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HEART FAILURE (HJ EISEN, SECTION EDITOR)

Acute Cardiorenal Syndrome in Heart Failure: from Dogmas to Advances

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Abstract

Purpose of Review This review aims to summarize our current understanding and management strategies of acute cardiorenal syndrome (CRS).

Recent Findings The definition of acute CRS remains debated, in part due to the lack of reliable insights into salt and water handling of the kidneys beyond impairment in glomerular filtration. Protocolized use of loop diuretics to ensure adequate delivery to their target of action, as well as segmental tubular blockade with adjunctive use of thiazide diuretics, acetazolamide, amiloride, or sodium-glucose transporter 2 (SGLT2) inhibitors, may result in more effective natriuresis in patients with acute CRS who exhibit diuretic resistance. Other strategies, such as modulating renal sodium avidity with the use of hypertonic saline, reduction of intra-abdominal pressure, or device-based salt and volume removal, are promising and warrant further investigation.

Summary Acute CRS remains a significant contributor of morbidity and mortality for the acute heart failure population. New strategies have challenged current dogmas in our understanding of its pathophysiology, which may lead to potential new treatment approaches.

Keywords Cardiorenal syndrome · Worsening renal function · Diuretic resistance · Heart failure · SGLT2 inhibitors · Hypertonic saline

Introduction

The concept of "cardiorenal" disease was first described in 1914 by Dr. Alfred Stengel [1]. He proposed the term "cardiorenal" that referred to "cases of combined cardiovascular and renal disease without such manifest predominance of either as to justify a prompt determination of the one element as primary and important and the other as secondary and unimportant." Dr. Stengel presented an empiric framework categorizing these patients into three groups that would each require different treatment strategies: (1) those with primary heart failure (HF) leading to secondary renal failure, (2) atherosclerotic vascular disease leading to both secondary HF and renal failure, and (3) primary renal failure leading to secondary HF [1]. By proposing this framework, Stengel's goal was to help clinicians better identify and treat the primary insult in any given patient presenting with "cardiorenal" disease. It is therefore important to appreciate that different and complex pathophysiologic processes leading to the disruption of the intricate interdependence of the heart and the kidneys have long been recognized for over a century, prior to any effective treatment strategies or diagnostic tests.

Today, the term "cardiorenal syndrome" (CRS) refers to any disease state where HF and renal dysfunction happen to be present simultaneously, which became too broad and nonspecific. A widely circulated classification scheme proposed by the Acute Dialysis Quality Initiative (ADQI) workgroup in 2008 categorized CRS from types 1 to 5 and was created in an effort to highlight the bidirectional nature of heart-kidney interactions [2]. However, such a classification scheme has yet to better define treatment strategies for CRS in clinical practice as it has provided limited incremental insights into what pathophysiologic mechanisms clinicians may target [3•]. This

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lack of progress over the century since Stengel's treatise, in part, has been due to the following: (1) the obscure and somewhat misleading terminologies used over the years in describing cardiorenal dysregulation across patients with CRS; (2) the lack of insights into underlying causes and contributing factors of renal insufficiency or diuretic ineffectiveness when treating patients with CRS; and (3) the lack of innovation and novel treatment approaches beyond loop diuretics despite testing of a wide range of proposals and randomized clinical trials. Without more precise and quantifiable definitions of CRS, its true prevalence and incidence can be difficult to ascertain.

It is very important to distinguish acute CRS as a defined subset of acute HF syndromes. In clinical practice, acute CRS in patients with heart failure is commonly described as "an extreme form of cardio-renal dysregulation in which therapy to relieve congestive symptoms of HF is limited by further decline in renal function" [4]. Previously known as "resistant edema" in the era of mercurial diuretics, this definition is far narrower than that of the ADQI classification scheme (restricting only to their "Type 1" category), and thus may not encompass the full spectrum of heart-kidney crosstalk. Yet, it captures the challenges commonly seen when escalating diuretic use for volume removal in the presence of clinical congestion (so-called diuretic resistance, which refers to the relatively insufficient responses to diuretic therapy) leads to progressive compromise in renal function patients with heart failure. The demonstration that impaired cardiac output can directly diminish renal perfusion pressures since the 1990s had dominated the "cardiocentric view" of acute CRS [5]. With new drug or device therapies available to tackle this morbid condition, we are now challenging the prevailing dogmas surrounding acute CRS. In this review, we will outline the recent advances in our contemporary approaches that include new insights into (1) pathophysiologic contributions of acute CRS; (2) adequacy and effectiveness of diuretic therapy; and (3) hemodynamic, neurohormonal, and metabolic interdependence.

Dogma #1: Acute Cardiorenal Syndrome Is Primarily Driven by Acute Kidney Injury Due to Cardiac Insufficiency

The primary driver in a large majority of cases of acute CRS may not be acute impairment of cardiac output or intrinsic kidney injury, but rather a complex set of perturbations in systemic and regional hemodynamic and/or neurohormonal responses that can be overcome by better appreciation of their pathophysiologic triggers. It is imperative that clinicians develop a better understanding of the trajectories of renal function that are relevant in the care of patients with heart failure, and appreciate the strengths and limitations of various bedside metrics that have been summarized in a recent consensus statement [6•].

Worsening Renal Function as a Flawed Metric in the Setting of Acute CRS

Originally thought to be primarily caused by arterial underfilling leading to impaired renal perfusion due to acute cardiac insufficiency [7], we now recognize that acute CRS often develops in the presence of adequate cardiac output (so-called warm and wet profile) [8, 9]. Nevertheless, acute CRS often presents with "worsening renal failure" (WRF) that manifests as a rise in serum creatinine of $\geq$ 0.3–0.5 mg/dL and/or a drop in estimated glomerular filtration rate (eGFR)—both have been associated with poorer clinical outcomes especially in the absence of adequate diuresis or decongestion. It is important to understand, however, that this metric was derived from a large observational cohort as the optimal "cut-off" between sensitivity and specificity in predicting in-hospital mortality [10•]. Whether or not a rise in serum creatinine (or a drop in eGFR) truly reflects a decline in renal function has been debated over the past decade, since different underlying causes of WRF determine different clinical courses. Theoretically in the setting of acute HF, a rise in serum creatinine may reflect a drop in glomerular filtration (as a result of decreased renal perfusion) or azotemia (accumulation of uremic solutes and nitrogen-rich compounds), both contributing to disease progression and adverse outcomes. However, patients who have advanced heart failure and have lower muscle mass may also have lower circulating creatinine (as a result with falsely lower serum creatinine or creatinine clearance), even though more specific markers of glomerular filtration have provided only marginally incremental prognostic values in both acute and chronic HF settings [11, 12].

Several recent observations have challenged the notion that WRF is clinically relevant in the absence of its clinical context. In the setting of adequate diuresis, a rise in creatinine was associated with better rather than worse long-term outcomes, since this may be driven by hemoconcentration as a result of successful diuresis (thereby not necessarily reflecting true damage to the renal tubules) [13•, 14–16]. Therefore, adequacy of diuresis in the congested state may serve as a more clinically relevant metric of therapeutic success. Indeed, this concept has been demonstrated in a post hoc analysis of the DOSE-AHF trial, where brisk diuresis during acute HF admissions with or without WRF was associated with better rather than worse long-term clinical outcomes, whereas "improvement" in renal function (represented by drop in serum creatinine) paradoxically tracked with worse clinical outcomes [17]. Furthermore, WRF as a result of initiation of drugs with known benefits (such as neurohormonal antagonists) have also been associated with better rather than worse

outcomes. In contrast, reducing WRF has not been found to be an effective therapeutic target as drugs targeting WRF have not improved clinical outcomes [18].

Lack of True Acute Kidney Injury in Diuretic-Responsive Patients with Acute CRS

To go a step further, not all WRF reflects true "worsening", meaning intrinsic kidney injury and clinical deterioration. We should all remember that contemporary clinical criteria for AKI in the nephrology literature include both rising serum creatinine and diminishing urine output [19]. In the acute HF setting, the majority of patients are diuretic responsive—their urine outputs are often robust in response to aggressive diuretic therapy despite fluctuating creatinine and blood urea nitrogen (BUN). Therefore, the propensity to develop a rise in creatinine following aggressive diuresis may simply reflect a lower circulatory reserve to maintain adequate renal perfusion to support aggressive diuresis (so-called effective arterial blood volume, effective circulating volume, or plasma refill rate in the nephrology literature). In fact, the kidneys have evolved to counter intravascular volume depletion by fully activating mechanisms to safely preserve salt and water for survival.

Early proponents of WRF as a therapeutic target have touted that a rise in circulating novel AKI biomarkers may indicate intrinsic renal damage that may be linked to poorer prognosis in acute CRS [20]. Certainly, true AKI may occur in the setting of acute CRS, but it is not common despite a third or more patients developing WRF following aggressive diuresis. In fact, acute CRS is likely driven by processes beyond "cardiogenic" alterations in renal hemodynamics, and often presents without clear evidence of intrinsic damage such as proteinuria or urinary sediments. Plasma and urinary biomarker levels often reflect different compartments of the body, as the large majority of biomarker filtered through the glomeruli are often reabsorbed at the proximal renal tubules, where direct injury at the renal tubular level can produce such biomarkers in the urine that may indicate AKI [21].

The lack of injury in the majority of WRF in acute HF was first reported by Dupont and colleagues when urinary neutrophil gelatinase-associated lipocalin (NGAL) was not elevated in those with acute HF treated with aggressive diuretic therapy despite experiencing WRF [22]. There is also clear evidence that blood and urine AKI biomarkers behave differently and reflect different aspects of renal dysfunction [21]. Several contemporary studies have now confirmed that there is no clear evidence that a general rise in AKI biomarkers was associated with worsening clinical outcomes upon aggressive diuresis, even in the setting of WRF or underlying chronic kidney disease [23, 24].

Volume Redistribution and Compartmentalization May Contribute to Acute CRS

One of the biggest paradigm shifts in understanding the pathophysiology of acute CRS has been the recognition that acute HF may in part be exacerbated by volume redistribution rather than solely the consequences of excessive and overwhelming fluid retention [25•]. Patients presenting with acute HF syndromes may have different degrees and distributions of "congestion," and not everyone responds in the same manner to loop diuretics. We should not assume that the kidneys are failing when WRF develops, while in fact they are appropriately responding to intravascular volume depletion and effectively protecting the body from excessive dehydration. Utilizing blood volume analyses, Miller and colleagues have challenged the notion that all acute HF patients have excessive volume overload and need aggressive diuresis, demonstrating that there are a substantial number of patients seen in the emergency department with minimal increase in blood volume, which may indicate that these patients have a vascular component of increased filling pressure that is independent of volume expansion [26]. To bypass such natural counter-regulatory measures with force, mechanical volume removal can further exacerbate dyshomeostasis. This has been best illustrated in CARRESS-AHF, where mechanical removal of volume by ultrafiltration (UF) was directly compared with goal-directed stepped pharmacologic therapy in patients with acute HF presenting with WRF, and was associated with more rather than less WRF and hyponatremia [27•, 28, 29]. Hence, the subjective perception of central congestion (even in the presence of peripheral edema) in these patients may have led to unnecessary diuresis that can lead to intravascular volume depletion. Fortunately, such cases are easily corrected by stepping down diuretic therapy. However, this also emphasizes the need to have an accurate assessment of volume status, and confirmation of clinical suspicion by blood testing or invasive hemodynamic assessment if in doubt or with unexpected treatment responses.

The causal relationship of increased renal venous pressure leading to decreased GFR has previously been described in animal models, which clearly illustrated that impaired "forward" cardiac output is only one of several factors leading to acute CRS [30–33]. Several groups have revived this concept over the past decade by demonstrating the association of venous congestion with WRF and impairment of diuretic responses in patients with acute HF [9, 34]. This has also been observed in the chronic HF setting [34]. Recently, Nijst and colleagues provided direct evidence in a series of mechanistic human studies, confirming the direct contributions of volume expansion on blunting natriuresis and renal venous flow in the kidneys [35, 36]. In addition, the potential contribution of gut edema and ascites leading to raised intra-abdominal pressure (IAP) has been theorized as a contributing factor to CRS [37]. In animal models, increased IAP can precipitate renal injury in acute HF [38]. Indeed, a subset of patients admitted with

advanced decompensated HF may exhibit abnormally elevated IAP as measured by bladder catheterization [39•]. While the majority of patients improve their IAP following effective diuresis, those that did not achieve adequate decongestion demonstrated persistently elevated IAP. The mechanism by which elevated IAP leads to worsening renal function is likely mediated by its direct impact on renal venous congestion from visceral edema due to increased blood volume across the splanchnic circulation—a phenomenon that has been recognized since the 1950s [40]. There is currently only anecdotal evidence to support the use of interventions directed towards elevated IAP (i.e., paracentesis) in the setting of acute HF [41], and thus, both retrospective and prospective studies are still needed to confirm benefit. In support of this approach, direct splanchnic nerve block to transiently relieve visceral congestion has demonstrated short-term improvement in hemodynamics and provided symptomatic relief in patients with acute and decompensated HF [42, 43]. However, understanding the long-term benefits and risks of such therapeutic approaches in acute CRS warrants further investigation.

Dogma #2: Decongestive Strategies with Loop Diuretics Exacerbate Acute Cardiorenal Syndrome

For a long time, overzealous use of loop diuretics has been faulted as being one of the contributors to acute CRS. For example, higher doses of loop diuretics has been associated with poorer long-term outcomes in a post hoc analysis from the ESCAPE trial [44]. As hypotension serves as a primary driver of WRF in advanced decompensated HF above and beyond central hemodynamics [45], intravascular volume depletion from aggressive use of loop diuretics has been considered a primary driver of acute CRS. However, in the CARRESS-AHF study in patients with persistent congestion and WRF, achieving net negative urine output regardless of treatment strategy was not associated with progressive AKI in the majority of patients with HF [29, 46]. This suggests that effective decongestion plays an important role in overcoming rather than precipitating perceived renal insufficiency that contributes to acute CRS, and that the large majority of patients are indeed "diuretic responsive" rather than "diuretic resistant." Furthermore, the need to tailor diuretic use in this vulnerable population requires more in-depth understanding of the role these drugs play in acute CRS [47].

Adequate Amounts of Loop Diuretics Should Be Administered in Persistent Congestion

Since their discovery in the 1950s, loop diuretics have become the mainstay of acute heart failure treatment largely because of their effective natriuretic and chlorouric properties [48]. In the setting of acute HF with fluid overload, patients are often admitted to receive intravenous loop diuretics boluses and may occasionally convert to continuous infusions or be augmented with thiazides and even vasoactive drugs [49]. The primary purpose is to deliver adequate inhibition of sodium reabsorption at the loop of Henle. This allows effective blockade of urinary sodium reabsorption, such that the downstream sodium reabsorptive mechanisms are overwhelmed, thereby achieving net negative sodium balance without excessive kaliuresis [50]. Fortunately, loop diuretics have a broad therapeutic window yet have a relatively short half-life to maintain their diuretic efficacies. One must therefore ensure that adequate loop diuretics are being delivered to maintain the patient above the threshold levels required in the upsloping portion of the loop diuretic dose-response curve (Fig. 1). Strategies to maintain adequate drug exposure in the therapeutic window (that can be affected by absorption, protein-binding in transport, secretion via proximal convoluted tubules, and renal clearance) include (1) giving higher doses; (2) giving more frequent dosing; (3) changing from oral to intravenous route of administration, or switching to more bioavailable loop diuretics; and (4) changing from bolus to continuous infusions [50].

One common cause of "acute CRS" is simply the inadequate use of loop diuretics or adjunctive drugs to produce adequate natriuresis. The DOSE-AHF study was designed to address the research question as to whether continuous and higher-dose intravenous loop diuretics are superior to bolus/standard dosing in a heterogenous patient population with substantial home oral loop diuretic use (≥ 80 mg furosemide equivalent) [51•]. The results have prompted much debate, as contrary to popular belief all groups showed similar clinical outcomes with the high-dose group achieving statistically significant better symptom relief without increased incidence of WRF [51•]. However, a post hoc analysis of the same study has perhaps shed some important mechanistic insight into the findings [52]. Notably, the design of the DOSE-AHF study compared 2.5-times the home dose vs the home dose, but in a patient population that was randomized with a wide range of home doses. As such, there is a large heterogeneity of doses delivered, some likely adequate and others potentially inadequate. In fact, almost a third of the standard dose group received total intravenous loop diuretic doses higher than those in the high-dose group [52]. When adjusted for the amount of volume of diuresis achieved, those in the high-dose group portend better outcomes than those in the low-dose group. These findings suggest that the different groups may be unequally distributed in their diuretic dosing after all as the randomization did not overcome their disparate diuretic efficiencies.

Prompt Assessment of Diuretic Responses May Guide Diuretic Dosing

The classic teaching in the diagnostic workup of acute renal failure has been to avoid measuring urine electrolytes due to the interference of diuretics. However, there has been

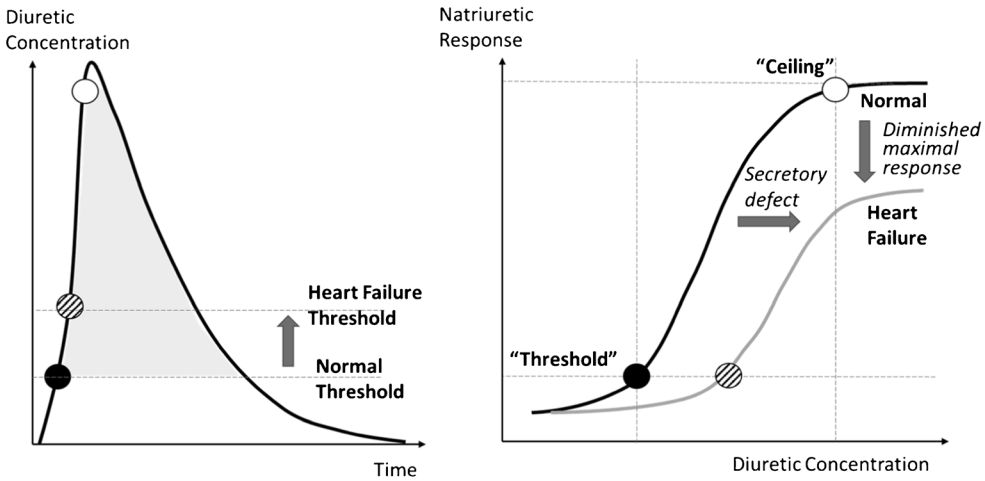

Fig. 1 Intravenous loop diuretic pharmacokinetics and dose-response curve in heart failure. In heart failure, the diuretic threshold is shifted upwards (from solid to shaded circle), thereby reducing the effective range of therapy (i.e., area under the curve) as well as increasing the amount of intravenous diuretics required to produce a natriuretic response. The development of acute CRS shifts the dose-response curve further to the right as a result of the renal secretory defect, requiring even higher diuretic doses for the same response. Meanwhile, the maximal natriuretic response is also diminished upon reaching the diuretic ceiling (open circle)

increasing recognition that urine sodium and other electrolytes are key metrics to assess diuretic response, and should be considered in the setting of acute CRS to determine whether the ineffective volume removal is a result of inadequate diuretic prescription and/or delivery. This concept has first been suggested by Singh and colleagues, upon assessing both urine sodium and furosemide levels in a cohort of patients receiving continuous intravenous furosemide therapy in the intensive care unit. They observed the discrepancies between natriuretic responses to loop diuretics and glomerular filtration rates, as well as the poor prognostication of impaired natriuresis despite adequate furosemide delivery (as directly measured by urine furosemide levels and calculating the relatively low urine sodium-to-furosemide ratios) [53]. Subsequently, the use of clinical parameters such as urine output or weight per set amounts of diuretics (e.g., 40 mg furosemide equivalent) has been proposed by several groups as a quantifiable metric to identify diuretic resistance and the need to adjust or augment diuretic therapy [54, 55]. This important point has been highlighted in the latest European Society of Cardiology Heart Failure Association Cardio-Renal Working Group consensus statement on the use of diuretics in acute HF (summarized in Fig. 2) [56], and are now supported by observations from multiple studies [57–60].

Goal-Directed Stepwise Pharmacologic Therapy May Overcome Inadequate Diuretic Responses

It has been recognized for decades that if diuretic responses are deemed insufficient with loop diuretics alone, additional drugs can be used to augment natriuresis to provide some short-term relief [61]. The concept of sequential nephron blockade builds on the premise that increase in sodium reabsorption occurs at the distal convoluted tubule in the setting of upstream Na-K-2Cl symporter inhibition by loop diuretics [62]. In most cases, the distal nephron has been the primary target, since targeting compensatory increases in sodium reabsorption at the distal convoluting tubules in response to loop diuretic use may overcome diuretic resistance [63].

Blocking distal renal tubular sodium reabsorption has been achieved by thiazide diuretics as illustrated in the stepwise pharmacologic arm of the CARRESS-AHF study (Table 1) [46]. Often used as a second-line strategy for persistent congestion despite high-dose loop diuretics, oral metolazone and hydrochlorothiazide or intravenous chlorothiazide have been added. In post hoc analyses of several studies, add-on thiazide use can produce greater diuresis and weight loss compared with loop diuretics alone in the setting of WRF [64]. Head-to-head comparisons, however, have yet to reveal significant advantages of one over another [65–68]. Vasopressin receptor antagonists have also been considered as an adjunctive therapy with or without hyponatremia, but randomized controlled trials did not show incremental clinical benefit [69].

Natriuretic doses of mineralocorticoid receptor antagonists (MRA) have spurred some interest in this arena especially given their established clinical benefits in patients with chronic HF as well as other edematous states like liver cirrhosis. Earlier single-center studies have suggested improvement in natriuresis with the addition of MRA in acute HF [60, 70]. However the ATHENA-AHF study did not show incremental clinical benefits when adding natriuretic-dose MRA (100 mg daily) to high-dose intravenous furosemide even in the setting of diuretic resistance [71, 72]. This may be explained by lower than anticipated concentrations of active metabolites of spironolactone (including the main metabolite canrenone,

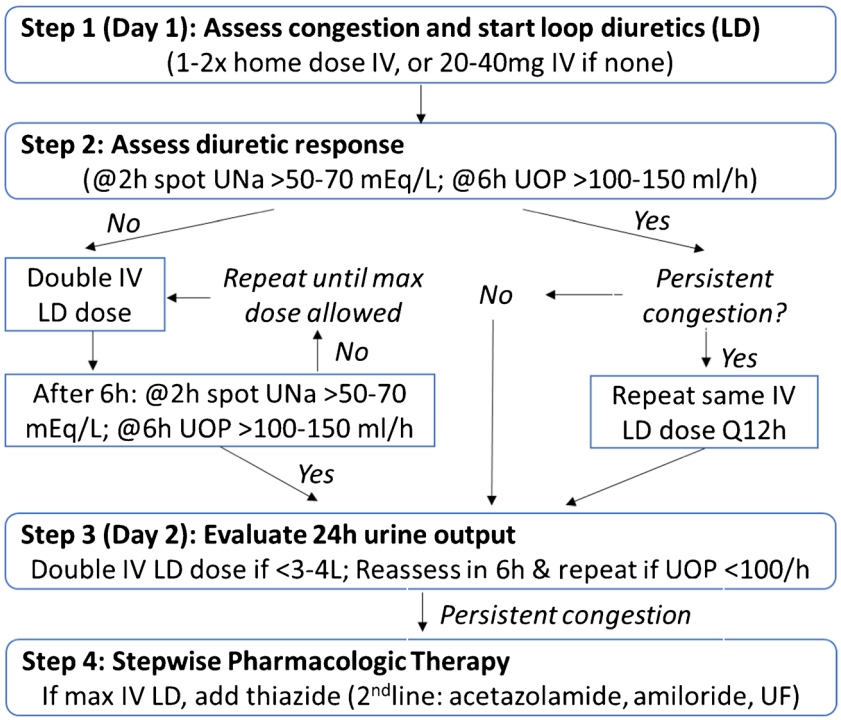

Fig. 2 Approach to goal-directed pharmacologic therapy in acute heart failure [56]. LD, loop diuretics; IV, intravenous; UNa, spot urine sodium; UOP, urine output; UF, ultrafiltration

which often takes a few days to accumulate) measured in the MRA group, suggesting that either there was a potential pharmacokinetic issue with the study drug or the potential benefits of MRA may not be fully realized when administered acutely [73].

Table 1 Stepwise pharmacologic care protocol for acute cardio-renal syndrome

Current Dose		Suggested Dose (goal 3-5 L urine/day)	
Loop (mg/day)	Thiazide	Loop (/day)	Thiazide
≤ 80	±	40 mg IVB + 5 mg/h	0
81–160	±	80 mg IVB + 10 mg/h	5 mg MTZ qd
161–240	±	80 mg IVB + 20 mg/h	5 mg MTZ bid
> 240	±	80 mg IVB + 30 mg/h	5 mg MTZ bid

Urine output goal set at 3–5 L/day and start intravenous loop diuretics at 2-times home oral dose. Reduce current diuretic regimen if urine output > 5 L/day, otherwise maintain dose. If inadequate urine output (< 3 L/day) at 24 h, recommend intravenous bolus followed by continuous infusion of loop diuretics according to furosemide equivalents. At 48 h if urine output still inadequate, may consider dopamine or dobutamine at 2 μg/kg/h if systolic blood pressure < 110 mmHg and LVEF < 40% or RV systolic dysfunction; nitroglycerin or nitroprusside if SBP > 120 mmHg and severe symptoms. Consider hemodynamic-guided therapy or ultrafiltration/dialysis when appropriate

Table based on CARRESS-AHF Study [27•]

Loop, intravenous loop diuretics (furosemide equivalents); *IVB*, intravenous bolus; *MTZ*, metolazone

Dogma #3: Withholding Neurohormonal Antagonists and Sodium Restriction Are Key Strategies to Restore Renal Function in Acute Cardiorenal Syndrome

In the setting of WRF (as well as hypotension or hyperkalemia), it is not uncommon for clinicians to avoid nephrotoxins, optimize renal perfusion, and improve total body sodium balance. Inhibitors of the renin-angiotensin-aldosterone system (RAAS) have long been associated with reducing glomerular filtration rates via their vasodilatory actions from blockade of angiotensin II-induced constriction of the efferent arteriole [47]. Once acute CRS ensues, clinicians often withhold RAAS inhibitors and advocate salt restriction while administrating high-dose loop diuretics, even though these strategies have very limited supportive evidence [74]. However, the "low-salt syndrome" in refractory heart failure can also contribute to diuretic resistance, rendering a reconsideration of the importance of electrolyte homeostasis in this vulnerable population.

Besides hyponatremia, other often-overlooked electrolyte derangements have been associated with acute CRS. Chloride is the key electrolyte for regulating both reabsorption of tubular electrolytes and water in the kidney through the RAAS and distribution of body fluid in each compartment of the body. In the era of mercurial diuretics, lysine chloride had been used to treat refractory fluid retention [75]. Recognition of low serum chloride as a marker of poor prognosis and revisiting the chloride-sensing renin release as part of tubuloglomerular

feedback has also prompted the concept that electrolyte depletion may exacerbate diuretic resistance [76–78]. As hypochloremia is intimately associated with diuretic resistance [79], careful selection and combination of various diuretics and their doses with careful considerations of not only sodium/volume but also chloride homeostasis (largely targeting the proximal renal tubule) could become an important therapeutic option for acute CRS.

Withholding and Rechallenging Neurohormonal Antagonists in Acute CRS

Inhibition of the RAAS and sympathetic nervous system is a cornerstone of HF management in improving long-term clinical outcomes [49]. However, most of the landmark trials that support their use have excluded patients with acute CRS, making the benefit of these agents uncertain in this population [80]. That being said, WRF associated with initiation of RAAS inhibitors have not been associated with worse outcomes, and in fact showed improvement in long-term outcomes [81, 82]. As discussed earlier, rise in serum creatinine alone is not associated with worse clinical outcomes, and therefore should not be a justifiable reason to withhold neurohormonal blocking agents which have proven mortality benefit [83]. Hyperkalemia on the other hand does occur in the setting of intravascular depletion in some patients, and can be countered by lowering doses or adding oral potassium binders [83]. Randomized controlled trials in this area are lacking. Nevertheless, post hoc analyses from contemporary studies have shown that use of RAAS inhibitors following hospital discharge from acute HF was associated with better clinical outcomes [84]. That being said, maximizing RAAS blockade with addition of aliskiren (renin inhibitors) did not show incremental benefits in patients admitted for acute HF [85], yet treatment with sacubitril/valsartan confer clinical benefits when compared with enalapril [86]. These findings are concordant with the fact that guideline-directed medical therapy that has been shown to improve the clinical trajectory of patients with heart failure should be maintained throughout the clinical course or re-administered as soon as possible if being withheld. Judicious rechallenging of these drugs is warranted, and if intolerance is encountered, it is imperative that patients are followed closely to consider restarting these medications following discharge.

Targeting Proximal Renal Tubules as a Novel Treatment Strategy for Acute CRS

The proximal renal tubules (PCT) have been largely overlooked in the cause and progression of acute CRS, in part due to the myopic focus on enhancing the effectiveness of loop diuretics and the assumption that PCT may contribute very little in the overall natriuretic potential, due to the belief that the distal nephron serves as the key driver of diuretic resistance [63]. Meanwhile, drugs that specifically target the PCT (such as acetazolamide) often produce a weak diuretic effect, and have often been used to modify acid-base status in specific conditions like high-altitude pulmonary edema. The potential "loop diuretic-sparing" role of acetazolamide, a carbon anhydrase inhibitor targeting the PCT, has been revisited in two pilot studies that compared add-on intravenous or oral acetazolamide with loop diuretics alone in patients admitted with acute HF. Both studies observed statistically significant increases in natriuresis with the addition of acetazolamide when adjusted for loop diuretic dose [87, 88]. Meanwhile in a retrospective case series of ambulatory patients with advanced heart failure, use of oral acetazolamide was also associated with an improvement in functional class and on surrogates of fluid overload [89]. While it is unclear whether acute administration of acetazolamide can alter the natural history of acute CRS, there is evidence that acetazolamide can preserve chloride homeostasis [90]. It is conceivable that early administration of acetazolamide may act synergistically with loop diuretics to improve decongestion in acute HF and clinical outcomes, which is the subject of an ongoing multicenter clinical trial [91].

Sodium-glucose transporter-2 (SGLT2) inhibitors have emerged as an important disease-modifying drug therapy in heart failure [92]. SGLT2 inhibitors exert their glycosuric and natriuretic effects through inhibition of glucose and sodium cotransport in the PCT. In several major cardiovascular outcome trials, SGLT2 inhibitors were found to significantly reduce progression of renal dysfunction [93–95]. One of the proposed mechanisms for renal protection by SGLT2 inhibitors is that the enhanced natriuresis results in increased sodium delivery to the macula densa, resulting in afferent arteriolar vasoconstriction and thereby reduced glomerular pressure [96]. Another hypothesis is that inhibition of SGLT2 activity reduces the oxygen demand of the nephron, rendering it less susceptible to oxidative stress injury in the setting of hypoxia or impaired renal perfusion [97–99]. Early insights suggested that SGLT2 inhibitor use in the acute HF population is safe and may improve overall diuresis [100–102]. Interestingly, empagliflozin has been shown to produce an additive natriuretic effect over time when given prior to bumetanide that is independent of glycosuria, and may be associated with increased erythropoietin levels and uric acid excretion [103]. SGLT2 inhibitors also appeared to preserve serum chloride levels in diabetic patients [104]. Yet, their role in acute CRS remains to be determined.

Direct Modulation of Sodium Avidity with Saline to Promote Excretion

Saline administration during aggressive diuretic therapy has long been considered as a controversial treatment strategy for

acute CRS. The proposed mechanism is that salt restriction leads to a reduction in chloride sensing by the macula densa in the distal nephron, which leads to a sodium-avid state in the kidney [105]. Beyond the initial reports from Italy [106], several groups have also demonstrated the potential benefits of concomitant saline infusion during aggressive diuresis during acute HF admissions [107–110]. However, a small single-center, pilot randomized trial in patients with underlying advanced chronic kidney disease failed to demonstrate incremental benefits of hypertonic saline use [111]. Recently, Griffin and colleagues reported their single-center experience on the use of hypertonic saline solution in patients with advanced HF and diuretic resistance [112]. In this nonrandomized retrospective cohort study, daily administration of a 150-mL bolus of 3% hypertonic saline via a standardized protocol was associated with improved diuresis without significant change in respiratory status, adverse neurologic effects, or sodium levels [112]. It is of interest that concomitant saline infusion with loop diuretic therapy has been tested in a device-based algorithm-driven approach, with a goal-directed dose adjustments based on natriuretic/diuretic feedback (so-called controlled decongestion), showing safety and potential effectiveness [113].

Conclusions and Future Perspectives

Our current understanding of acute CRS remains limited in part because of the lack of a uniform clinical definition as a result of the lack of a unifying pathophysiologic mechanism. Clinicians and investigators have been distracted by largely inaccurate assertions that the underlying renal pathophysiology parallels other forms of oliguric AKI and that our indiscriminatory use of intravenous loop diuretics without mechanistic insights can effectively alter the natural history of what has triggered the congestion to begin with. Loop diuretics remain the mainstay of any congested state although their effective usage could potentially circumvent a subset of otherwise (real or conceived) iatrogenic situations leading to acute CRS. Meanwhile, new treatment strategies have the potential of providing adjunctive support or even directly targeting the pathologic states of congestion or organ perfusion that may be independent of loop diuretic use.

Further research is needed to better elucidate the underlying mechanisms of cardiorenal syndrome and potential targets for treatment. From a diagnostic standpoint, we need a better definition of cardiorenal syndrome that, when used, prompts the clinician to approach the case in a different manner from the routine care of an acute HF patient. From a therapeutic standpoint, novel therapeutic strategies targeting PCT or upfront segmental nephron blockade of sodium reabsorption and those that modify renal sodium avidity should be further investigated. Meanwhile, exciting new device-based therapies aimed at improving cardiorenal hemodynamics and salt/volume homeostasis are currently under intensive investigation in pilot first-in-human studies [114–119]. These novel strategies provide unique regional modulations that may offer promising avenues of therapy for selected patients with acute CRS in the future while providing important mechanistic insights into the complex pathophysiology of acute CRS [120].

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Compliance with Ethical Standards

Conflict of Interest Alan Kiang declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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