mechanism of AKI and rising creatinine in heart failure patients on starting SGLT2i (top right panel) and ACEi/ARB (bottom right panel).

stages 2 and 3 may be due to urine infection, sepsis or interstitial nephritis, which are associated with adverse outcomes (Table 3).

We do not know the long-term outcomes of AKI stages 1–3 without decongestion. This will require further studies with longer follow-up data.

There are significant differences in outcomes between subgroups of heart failure based on ejection fraction, particularly in the presence of CKD. However, the differences in outcome of AKI in these different subgroups is unknown and require further research.

With available knowledge we suggest a 'traffic light system' for management of *de novo* AKI after hospital admission for ADHF as shown in Table 3.

The area for future research include longer term follow-up—1 year or more—of all patients in amber group in the table in order to better understand the prognosis. We need research to test the predictability of kidney and heart, blood and radiological biomarkers on long-term outcome.

CONCLUSION

In conclusion, a degree of acute renal impairment would be expected and acceptable while trying to achieve adequate decongestion in patients with acute or decompensated heart failure. If clinicians are not aware that this can hamper the initiation or continuation of heart failure medications such as angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB), angiotensin receptor/neprilysin inhibitor or mineralocorticoid receptor antagonist. The introduction of RAAS inhibitor medications is associated with efferent arteriolar vasodilatation, drop in intraglomerular filtration pressure and decrease in GFR. The introduction of SGLT2 inhibitors is associated with increased sodium delivery to distal tubule, causing afferent arteriolar vasoconstriction and a drop in GFR, which aids in preservation of the kidney function in the long run as shown in the large SGLT inhibitor studies of heart failure with reduced and preserved ejection fraction [57–62] (Fig. 2). While concerns regarding worsening renal function and hyperkalemia in progressive CKD frequently lead to discontinuation of RAAS inhibitors, the Renin–Angiotensin System Inhibition in Advanced Chronic Kidney Disease or STOP – ACEi trial has shown that stopping RAAS inhibitors is not associated with change in the long-term rate of decline in eGFR [63].

AKI is common in patients at admission with acute heart failure, related to renal arterial hypoperfusion and renal venous congestion. Further AKI happens during hospital admission due to decongestion and further haemodynamic changes. These haemodynamic changes are potentially reversible and do not have long-term adverse consequences, as shown in a meta-analysis of 13 studies where AKI with decongestion was associated with lower mortality and patients who had no AKI and remained congested [64]. AKI can also happen due to non-haemodynamic tubular injury such as sepsis and nephrotoxic drugs, and it is important to distinguish between the two to guide further decongestion therapy and predict prognosis. The rise in serum creatinine and tubular injury markers during adequate decongestion predicts a better prognosis, compared with patients with no decongestion and no rise in creatinine. Hence it is important to achieve rapid and adequate diuresis or decongestion with acute heart failure in hospital, perhaps within first 3 days of admission, accepting minor AKI that usually recovers; however, patients should be closely monitored to identify and treat for sepsis and other non-haemodynamic causes to avoid irreversible AKI. Worsening or persistent congestion despite adequate diuretic therapy characterized by worsening or

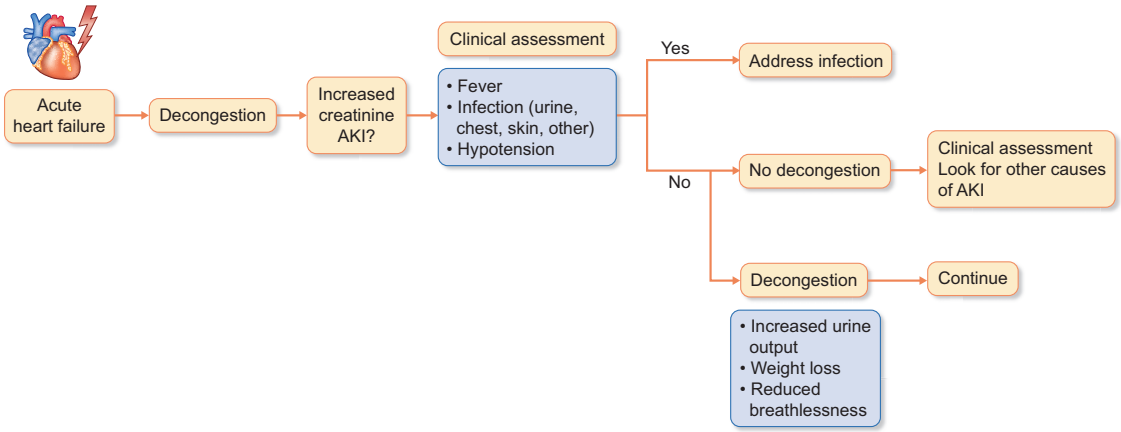

Figure 3: Pathway for identification and management of cause of AKI in acute heart failure patients.

persistent symptoms of heart failure with concomitant worsening renal impairment would be a cause for concern and may indicate irreversible AKI (Fig. 3).

ACKNOWLEDGEMENTS

The authors would like to thank Dr Anderson for her contributions.

FUNDING

Debasish Banerjee is partially funded by NIHR Grant 207236.

AUTHORS' CONTRIBUTIONS

D.B. and M.A.A. wrote the manuscript. A.Y.-M.W. reviewed the manuscript. V.J. contributed to conception and review of manuscript

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article itself.

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflict of interest related to this publication.

REFERENCES

1. British Society For Heart Failure. n.d. *25IN25*. [Online]. Available at: https://www.bsh.org.uk/25in25 (30 March 2023, date last accessed).
2. Leatherby RJ, Theodorou C, Dhanda R. Renal physiology: blood flow, glomerular filtration and plasma clearance. *Anaesth Intensive Care Med* 2021;**22**:439–42. ISSN 1472-0299.
3. Burke M, Pabbidi MR, Farley J *et al.* Molecular mechanisms of renal blood flow autoregulation. *Curr Vasc Pharmacol* 2014;**12**:845–58. PMID: 24066938; PMCID: PMC4416696. https://doi.org/10.2174/15701611113116660149
4. Forman DE, Butler J, Wang Y *et al.* Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol* 2004;**43**:61–7. https://doi.org/10.1016/j.jacc.2003.07.031
5. Rastogi A, Fonarow GC. The cardiorenal connection in heart failure. *Curr Cardiol Rep* 2008;**10**:190–7. https://doi.org/10.1007/s11886-008-0033-1
6. McMurray JJ, Adamopoulos S, Anker SD *et al.*; ESC Committee for Practice Guidelines. ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33**:1787–847.
7. Gheorghiade M, Filippatos G, Felker M. Diagnosis and management of acute heart failure syndromes. In: Bonow R, Mann D Zipes D *et al.* (eds) *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 9th edn. Philadelphia, PA: Elsevier, Saunders, 2012.
8. Farmakis D, Parissis J, Lekakis J *et al.* Acute heart failure: epidemiology, risk factors, and prevention. *Rev Esp Cardiol (Engl Ed)* 2015;**68**:245–8. https://doi.org/10.1016/j.rec.2014.11.004
9. Di Lullo L, Bellasi A, Barbera V *et al.* Pathophysiology of the cardio-renal syndromes types 1-5: an uptodate. *Indian Heart J* 2017;**69**:255–65. PMID: 28460776; PMCID: PMC5415026. https://doi.org/10.1016/j.ihj.2017.01.005
10. Rangaswami J, Bhalla V, Blair JEA *et al.* Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation* 2019;**139**:e840–78. https://doi.org/10.1161/cir.0000000000000664
11. Jain AK, Chen HH. ROSE-AHF and lessons learned. *Curr Heart Fail Rep* 2014;**11**:260–5.
12. Jackson K, Hodson D, Ahmad T *et al.* Acute tubular injury is not a major mechanism for worsening renal function in patients treated for acute heart failure. *J Card Fail* 2017;**23**:S6. https://doi.org/10.1016/j.cardfail.2017.07.010
13. Rao VS, Ahmad T, Brisco-Bacik MA *et al.* Renal effects of intensive volume removal in heart failure patients with pre-existing worsening renal function. *Circ Heart Fail* 2019;**12**:e005552. https://doi.org/10.1161/circheartfailure.118.005552
14. Rademaker MT, Pilbrow AP, Ellmers LJ *et al.* Acute decompensated heart failure and the kidney: physiological, histological and transcriptomic responses to development and recovery. *J*

Am Heart Assoc 2021;**10**:e021312. https://doi.org/10.1161/jaha.121.021312
15. Chahal RS, Chahal RS, Kalra PR *et al.* Heart failure and acute renal dysfunction in the cardiorenal syndrome. *Clin. Med* 2020;**20**:146–50. https://doi.org/10.7861/clinmed.2019-0422
16. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. *J Am Coll Cardiol* 2012;**60**:1031–42. https://doi.org/10.1016/j.jacc.2012.01.077
17. Turner N, Lamiere N Goldsmith D *et al.* (eds). *Oxford Textbook of Clinical Nephrology*, 4th edn. Oxford: Oxford University Press, 2015.
18. Mullens W, Verbrugge FH, Nijst P *et al.* Renal sodium avidity in heart failure: from pathophysiology to treatment strategies. *Eur Heart J* 2017;**38**:1872–82. PMID: 28329085. https://doi.org/10.1093/eurheartj/ehx035
19. Go AS, Hsu C-y, Yang J *et al.* Acute kidney injury and risk of heart failure and atherosclerotic events. *Clin J Am Soc Nephrol* 2018;**13**:833–41. https://doi.org/10.2215/CJN.12591117
20. Zhou Q, Zhao C, Xie D *et al.* Acute and acute-on-chronic kidney injury of patients with decompensated heart failure: impact on outcomes. *BMC Nephrol* 2012;**13**:51. https://doi.org/10.1186/1471-2369-13-51
21. Guaricci AI, Sturdà F, Russo R *et al.* Assessment and management of heart failure in patients with chronic kidney disease. *Heart Fail Rev* 2023;**29**:379–94. https://doi.org/10.1007/s10741-023-10346-x
22. Butman S, Ewy G, Standen J *et al.* Bedside cardiovascular examination in patients with severe chronic heart failure: importance of rest or inducible jugular venous distension. *J Am Coll Cardiol* 1993;**22**:968–74. https://doi.org/10.1016/0735-1097(93)90405-P
23. Boerrigter G, Burnett JC. Cardiorenal syndrome in decompensated heart failure: prognostic and therapeutic implications. *Curr Heart Fail Rep* 2004;**1**:113–20. https://doi.org/10.1007/s11897-004-0020-9
24. Hatamizadeh P, Fonarow GC, Budoff MJ *et al.* Cardiorenal syndrome: pathophysiology and potential targets for clinical management. *Nat Rev Nephrol* 2013;**9**:99–111. https://doi.org/10.1038/nrneph.2012.279
25. Nohria A, Hasselblad V, Stebbins A *et al.* Cardiorenal interactions: insights from the ESCAPE trial. *J Am Coll Cardiol* 2008;**51**:1268–74. https://doi.org/10.1016/j.jacc.2007.08.072
26. Mullens W, Abrahams Z, Francis GS *et al.* Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol* 2009;**53**:589–96. https://doi.org/10.1016/j.jacc.2008.05.068
27. Husain-Syed F, Gröne HJ, Assmus B *et al.* Congestive nephropathy: a neglected entity? Proposal for diagnostic criteria and future perspectives. *ESC Heart Fail* 2021;**8**:183–203. PMID: 33258308; PMCID: PMC7835563. https://doi.org/10.1002/ehf2.13118
28. Trpkov C, Grant ADM, Fine NM. Intrarenal Doppler ultrasound renal venous stasis index correlates with acute cardiorenal syndrome in patients with acute decompensated heart failure. *CJC Open* 2021;**3**:1444–52. PMID: 34993456; PMCID: PMC8712550. https://doi.org/10.1016/j.cjco.2021.07.010
29. Kitani T, Kidokoro K, Nakata T *et al.* Kidney vascular congestion exacerbates acute kidney injury in mice. *Kidney Int* 2022;**101**:551–62. PMID: 34843756. https://doi.org/10.1016/j.kint.2021.11.015
30. Boorsma E, ter Maaten J, Voors A *et al.* Renal compression in heart failure. *JACC Heart Fail* 2022;**10**:175–83. https://doi.org/10.1016/j.jchf.2021.12.005
31. Ahmad T, Jackson K, Rao VS *et al.* Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury. *Circulation* 2018;**137**:2016–28. Erratum in: *Circulation* 2018;**137**:e853. PMID: 29352071; PMCID: PMC6066176. https://doi.org/10.1161/CIRCULATIONAHA.117.030112
32. Rubinstein J, Sanford D. Treatment of cardiorenal syndrome. *Cardiol Clin* 2019;**37**:267–73. https://doi.org/10.1016/j.ccl.2019.04.002
33. Metra M, Davison B, Bettari L *et al.* Is worsening renal function an ominous prognostic sign in patients with acute heart failure? *Circ Heart Fail* 2012;**5**:54–62. https://doi.org/10.1161/CIRCHEARTFAILURE.111.963413
34. Testani JM, Chen J, McCauley BD *et al.* Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation* 2010;**122**:265–72. https://doi.org/10.1161/CIRCULATIONAHA.109.933275
35. Nohria A, Hasselblad V, Stebbins A *et al.* Cardiorenal interactions. *J Am Coll Cardiol* 2008;**51**:1268–74. https://doi.org/10.1016/j.jacc.2007.08.072
36. Diebold M, Kozhuharov N, Wussler D *et al.* Mortality and pathophysiology of acute kidney injury according to time of occurrence in acuteheart failure. *ESC Heart Fail* 2020;**7**:3219–24. https://doi.org/10.1002/ehf2.12788
37. Horiuchi Y, Wettersten N, van Veldhuisen DJ *et al.* Decongestion, kidney injury and prognosis in patients with acute heart failure. *Int J Cardiol* 2022;**354**:29–37. https://doi.org/10.1016/j.ijcard.2022.02.026
38. Jain AK, Chen HH. ROSE-AHF and lessons learned. *Curr Heart Fail Rep* 2014;**11**:260–5. PMID: 24966060; PMCID: PMC4151258. https://doi.org/10.1007/s11897-014-0208-6
39. Kazory A, Costanzo MR. Extracorporeal isolated ultrafiltration for management of congestion in heart failure and cardiorenal syndrome. *Adv Chronic Kidney Dis* 2018;**25**:434–42. https://doi.org/10.1053/j.ackd.2018.08.007
40. Chitturi C, Novak JE. Diuretics in the management of cardiorenal syndrome. *Adv Chronic Kidney Dis* 2018;**25**:425–33. https://doi.org/10.1053/j.ackd.2018.08.008
41. Felker GM, Lee KL, Bull DA *et al.* Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;**364**:797–805. PMID: 21366472; PMCID: PMC3412356. https://doi.org/10.1056/NEJMoa1005419
42. Jain A, Agrawal N, Kazory A. Defining the role of ultrafiltration therapy in acute heart failure: a systematic review and meta-analysis. *Heart Fail Rev* 2016;**21**:611–9. https://doi.org/10.1007/s10741-016-9559-2
43. Costanzo MR, Guglin ME, Saltzberg MT *et al.*; UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007;**49**:675–83. Erratum in: *J Am Coll Cardiol* 2007;**49**:1136. PMID: 17291932. https://doi.org/10.1016/j.jacc.2006.07.073
44. Bart BA, Goldsmith SR, Lee KL *et al.* Ultrafiltration in decompensated heart failure with Cardiorenal syndrome. *N Engl J Med* 2012;**367**:2296–304. https://doi.org/10.1056/NEJMoa1210357
45. Costanzo MR, Negoianu D, Jaski BE *et al.* Aquapheresis versus intravenous diuretics and hospitalizations for heart failure. *JACC Heart Fail* 2016;**4**:95–105. PMID: 26519995. https://doi.org/10.1016/j.jchf.2015.08.005
46. Krämer BK, Schweda F, Riegger GAJ. 'Diuretic treatment and diuretic resistance in heart failure. *Am J Med* 1999;**106**:90–6. https://doi.org/10.1016/S0002-9343(98)00365-9

47. Komlosi P, Fintha A, Bell PD. Current mechanisms of macula densa cell signalling. *Acta Physiol Scand* 2004;**181**:463–9. https://doi.org/10.1111/j.1365-201X.2004.01319.x
48. Bernstein AM, Willett WC. Trends in 24-h urinary sodium excretion in the United States, 1957–2003: a systematic review. *Am J Clin Nutr* 2010;**92**:1172–80. https://doi.org/10.3945/ajcn.2010.29367
49. Cox ZL, Hung R, Lenihan DJ *et al.* Diuretic strategies for loop diuretic resistance in acute heart failure. *JACC Heart Fail* 2020;**8**:157–68. https://doi.org/10.1016/j.jchf.2019.09.012
50. Mullens W, Dauw J, Martens P *et al.* Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med* 2022;**387**:1185–95. https://doi.org/10.1056/NEJMoa2203094
51. Dauw J, Charaya K, Lelonek M *et al.* Protocolized Natriuresis-guided decongestion improves diuretic response: the multicenter ENACT-HF study. *Circ Heart Fail* 2024;**17**:e011105. PMID: 38179728. https://doi.org/10.1161/CIRCHEARTFAILURE.123.011105
52. Yeoh SE, Osmanska J, Petrie MC *et al.* Dapagliflozin vs. metolazone in heart failure resistant to loop diuretics. *Eur Heart J* 2023;**44**:2966–77. PMID: 37210742; PMCID: PMC10424881. https://doi.org/10.1093/eurheartj/ehad341
53. Trullàs JC, Morales-Rull JL, Casado J *et al.* Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. *Eur Heart J* 2023;**44**:411–21. PMID: 36423214. https://doi.org/10.1093/eurheartj/ehac689
54. Biegus J, Voors AA, Collins SP *et al.* Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial. *Eur Heart J* 2023;**44**:41–50. PMID: 36254693; PMCID: PMC9805406. https://doi.org/10.1093/eurheartj/ehac530
55. Mentz RJ, Anstrom KJ, Eisenstein EL *et al.* Effect of Torsemide vs Furosemide After Discharge on All-Cause Mortality in Patients Hospitalized With Heart Failure: the TRANSFORM-HF randomized clinical trial. *JAMA* 2023;**329**:214–23. PMID: 36648467; PMCID: PMC9857435. https://doi.org/10.1001/jama.2022.23924
56. Ter Maaten JM, Beldhuis IE, van der Meer P *et al.* Natriuresis-guided diuretic therapy in acute heart failure: a pragmatic randomized trial. *Nat Med* 2023;**29**:2625–32. PMID: 37640861; PMCID: PMC10579092. https://doi.org/10.1038/s41591-023-02532-z
57. McMurray JJV, Solomon SD, Inzucchi SE *et al.* Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008. https://doi.org/10.1056/NEJMoa1911303
58. Nespoux J, Vallon V. SGLT2 inhibition and kidney protection. *Clin Sci (Lond)* 2018;**132**:1329–39. https://doi.org/10.1042/CS20171298
59. Perkovic V, Jardine MJ, Neal B *et al.* Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;**380**:2295–306. https://doi.org/10.1056/NEJMoa1811744
60. Investigators SOLVD, Yusuf S, Pitt B *et al.* Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302. https://doi.org/10.1056/NEJM199108013250501
61. Clark AL, Kalra PR, Petrie MC *et al.* Change in renal function associated with drug treatment in heart failure: national guidance. *Heart* 2019;**105**:904–10. PMID: 31118203; PMCID: PMC6582720. https://doi.org/10.1136/heartjnl-2018-314158
62. Wright JT, Jr. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease results from the AASK trial. *JAMA* 2002;**288**:2421. https://doi.org/10.1001/jama.288.19.2421
63. Bhandari S, Mehta S, Khwaja A *et al.* Renin–angiotensin system inhibition in advanced chronic kidney disease. *N Engl J Med* 2022;**387**:2021–32. https://doi.org/10.1056/NEJMoa2210639
64. Yamada T, Ueyama H, Chopra N *et al.* Systematic review of the association between worsening renal function and mortality in patients with acute decompensated heart failure. *Kidney Int Rep* 2020;**5**:1486–94. https://doi.org/10.1016/j.ekir.2020.06.031

Received: July 2, 2023; Editorial decision: May 17, 2024