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Review Article

Chronic Cardiorenal Syndrome: Review: Part 3

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ABSTRACT

Chronic heart failure (CHF) induces gradual kidney damage, leading to chronic cardiorenal syndrome (cCRS). This condition is linked with an increase in morbidity and death rate. The commonest cause of cCRS is CHF with a low ejection fraction. CHF causes alteration of hemodynamic variables, such as low cardiac output, neuroendocrine activation, venous congestion, and chronic inflammatory reaction activation. cCRS is a chronic condition that leads to hemodynamic and chronic heart and kidney fibrosis. There are no specific biomarkers to diagnose the cCRS. There is a debate regarding the causal relationship between CHF and kidney function impairment in cCRS. The debate has centered on the efficacy, safety, and cost-effectiveness of the currently available therapeutic options, such as diuretics and angiotensin-converting enzyme inhibitors. Full, clear scientific recommendations for the prevention and treatment of cCRS are required.

Key words: Cardiorenal syndrome type 2, chronic CRS, update in chronic CRS pathophysiology, chronic CRS therapy update, worsening renal function, diuretic resistance, intravenous diuretics, isolated ultrafiltration

INTRODUCTION

In the previous part of this series, we discussed the pathophysiology and management of acute cardiorenal syndromes (CRS Types 1 and 3). This review, Part 3, will focus exclusively on the chronic cardiorenal syndrome (cCRS; CRS Type 2). In the EU, heart and circulatory illnesses cause 4.3 million annual fatalities. The leading causes of cardiovascular mortality include stroke and coronary heart disease. The 2006 European Union economic cost of cardiovascular disease was 127 billion Euros. Around 82.6 million Americans have one type of cardiovascular disease. Stroke and heart failure (HF) hospitalizations are more prevalent in women, but heart disease and acute myocardial infarction are more common in men. [1] The expense of cardiovascular illness and congestive HF may be significant, and was about $29 billion in 2004 in the United States. [2] Multiple risk factors for HF include hypertension, diabetes, and underlying atherosclerosis. As expected, these risk factors

contribute to renal impairment, heart failure, and cardiac dysfunction. Research indicates that poor renal function in conjunction with HF results in poor outcomes. These patients' type may need more intense targeted treatment due to their increased risk of death. [2–4] In recent decades, more people have developed cardiorenal syndrome (CRS), heart and kidney failure. The conceptual link between the heart and kidney was notably emphasized in 1913 by Thomas Lewis. [5,6] CRS pathophysiology, categorization, and treatment have made significant progress since then. However, clinical practice faces challenges in terms of accurate patient categorization and early CRS detection before organ damage.

Historically, since its initial reference in 1913, [5] the National Heart, Lung, and Blood Institute working group conducted a comprehensive characterization in 2004. Despite the efficacy of the early definition in understanding the heart–kidney relationship and how acute or chronic renal or cardiac illness harms other organs, the complexity of the syndrome remains unclear. Ronco et al. described CRS in 2008 as a heart and renal illness where one organ's malfunction might cause the other to experience dysfunction. [7] The Acute Disease Quality Initiative (ADQI) working group identified five categories of CRS based on major organ injuries in the same year. Type 1 and 2 CRS refer to injuries to the heart as the primary organ, whereas CRS types 2 and 4 refer to injuries to the kidney as the primary organ. In comparison, type 5 CRS involves concomitant organ failure due to systemic insults such as cirrhosis or sepsis. Moreover, each type of CRS was subdivided into acute and chronic. [7]

Hatamizadeh et al. identified seven subcategories of CRS based on pathophysiology and clinical manifestations: hemodynamic, uremic, vascular, neurohumoral, anemia/iron-metabolism, mineral-metabolism, and malnutrition-inflammation-cachexia. [8] Clinical application of the ADQI classification (referring to RIFLE criteria) is limited. The biggest drawback is that doctors have difficulty distinguishing between renal-cardiac and cardiorenal illnesses in most situations. Acute heart failure (AHF) and chronic heart failure (CHF) exist with acute kidney damage (AKI), making it challenging to classify patients into Type 1, 2, and 3 CRS. [6] In cases of reno-cardiac syndrome (RCS), it may be difficult to ascertain whether AKI causes cardiac damage. Additionally, overlapping subcategories complicate patient classification and treatment throughout illness progression.

The use of a combined evaluation method to classify individuals using CRS or RCS is beneficial. This categorization relies on patient history, clinical examination, and cardiac and renal ultrasonography findings. Small kidneys with abnormal echogenicity may suggest RCS. In contrast, normal-sized kidneys with reduced heart function may indicate CRS. The response to the treatment strategy may assist in this categorization. A reduction in serum creatinine (Scr) after diuretic medication may indicate acute or chronic CRS. Conversely, an increase in Scr during fluid removal treatment may indicate RCS due to overestimated glomerular filtration rate (GFR) and kidney failure due to volume overload. [6]

Proposed categorization of CRS according to hemodynamic profiles based on clinical phenotype. [9] This categorization approach assesses tissue perfusion, cardiac output (CO), effective circulation fluid volume (ECFV), and pulmonary congestion using central venous pressure (CVP) or pulmonary capillary wedge pressure (PCWP). The classification of patients includes four subcategories: "wet or dry" and "warm or cold." [10] Although beneficial for predicting urgent interventions and directing decongestion treatment, it is often not used in routine evaluations because of the necessity for sophisticated hemodynamic indicator testing.

PATHOGENESIS OF CCRS

cCRS is defined as chronic cardiac dysfunction leading to chronic kidney disease/dysfunction, not necessarily reaching the specific threshold of CKD. [7] The pathogenesis of cCRS is due to failure, leading to a reduction in kidney perfusion due to diminished CO. However, it is not only due to poor CO; other factors such as reactive oxidative stress, inflammatory response, sympathetic nervous system (SNS), and renin angiotensin aldosterone system (RAAS) activation play an essential role in the pathogenesis of CKD and chronic RF in cCRS in CHF patients. [2,11] Factors that precipitate cCRS and their mechanisms are summarized in **Figure 1**.

Impaired kidney perfusion

In HF, reductions in the diastolic or systolic function of the LV lead to diminished stroke volume, CO, and inadequate filling and arterial pressure, causing decreased renal perfusion. [12] Compromised renal perfusion pressure can result from the combination of low systemic pressures and elevated CVP or PWAP in HF and volume overload patients. [13] Moreover, these patients have underlying atherosclerotic changes brought about by comorbidities such as hypertension and DM. Reduction in renal perfusion can swiftly exacerbate pre-existing renal dysfunction.

CRS-associated renal dysfunction may result from multiple factors. This study investigated the correlation between elevated CVP levels, renal dysfunction, and mortality in patients with heart failure. In addition to orthopnea and increased jugular venous pressure, ascites and peripheral edema, characterized by congestion, were noted. Furthermore, congestion-related symptoms, specifically ascites, might exhibit an association with elevated intravascular pressures and heightened abdominal pressure. [14] It is hypothesized that these elevated pressures could significantly affect renal function in patients with AHF. Additionally, congestion symptoms may be associated with elevated left-sided filling pressure and increased CVP on the right side. In contrast, others propose an alternative theory to the widespread belief that renal impairment is an exclusive consequence of reduced CO. [12,14] Pulmonary hypertension can lead to increased CVP and congestion in certain instances of HF.

Elevated CVP appears to be associated with deteriorating renal function, tubular dysfunction, and proteinuria. Reduced renal perfusion and renal impairment resulting from decreased CO are believed to initiate a neurohormonal cascade that causes water and sodium retention. In contrast, Damman et al. presented findings that contradicted this hypothesis. [15] Their research demonstrated that renal function deteriorated most significantly in the presence of obstruction, particularly in patients with well-preserved left ventricular ejection fraction. [15]

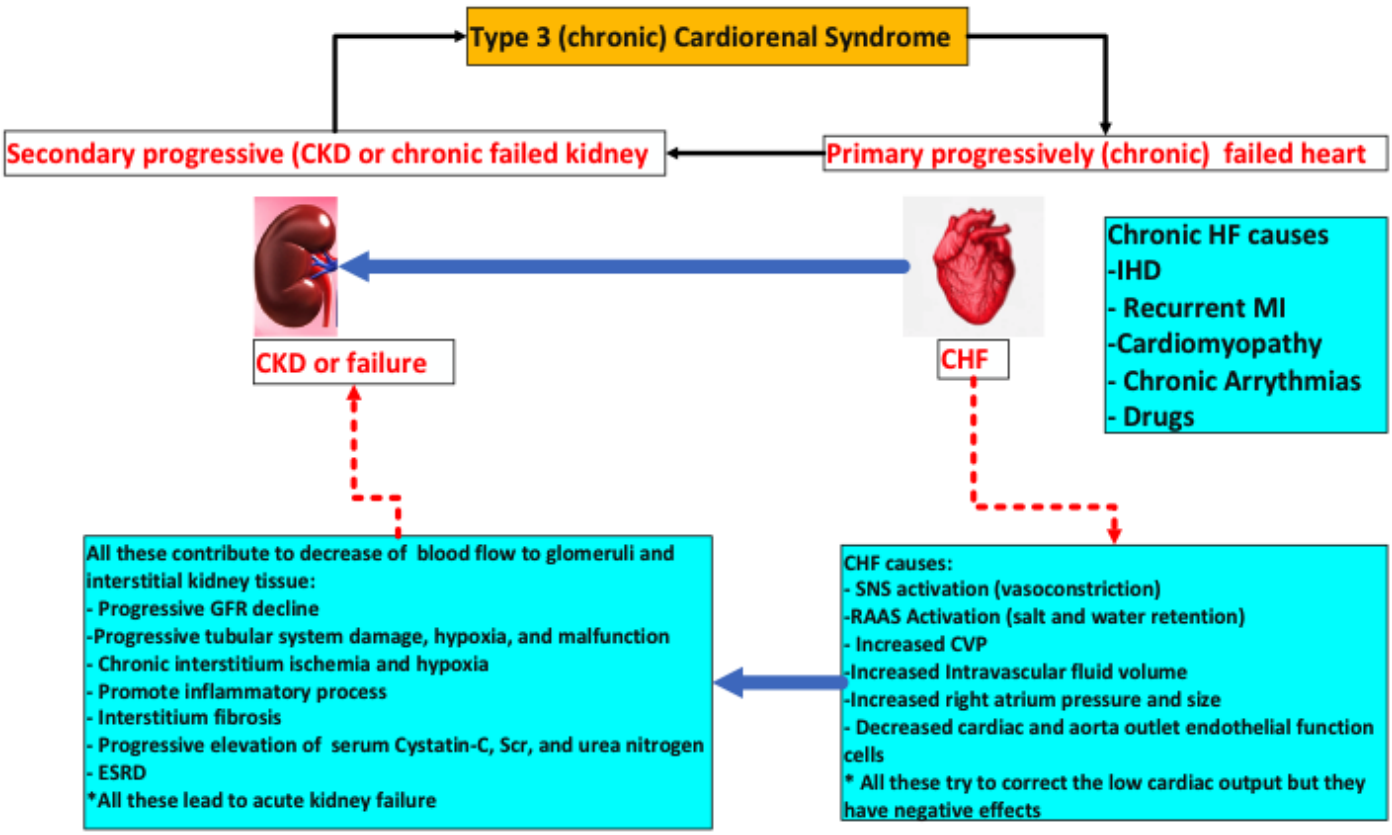

Figure 1: Summary of the mechanisms of chronic cardiorenal syndrome. ESRD: end-stage renal disease; RAAS, renin angiotensin aldosterone system; CHF: congestive heart failure; Scr: serum creatinine; CVP: central venous pressure; CKD: chronic kidney disease; SNS: sympathetic nervous system; MI: myocardial infarction; IHD: ischemic heart disease; GFR: glomerular filtration rate.

The decrease in arterial filling pressures induces the secretion of neurotransmitters, such as endothelin and epinephrine, and the production of vasoconstrictors (renin, angiotensin), and aldosterone. [16] Vasoactive agents induce vasoconstriction in the periphery and kidneys, resulting in a reduction in the GFR and kidney blood flow (BF). Progressive renal hypoxia, cytokine release, inflammation, and, ultimately, loss of structural integrity and function are the consequences of endogenous hormone-neurotransmitter-mediated vasoconstriction. [15,17]

Alterations in the sensitivity and secretion of endogenous vasodilators, including natriuretic peptides and nitric oxide, are indicative of neurohormonal abnormalities. When combined with excessive vasoconstrictive mechanisms, sodium and fluid retention, as well as progressive renal function decline culminating in irreversible kidney injury, manifest as a clinical syndrome known as cCRS. [18]

In severe HF, declining CO and renal arterial tree underfilling activate SNS and RAAS. [19] Since patients with HF produce large quantities of renin in the blood, [20,21] leading to increased angiotensin II production. Angiotensin II mediates its effects primarily through the AT1 receptor, leading to widespread actions. It increases systemic vascular resistance, venous tone, and congestion and stimulates SNS and thirst. Angiotensin II also increased kidney tubular salt reabsorption. Its potent vasoconstriction preferentially constricts the efferent arteriole, increases the glomerular filtration fraction and peritubular capillary oncotic pressure, and improves sodium and fluid return. The RAAS system is crucial to this process in animal models of coronary artery ligation, infarction, and HF. [22,23]

In a dog model, Kishimoto et al. demonstrated renal venous hypertension, independent of systemic arterial blood pressure (BP), decreased renal blood flow, GFR, and renin release, supporting clinical observational data implicating high venous pressure as an alternative and noble cause of worsening GFR in HF, particularly with preserved EF and normal or high BP. This suggests that RAAS activation may occur in HF with venous hypertension and congestion without decreasing the effective circulatory volume. [24,25]

Along with maladaptive pressure and volume overload, persistent SNS and RAAS activation may also contribute to cCRS's CKD development. In an elegant animal model of chronic volume overload, Rafiq et al. surgically induced aortic regurgitation in unilateral nephrectomized rats and examined intrarenal norepinephrine and angiotensin II levels, albuminuria, renal function, podocyte injury, and reactive oxygen species production. [25,26] Renal denervation and angiotensin receptor inhibition prevented progressive kidney damage, as chronic volume overload caused expected structural and functional changes in the heart and increased intrarenal SNS and RAAS activity. The authors argue that SNS and local angiotensin II activation drive kidney NADPH oxidase-dependent reactive oxygen species production, which causes podocyte damage and albuminuria.

Angiotensin II also stimulates the adrenal gland to secrete aldosterone, which increases the distal nephron sodium reabsorption, pressure, and volume overload. Aldosterone seems to accelerate CKD and renal fibrosis in several clinical settings and mechanisms. [27] Increased kidney aldosterone levels cause oxidative stress due to signaling from the paracrine glycoprotein galectin-3, leading to TGF-β and fibronectin upregulation, resulting in renal fibrosis and glomerulosclerosis. In cCRS, Onozato et al. found that elevated aldosterone levels in Dahl salt-sensitive HF mice led to worsened renal function by increasing oxidative stress and TGF-β production. In this study, untreated HF mice showed proteinuria, increased creatinine, glomerulosclerosis, and increased NADPH oxidase, TGF-β, and fibronectin expression. [28] The study found that angiotensin-converting enzyme (ACE) inhibition and aldosterone blockage with eplerenone reduced oxidative stress and inhibited TGF-β more efficiently than ACE inhibition. The combination-controlled creatinine and proteinuria prevented histological kidney damage. However, this model could not distinguish between hypertension and CHF in the development of renal diseases. However, hypertension- and HF-associated kidney damage may involve mutually reinforcing mechanisms.

CKD development in patients with HF may also involve non-hemodynamic causes. Mechanical tension or ischemia may cause cardiac myocytes to produce several inflammatory cytokines and activate the innate immune system. [29] Venous congestion alone stimulates peripheral inflammatory mediator production and release, whereas it may enhance gut endotoxin absorption and inflammatory responses. [30] Patients with severe HF exhibit increased levels of TNF-α, soluble TNF receptors, IL-1β, IL-18, IL-6, and cellular adhesion molecules, indicating a pro-inflammatory state.

Although direct evidence of this cardiorenal relationship is developing, systemic reactions to HF may cause distant kidney injury. In mice with acute myocardial infarction, Lu et al. reported reduced LV function and increased pro-oxidant and pro-inflammatory responses. [31] In animal CRS models, histological analysis has revealed pro-inflammatory molecules such as IL-1b, VCAM-1, TGF, and β in the kidneys. Later, animals that died showed perivascular, periglomerular, and peritubular fibrosis with enhanced collagen synthesis, corresponding to the human phenotype of cCRS. Early alterations include inflammatory cellular infiltrates. Deletion of the pro-inflammatory molecule lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) in knockout mice eliminates these reactions and enhances renal and cardiac function and shape.

Over 30 days after left anterior descending coronary artery closure, rats with renal impairment progressed to severe CKD in a cCRS rat model. [32] Biomarkers of renal injury, neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule 1 (KIM-1) were increased in HF rats, similar to patchy atrophic scarring with prominent CD3+ and CD68+ immune cell clusters and renal tissue interstitial fibrosis. In another rat model of CRS2, induced HF by ligating the left anterior descending coronary artery, and euthanized the animals after 16 weeks of CHF. [33] Animal models of HF showed elevated production of KIM-1, IL-6, and TGF-β. CD68+ immune cell infiltration and substantial interstitial fibrosis with these inflammatory markers were observed. In a rat model of right-sided HF, neurohormonal activation with elevated BNP, angiotensin II, and inflammation was seen. [34] IL-1α, IL-β, IL-2, IL-4, IL-6, IL-10, and TNF-α levels increase, leading to apoptosis in vascular smooth muscle, heart, skeletal muscle, lung, and kidney tubular and glomerular cells. HF rats had higher NGAL mRNA levels than controls in this condition. [6]

Human data corroborate the conclusions of animal studies. In a small autopsy investigation of eight CHF-related renal dysfunction patients, renal tissue exhibited increased interstitial fibrosis, CD68+ immune cells, and oxidative stress indicators (Rac1 expression and protein nitrosylation). [35] Dilated peritubular capillaries are indicators of higher CVP. Other investigations found that elevated CVP or right atrium pressures decreased renal function and independently predicted all-cause mortality in a wide range of CVD patients, including AHF and CHF. [36–38] This connection was more substantial with lower renal perfusion. [36] Animal studies imply that elevated CVP is transmitted to the renal veins, elevating renal interstitial pressure and activating the RAAS and SNS systemically and inside the kidneys.

Investigating cCRS in humans, targeting specific pathophysiological pathways, is useful. Although most of the randomized available clinical studies in CHF concentrate on cardiovascular mortality and adverse cardiac events, with renal outcomes as safety objectives, few studies documented that long-term changes in creatinine or GFR or micro- or macroalbuminuria are indicators for kidney fibrosis or inflammation. [39]

Several CHF trials have studied RAAS blockade using ACEIs and angiotensin II receptor blockers (ARBs). Most studies have focused on the ACEIs enalapril, captopril, and the ARBs valsartan and candesartan. Enalapril caused a more significant net worsening of estimated glomerular filtration rate (eGFR) from baseline to 14 days than placebo in the SOLVD CHF trial. Early renal function decline was linked with higher mortality in the placebo group but not in the enalapril group. [40] Another study of diabetics treated with enalapril showed less proteinuria than those treated with a placebo. [41] In contrast, a second multivariable analysis showed that enalapril did not affect eGFR over time, even though it had a greater rate of early renal function decline than placebo. [42] Enalapril increased creatinine by 10% to 15% in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). [43] As renal function declined following the acute event, Hillege et al. found that captopril maintained GFR relative to placebo in post-MI HF patients. [44] Valsartan decreased GFR (−3.9 vs. placebo) in the Valsartan Heart Failure Trial (Val-HeFT) study. Dipstick proteinuria detection is associated with increased mortality by 28%. [45] The Candesartan in Heart Failure—Added (CHARM-Added) study with candesartan showed a 62% and 76% higher risk of mortality in the microalbuminuria and macroalbuminuria groups, respectively, with insufficient proteinuria prevention with candesartan. [46] Current published research is unclear on whether ACEIs or ARBs prevent cCRS development in these patients.

RAAS inhibitors (ACE inhibitors, ARBs, and MRAs) are cornerstone therapies in cCRS, yet their effects on renal function vary across trials. Some studies show early worsening renal function (WRF; increased Scr), while others demonstrate long-term renal protection. The controversies and the possible explanations are as follows. RAAS inhibitors dilate

efferent arterioles, which decreases intraglomerular pressure, causing an initial GFR drop, mainly due to functional rather than structural damage, and this effect was noticed to be more pronounced in severe HF or volume depletion due to exaggerated hemodynamic effect. RAAS inhibitors reduce angiotensin II/aldosterone-mediated fibrosis, slowing CKD progression.

This hemodynamic effect underscores a critical clinical point: a small, early rise in serum creatinine following RAAS inhibition often reflects a reversible reduction in intraglomerular pressure and is not synonymous with intrinsic kidney injury or a worse long-term prognosis. This phenomenon highlights the limitation of relying solely on serum creatinine changes to define renal injury in this context. [40]

Another factor that may cause the discrepancy between the results of the studies is patient-related factors. These factors include baseline volume status, diuretic doses, baseline CKD stage, and patient phenotype. Furthermore, the studies' endpoint definitions. Some trials define WRF as ↑Cr >0.3 mg/dL, which may not reflect true injury, while others track hard outcomes, such as using dialysis, and including mortality, where RAAS inhibitors are beneficial. Lastly, chronic RAAS inhibition triggers alternative pathways (e.g., ACE2/angiotensin 1-7, endothelin), leading to variable renal effects due to the neurohormonal escape phenomenon, as in dual RAAS blockade (ACEi + ARB) increased Scr/K^+ (ALTITUDE, VA NEPHRON-D trials). **Table 1** summarizes the patients' factors that may have affected the studies' discrepancies.

Direct aldosterone receptor inhibitors improve survival and hospitalization in patients with CHF. Despite decreased renal function in 17% of treated individuals compared to 7% in the placebo group, spironolactone reduced mortality in the RALES study. After 1 year, spironolactone increased creatinine by 0.05 to 0.1 mg/dL, but the placebo did not. The RALES trial was the first of a series of prospective trials investigating the mortality benefits of aldosterone antagonists in heart failure with reduced ejection fraction (HFrEF). [47] In the EPHESUS trial using eplerenone in post-myocardial infarction CHF patients, creatinine increased by 0.06 mg/dL after 1 year and 4.6 mg/dL after 2 years. By contrast, the placebo group increased by 2.7 mg/dL. Eplerenone raised creatinine 0.09 mg/dL at the trial cut-off in EPHESUS. [48,49] Spironolactone therapy decreased surrogate indicators of collagen production (PINP, PICP, PIIINP), suggesting that anti-aldosterone treatment may diminish fibrosis. [50]

A minor anticipated increase in blood creatinine, especially in studies with RAAS inhibitors, does not necessarily indicate cCRS progression. Despite a slight increase in blood creatinine levels, these medications show survival symptoms, exercise capacity, proteinuria, and albuminuria. Serum creatinine, as a marker for GFR, may not be a promising biomarker for disease progression because it is difficult to distinguish true progressive CKD from hemodynamic (and potentially reversible) GFR changes due to RAAS blockade and filtration fraction.

After the publication of the COPERNICUS, CAPRICORN, and CIBIS studies, β-blockers have become the primary therapy for CHF. A meta-analysis of CAPRICORN and COPERNICUS trials found that carvedilol raised transient blood creatinine levels without dialysis in CKD patients ($P < 0.001$). [51] The CIBIS study found a reduced GFR in congested patients. Bisoprolol outperformed placebo in patients with CKD (GFR < 45), [52] although β-blocker medication did not increase serum creatinine. In older individuals, nebivolol did not affect GFR. [53] The evidence on the effects of β-blockers on creatinine in these studies is inconsistent.

Inflammation contributes to the progression of heart damage and the clinical worsening of HF. Inflammation causes kidney damage and degrades renal function. Several researchers have used TNF-α inhibitors to treat HF. Infliximab and etanercept have yielded poor results. These medicines have demonstrated futility and high mortality rates despite a reduction in CRP and IL-6 levels. However, the ATTACH, RENAISSANCE, and (RENEWAL) RECOVER trials did not report renal function. [54,55]

Cardiac resynchronization or left ventricular assist devices ameliorate HF hypoperfusion. One study found that cardiac resynchronization enhanced GFR by 2.7 mL/min in individuals with GFR by 30 to 60 mL/min. [56] It was found that the left ventricular assist device bridging to cardiac transplantation improves renal function. [57] The prevalence of kidney disease is high in congenital heart disease, primarily due to decreased renal perfusion. [58] Observational research on 10 infants with cyanotic congenital heart disease found that palliative heart surgery dramatically reduced urine albumin excretion and tubular damage indicators, including brush-border leucine-aminopeptidase and lysosomal N-acetyl-β-D-glucosaminidase (NAG). As oxygen saturation increased, hematocrit decreased to near-normal levels. [59]

Anemia in cCRS

Anemia in CRS and RCS is a pathological triad in which failed kidney and heart function may cause anemia. [6] Anemia may aggravate HF and renal dysfunction, leading to a vicious

Table 1: Patient factors affect trial discrepancies.

Factor	Effect on RAASi response	Example trials
Baseline volume status	Hypovolemia → ↑Scr (excessive efferent vasodilation)	SOLVD (↑Scr in dehydrated patients)
Baseline CKD	Severe CKD (eGFR <30) → ↑Scr/K^+ risk	ONTARGET (ARB + ACEi ↑Cr in CKD)
Concurrent diuretics	High-dose diuretics + RAASi → prerenal AKI	DOSE Trial (↑Scr with aggressive diuresis)
HF phenotype	HFpEF → less benefit (more volume-sensitive)	TOPCAT (spironolactone ↑Scr in HFpEF)

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; RAASi: renin-angiotensin-aldosterone system inhibitors; Scr: serum creatinine.

loop that negatively impacts morbidity and mortality. [60] In CHF patients, anemia is common and linked to higher death rates. [61] Anemia prevalence ranged from 14% to 70% and increased with the severity of CHF, CKD stage, and age. Treating anemia improves cardiac and renal function and reduces hospitalizations for HF. [62]

The optimized HF registry links anemia to a 30% increase in all-cause mortality and morbidity. [63] The ANCHOR study assessed the influence of CRS and anemia on mortality. A study found that high hemoglobin levels (>17 g/dL) or low hemoglobin levels (<13 g/dL) independently increased the risk of mortality and hospitalization in CRS patients with impaired or intact systolic function. [60] In anemic CHF patients, reduced oxygen delivery to tissues leads to hemodynamic and non-hemodynamic responses, which contribute to higher mortality. Anemia responses, such as increased left ventricle workload, RAAS, and SNS activation, sodium and water retention, reduced GFR, and renal BF, lead to HF deterioration and adverse outcomes. [64]

Multiple contributing factors have been identified in the development of cCRS. Advanced age, low body mass index, diabetes, lower LVEF, omission of RAAS inhibitors, and use of intravenous loop diuretics independently correlated with anemia severity. [1] Anemia in patients with HF can be caused by folate and vitamin B12 deficiencies, iron deficiency, blood loss from aspirin and anticoagulants, increased plasma volume and hemodilution, inflammation, renal insufficiency, poor nutrition, and intestinal malabsorption due to edema.

CKD anemia has several causes, such as insufficient EPO synthesis, restricted iron availability, elevated hepcidin levels, decreased EPO receptors, and the use of ARBs and ACE inhibitors, which are known factors of CKD-induced anemia. [64,65] In HF patients, chronic inflammation leads to elevated EPO levels and inhibits erythropoiesis in the bone marrow. [65,66] Additionally, prolonged inflammation increases hepcidin production, limiting iron absorption and bioavailability for hemoglobin formation. [67]

There are no evidence-based guidelines for the treatment of patients with cCRS. However, for these patients, it is necessary to manage anemia, renal insufficiency, and heart failure at the same time. KDIGO's international conference found that erythropoiesis-stimulating agents (ESAs) could neither prevent nor cure HF in CKD patients. [68,69] In contrast, in many trials, intravenous iron therapy for CHF patients with iron deficiency, including anemia, eGFR, increased functional capacity, and symptoms. [70] Intravenous iron and ESAs are the primary treatment for anemia in CKD patients. [71] ESAs are not advised for patients with HF anemia because of the unfavorable results of anemia overcorrection, leaving intravenous iron as the primary treatment. Intravenous iron treatment improves iron parameters, NYHA functional status, and life quality in HF anemic or non-anemic patients or CKD. [70,72,73] ESA treatment may reduce LV thickness and mass and improve renal parameters. [74] Darbepoetin alfa treatment for anemia did not improve the outcomes in mild or severe anemia and systolic HF and may even increase thromboembolic rates. [74] The American College of Cardiology Foundation, Heart Failure Society of America, and European Society of Cardiology advise against using ESAs for anemia management in HF patients. [75] ESA trials in anemic and CKD patients show a greater risk of cardiovascular events with higher Hb values. [76,77] ESA medication is administered to a limited percentage of cCRS patients, following KDIGO guidelines for treating anemia in CKD patients. [78] Furthermore, intravenous iron in cCRS is beneficial for patients with HF anemias.

Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs; vadadustat, daprodustat, and desidustat) are a new family of medicines used for anemia therapy in patients with CKD and cCRS. These inhibitors increase physiological EPO synthesis by blocking prolyl hydroxylase enzymes, which degrade hypoxia-inducible factors (HIF) and trigger EPO expression in hepatic cells and kidneys. HIFs affect EPO and initiate a coordinated response that increases iron absorption and decreases hepcidin levels, resulting in improved iron mobilization and utilization. Clinical experiments using HIF-PHIs revealed reduced ferritin and hepcidin levels, increased erythropoiesis, and raised overall iron binding capacity. [79] Recent studies on oral HIF-PHIs have shown results in maintaining or improving anemia in CKD patients. [80] HIFs may have adverse impacts on many organs, cellular functioning, angiogenesis, tumor development, and glucose metabolism. [80] HIFs' long-term use requires further research in future trials to establish their importance.

PRESENTATION AND DIAGNOSTIC MARKERS OF CCRS

In the early stage of cCRS, symptoms of heart failure predominate. Patients usually have a history of breathlessness on exertion, which gradually increases. Cough and whitish sputum with some blood tinges may present with symptoms. As HF progresses, breathlessness with minimal exertion, orthopnea, and lower extremity edema begin to appear. If CO cannot maintain kidney perfusion, the amount of urine will decrease, which leads to the accumulation of BUN and uremia symptoms. Once combined cardiac and kidney failure has occurred, the patient's clinical presentation features get worse. Clinical examination at this stage may reveal features of pleural effusion, ascites, massive edema, third heart sounds, tachycardia, hypotension, and cyanosis. Furthermore, the features of malnutrition and malabsorption may be noted at this stage.

Clinical HF investigations have primarily used creatinine (or eGFR), urine protein, and albumin excretion to determine renal impairment. Elevated creatinine or reduced eGFR and increased urine albumin excretion are strong and independent prognostic factors in CHF. [46] Both maintaining and lowering LVEF increase the risk of mortality, cardiovascular death, and hospitalization. In CKD, eGFR and albuminuria predict long-term renal outcomes [81] but not in CHF. [82] Recent studies have examined new renal biomarkers such as CysC, NGAL, KIM-1, and NAG in CHF patients. [83–86] Even in patients with normal renal function, the levels of these biomarkers are somewhat higher in patients with CHF than in the controls. Some of these indicators may predict unfavorable cardiovascular events, but no study has examined long-term renal function changes.

Plasma CysC, a more sensitive measure of decreased GFR than creatinine, predicts mortality, heart transplantation, and HF hospitalizations independently. [84] CysC is also linked with NT-pro-BNP and LV dysfunction. [84] Urinary CysC studies on CHF are sparse.

A recent systematic study looked at NGAL in several cardiovascular disorders, including CHF. [83] Animal and human tissue investigations have shown that failing myocardia, myocarditis, and atherosclerotic plaques express NGAL. Also described above are NGAL data from a cCRS rat model. [32] In clinical trials, blood and urine NGAL levels correlate with creatinine or eGFR and various clinical and biochemical indicators of HF severity (e.g., natriuretic peptides). [83] Additionally, systemic NGAL levels promote HF hospitalization and death. [83,85,86]

Comparable results were obtained for NAG and KIM-1. KIM-1 levels in urine were higher in symptomatic HF patients than in controls, but not in NAG or NGAL.KIM-1 and NAG levels indicated HF severity and predicted all-cause death and HF hospitalization on survival curve analysis. Death or HF hospitalization in 2130 GISSI-HF trial participants was associated with a decreased eGFR and increased urine excretion of albumin, NAG, KIM-1, and NGAL. [85] Urinary NAG was more associated with multivariable regression.

In future large randomized controlled trials of HF, new renal biomarkers in CHF might improve our knowledge of cCRS pathogenesis. The minerAlocorticoid Receptor Antagonist Tolerability Study (ARTS) will explore how the non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 affects cardiac and renal function and damage biomarkers such as KIM-1, NGAL, and CysC. [87] The results of this study can guide future cCRS studies.

CCRS THERAPY

The main therapeutic challenges of cCRS are preventing new-onset renal dysfunction in CHF or adequately counteracting renal dysfunction once it develops by promoting cardiac and renal damage attenuation or regression. In chronic CRS, the pathogenetic mechanism by which cardiac dysfunction causes new-onset renal dysfunction or worsens CKD remains unclear. Indeed, renal filtration deteriorates in individuals without hemodynamic destabilization. Thus, the WRF mechanisms may vary between AHF and CHF. Renal venous congestion, decreased intrarenal perfusion, and filtration gradients are common in patients with CHF. Microvascular and macrovascular renal diseases (chronic ischemic nephropathy) may also impair renal function. In this scenario, CHF pharmacotherapies that decrease renal function when improperly administered play a significant pathogenic role. The long-term causes of chronic CRS include diuresis-associated hypovolemia, drug-induced hypotension, and the use of early RAAS inhibitors. In addition, resistance to diuretics may lead to overzealous therapeutic approaches with excessive diuretic dosing, which can cause harmful phenomena such as exaggerated stimulation of the tubule-glomerular feedback mechanism and activation of the RAAS, which can cause reactive vasoconstriction of the renal afferent arterioles and GFR decline, which increases Scr.

Diuretic resistance has also been disputed and has not been described. CHF patients need greater loop diuretic dosages to produce equivalent sodium excretion, and their "maximal" response is too little. [88] In CHF with CKD, extremely lengthy oral diuretic medication (months or years previously) weakens this response to loop diuretics, causing what is known as the braking phenomenon. Long-term diuretic treatment reduced natriuresis after successive doses. The presence of signs and symptoms of refractory fluid retention, poor urine output (<1000 mL/day), and the maximum tolerated oral dose of a loop diuretic (e.g., 250 mg of furosemide per day) suggests diuretic resistance. This should encourage doctors to modify oral diuretic regimens to overcome apparent refractoriness. The modification strategies of diuretics use combining thiazide diuretics with loop diuretics (to block increased distal sodium reabsorption), preferably administering loop diuretics intravenously (at the same or higher doses than orally), using continuous diuretic infusions to avoid post-diuretic salt retention; [39] and aldosterone receptor antagonists as an adjunctive treatment to resolve congestion and to decrease the diuretic dosages. [16]

Combining intravenous loop diuretics with RAAS inhibitors (ACE inhibitors or ARBs) is common in patients with CHF. High doses of intravenous loop diuretics in CHF patients with well-controlled symptoms should be avoided because of the risk of neurohormonal activation, hypokalemia, hypotension, and renal impairment. When used with an intravenous diuretic, an ACE inhibitor, or an ARB at the total dosage, the risk of intravenous loop diuretic WRF is increased. The intravenous diuretic and angiotensin II blockade affect the glomerular efferent arteriole constrictive tone, causing an exaggerated drop in the effective intraglomerular BP and volume. Drugs alter the tubular function, and tubule-glomerular feedback lowers intraglomerular pressure over time. [89] In CHF, combination treatment with Ag II blockades and loop diuretics at high doses may reduce congestion. However, it may diminish the renal BF and GFR, causing WRF.

Renal insufficiency in chronic CRS can be caused by venous congestion, decreased kidney perfusion due to CO or hypotension (decreased preload), or neurohormonal cascade activation, resulting in vasomotor nephropathy with marked and persistent renal reactive vasoconstriction. Hence, iatrogenic factors may cause kidney impairment as much as congestive nephropathy in chronic CRS. [90,91] Higher dosages of loop diuretics and RAAS inhibitors may identify people with significant hemodynamic impairment and susceptibility to renal dysfunction, not WRF. [7,92] ACE inhibitors affect intrarenal hemodynamics and lower filtration fractions without harming the kidneys. This protects against hypertension, chronic glomerulonephritis, diabetic nephropathy, and albuminuria. [7] However, ACE inhibitor-related glomerular filtration fraction reduction loses renal protective implications when combined with reduced renal BF due to a pathological decline in the kidney's perfusion gradient, which typically occurs in congestive nephropathy in congestive CHF. In CHF with markedly reduced effective intravascular volume because of overtreatment for hemodynamic overload following high-dose diuretic, adding any other drugs that induce a drop in filtration fraction is harmful. [93–95]

Combined cardiac and kidney impairment in chronic cardiac failure therapies

The treatment of renal impairment-complicated HF currently involves the use of numerous supplementary medications with ambiguous or questionable efficacy. Concerning the number of novel drugs suggested for the management of heart failure with renal impairment, a subset has been approved for routine use (e.g., nesiritide) in ADHF treatment in the US. Moreover, as an illustration, although bosentan and other ERAs have

stimulated investigation regarding primary or secondary pulmonary hypertension, their efficacy in managing chronic CRS or left ventricular failure has not been validated. [96]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors offer benefits beyond glycemic control, including BP reduction, anti-inflammatory effects, heart failure improvement, and prevention of CKD progression. SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin) reduce cardiovascular mortality, HF hospitalizations, and CKD progression in cCRS. EMPEROR-Reduced and DAPA-HF reported 30% lower HF hospitalizations in HFrEF patients, regardless of CKD. [97,98] A Similar effect was reported in heart failure preserved ejection fraction (HFpEF) patients. [99] SGLT2 inhibitors cause natriuresis and osmotic diuresis that reduce volume overload without activating RAAS and SNS. [100] Moreover, they improve renal oxygenation by lowering intraglomerular pressure via Tubuloglomerular feedback inhibition. [101] Additionally, SGLT2 inhibitors improve ketogenesis, providing an alternative cardiac energy source. [102] Interestingly, SGLT2 inhibitors reduce inflammation and prevent fibrosis of the heart [103] and kidney by decreasing IL-6, TGF-β, and albuminuria. [104] There is a significant amount of evidence that supports SGLT2 inhibitors as therapeutic agents for cCRS due to their cardiorenal protection, safety in CKD, and pleiotropic benefits beyond glycemia. Besides all these measures, lifestyle modifications are an essential method to prevent and treat cCRS. **Table 2** summarizes the therapeutic approaches in cCRS.

Nesiritide

The ventricular myocardium secretes nesiritide. It acts like a natural peptide, relaxing venous and arterial smooth muscle cells in response to acute ventricular volume increases and opposing the vasoconstriction, salt retention, and antidiuretic effects of activated RAAS. Cyclic guanosine monophosphate activation by nesiritide relaxes the vascular smooth muscle. The US has long used nesiritide to treat ADHF, but Europe, the Middle East, and Africa (EMEA/EMA) have not approved it. As it is only accessible in intravenous form, it can only treat AHF. This drug's renal safety profile supports its usage in chronic CRS with symptom aggravation. [105] Nesiritide effects mimic some nitroglycerin hemodynamic effects, including a rapid and effective ventricular preload drop because of the blood pooling effect in large veins, which is helpful in acute or subacute lung congestion. [106] The other drawback of nesiritide is its cost. The nesiritide dosage was 40 times that of nitroglycerin. This made some US institutions advocate administering nitroglycerin and intravenous diuretics (with >2× the average daily diuretic dosage) before employing nesiritide due to the substantial cost load. [107]

Antidiuretic hormone antagonists

HF treatment targets hypervolemic hyponatremia, which leads to vasopressin receptor antagonists, conivaptan, tolvaptan, and lixivaptan. The EVEREST Clinical Status Trials examined tolvaptan's potential in HF therapy. [108,109] These studies examined the impacts of tolvaptan on cardiovascular

Table 2: Chronic cardiorenal syndrome treatment chart.

Treatment strategy	Medications/interventions	Notes/considerations
Neurohormonal blockade	ACE inhibitors/ARBs ARNI (e.g., sacubitril/valsartan) Beta-blockers (e.g., carvedilol, bisoprolol)	Improves cardiac function Monitor for worsening renal function, hyperkalemia
Volume management	Loop diuretics (e.g., furosemide, torsemide) Thiazides Ultrafiltration in refractory cases	Monitor electrolytes and kidney function. Risk of diuretic resistance in advanced CKD
RAAS modulation	Mineralocorticoid receptor antagonists (e.g., spironolactone, eplerenone)	Careful use in CKD due to hyperkalemia risk
SGLT2 inhibitors	Dapagliflozin, Empagliflozin	Beneficial for both heart failure and CKD Reduces hospitalization and slows CKD progression
Anemia management	ESA (Erythropoiesis-Stimulating Agents) Iron supplementation (oral or IV)	Target Hb ~10–11.5 g/dL Avoid overcorrection
Control of hypertension	ACEi/ARB, beta-blockers, CCBs	Individualize BP goals (e.g., <130/80 mmHg)
Management of hyperkalemia	Patiromer, sodium zirconium cyclosilicate Low-potassium diet	Facilitates continuation of RAAS inhibitors
Management of metabolic acidosis	Oral bicarbonate supplementation	Maintain serum bicarbonate ≥ 22 mmol/L
Treatment of comorbidities	Diabetes: use metformin (if eGFR >30), GLP-1 RA	Avoid nephrotoxic drugs (e.g., NSAIDs)
Device therapy	CRT, ICD in eligible heart failure patients	Evaluate ejection fraction, QRS duration
Renal replacement therapy (RRT)	Hemodialysis or peritoneal dialysis	Consider if ESRD or refractory volume overload

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; BP: blood pressure; CCB: calcium channel blocker; CRT: cardiac resynchronization therapy; CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; eGFR: estimated glomerular filtration rate (mL/min/1.73 m^2); ESRD: end-stage renal disease; GLP-1 RA: glucagon-like peptide-1 receptor agonist; Hb: hemoglobin; ICD: implantable cardioverter-defibrillator; IV: intravenous; NSAIDs: non-steroidal anti-inflammatory drugs; RAAS: renin-angiotensin-aldosterone system; RRT: renal replacement therapy; SGLT2i: sodium-glucose cotransporter-2 inhibitor.

outcomes in DHF, including weight loss, dyspnea, renal function, long-term death risk, and HF rehospitalization. In hospitalized ADHF patients, adding tolvaptan to conventional medication increased weight reduction and dyspnea improvement without a significant effect on renal function. [108] Additionally, tolvaptan medication started during ADHF hospitalization did not reduce HF death or rehospitalization rates. [109] Tolvaptan use is approved in SIADH, euvolemic, and hypervolemic hyponatremia in HF and cirrhosis patients in the US, while in Europe, it is authorized for adult SIADH-related hyponatremia treatment. [110]

Endothelin receptor antagonists

During the late 1990s, endothelin receptor antagonists (non-selective ERAs) were suggested for HF therapy. The ENABLE study investigated bosentan use in patients with severe HF. The study revealed disappointing results, dampening early excitement for ERAs' therapeutic promise in HF. [111] The study noted increased fluid retention that exacerbated HF and hospitalization stays. However, new research with lower bosentan dosages or more intensive concurrent diuretic treatment is needed to prove or disprove the long-term effects. [96,112]

Serelaxin

Serelaxin, a recombinant human relaxin-2, has adaptive cardiovascular effects during pregnancy, primarily via a nitric oxide-mediated vasodilator effect, which may benefit patients with HF. However, the EMEA and FDA have rejected serelaxin for HF patients. [112] Since then, no large-scale studies have assessed the use of serelaxin in HF or chronic CRS therapy.

Ultrafiltration for cCRS

The primary justification for using ultrafiltration only in chronic CRS is to promptly address fluid excess that persists despite conventional treatment methods, such as administering large intravenous diuretic doses plus or minus inotropes. [92,113] According to the current treatment guidelines from the American Heart Association/American College of Cardiology and the European Society of Cardiology, using ultrafiltration is a reasonable choice for patients with overloading when medical therapy has been proven to be ineffective in improving the change in the fluid status in class IIa cardiac decompensation patients. [114,115] Interestingly, isolated ultrafiltration, unlike diuretics, does not stimulate any macula densa additional neurohormonal response because the removal of fluids occurs via a circuit that bypasses the kidneys and renal chemoreceptor of the macula densa.

Researchers have investigated the use of ultrafiltration as an alternative to diuretics owing to the occurrence of adverse effects and resistance. Isolated ultrafiltration is a convection-dependent method for removing plasma fluid that does not involve infiltration without any further fluid replacement that alters the electrolyte concentration. [92,113,116] The fluid volume extracted using the IUF may be precisely anticipated because it can be predetermined by modifying the instrument settings. In continuous hemofiltration, the replacement rate is typically 2-3 L/hour, whereas in high-volume hemofiltration/hemodiafiltration, the replacement rate can be as high as 6-8 L/hour. Clearly, the depurative efficiency of hemofiltration is much higher than that of isolated ultrafiltration. [116]

Ultrafiltration and intravenous diuretics comparison in cCRS therapy

Loop diuretics are used to treat clinical or hemodynamic congestion in patients with HF and any CRS type. However, it is essential to note that their effectiveness and safety have not been evaluated via randomized controlled studies. The appropriate diuretic dosage remains a subject of debate. There are limited RCTs in the literature specifically intended to evaluate the effectiveness of isolated ultrafiltration plus intravenous diuretics for exacerbated congestive HF or diuretic-resistant cardiac decompensation. Furthermore, this study included a limited patient population. The presence of significant methodological variations, such as varying time limits for the selected endpoints when comparing various research studies, prevents the subsequent meta-analysis of data from some studies. [66] Nevertheless, it is feasible to perform a qualitative analysis, even without the necessary conditions for methodological uniformity that are required for conducting a quantitative analysis, such as a meta-analysis. The two most significant trials, UNLOAD [88, 117] and CARRESS-HF [118], conducted a comparison between intravenous diuretics and ultrafiltration in patients with congestive HF.

The UNLOAD trial compared the early use of isolated ultrafiltration with conventional diuretic therapy in 200 patients with ADHF. The primary outcome measures were shortness of breath and weight loss 48 hours after therapy. Additionally, the trial evaluated secondary outcome measures, such as total fluid loss after 48 hours, HF-related rehospitalizations, functional capacity, and unscheduled visits within 90 days. The results showed that after 48 hours, the weight reduction (P = 0.001) and total fluid loss (P = 0.001) were lower in the diuretic group than in the isolated ultrafiltration group. However, dyspnea levels were equal in both groups. After 90 days, the isolated ultrafiltration group experienced a decrease in unscheduled attendance to the emergency department (P = 0.009), a lower rate of patients being hospitalized for HF (P = 0.037), and a shorter hospitalization period for rehospitalization (P = 0.022). [88,117,119] There was no considerable difference in Scr increase after 48 hours when comparing patients receiving isolated ultrafiltration treatment with intravenous diuretic-medicated patients.

The CARRESS-HF trial included 188 patients with ADHF and deteriorated kidney parameters. [118] The patients received either stepwise diuretic treatment (94 patients) or isolated ultrafiltration (94 patients). The primary outcome measure was the combined change in baseline Scr and body weight, evaluated 96 hours after starting the therapies. The patients were monitored for 60 days. After 96 hours, the average change in the Scr was much higher following isolated ultrafiltration therapy (−3.5 ± 46.9 μmol/L after diuretic/ (20.3 ± 61.9 μmol/L) after isolated ultrafiltration [P = 0.003]). Simultaneously, a more considerable proportion of patients who had isolated ultrafiltration had at least one severe adverse event than those who received diuretics (P = 0.03). There was no notable difference in weight reduction 96 hours after the two interventions (P = 0.58).

Scr increased significantly after 96 hours in patients with ADHF and CRS, who had isolated ultrafiltration, more than after diuretics. It would be interesting to identify the primary factors that might explain the discrepancies between the UNLOAD [88] and CARRESS-HF [118] trials. The initial results were sufficient

to suggest that the CARRESS-HF patients had worsened renal parameters at the beginning compared to the participants in the UNLOAD study. Specifically, the initial Scr was 1.71 to 2.65 mg/dL and 1.57 to 2.37 mg/dL for the intravenous loop diuretics and isolated ultrafiltration groups, respectively. By comparison, the baseline Scr was lower in UNLOAD patients, with an average of 1.5 ± 0.5 mg/dL for the intravenous loop diuretics and isolated ultrafiltration groups. [88]

In the CARRESS-HF trial, the BUN values ranged between 39 to 64 mg/dL in the intravenous loop diuretics and 39.5 to 66 mg/dL in the isolated ultrafiltration group. In comparison, the BUN baseline for UNLOAD patients was 33 ± 20 mg/dL in the intravenous diuretic group and 32 ± 16 mg/dL in the isolated ultrafiltration arms. Based on these findings, it is probable that cardiorenal syndrome (CRS) was present in most patients with CARRESS-HF at the beginning of the study. However, UNLOAD patients did not have comparable kidney problems when they entered the study. While chronic kidney insufficiency at the beginning may not prevent ultrafiltration itself, it may increase the likelihood of adverse renal outcomes due to the relatively quick removal of fluid obtained by isolated ultrafiltration. [120] When there is severe kidney dysfunction, it is generally advised to avoid isolated ultrafiltration and instead employ alternative renal replacement procedures that are more effective in removing waste products from the blood, such as continuous hemofiltration or high-volume hemofiltration/hemodiafiltration. [120] In the CARRESS-HF study, the isolated ultrafiltration group showed a rise in Scr of +0.23 ± 0.7 mg/dL after 96 hours, while the diuretics group had a decrease in Scr reduction of −0.04 ± 0.53 mg/dL (P = 0.003); however, the Scr increase did not meet the criteria specified for WRF, which requires an increase of more than 0.3 mg/dL from the baseline. The isolated ultrafiltration findings from the CARRESS-HF study, which may seem disappointing, require re-evaluation. It is important to note that the recruited patients, who all had significant underlying renal failure, should have received an alternative type of renal replacement therapy (RRT). On the other hand, intermittent ultrafiltration should be considered a fundamental treatment strategy in instances of ADHF with mild kidney impairment, mainly when there is evidence of diuretic failure or resistance. [121]

A final consideration in managing cCRS, especially during acute decompensations or in patients on advanced support, is the inherent limitation of serum creatinine. In states of rapidly changing hemodynamics, serum creatinine becomes an even less reliable metric due to fluid shifts, altered volume of distribution, and fluctuating CO, complicating the assessment of true renal injury. [122]

In summary, the first-line for cCRS includes SGLT2 inhibitors that act as cardio-renal protectors plus RAAS inhibitors if the patient has HFrEF. Diuretics are necessary for congestion, but minimize the dose to avoid resistance/toxicity. Ultrafiltration is a last-line option for diuretic-resistant congestion; however, it should be avoided in patients with severe baseline CKD, where continuous renal replacement therapy (CRRT) may be more appropriate. Lastly, for anemia management, intravenous iron is preferred over ESAs due to ESAs increasing the thromboembolic risk more than iron therapy. **Table 3** compares the available therapies for cCRS.

Table 3: A comparison of the chronic cardiorenal syndrome therapeutic options.

Therapeutic strategy	Key role and mechanism	Clinical considerations and cautions
SGLT2 inhibitors (e.g., Empagliflozin, Dapagliflozin)	First-line cardio-renal protector. Reduces HF hospitalizations and slows CKD progression via osmotic diuresis, improved renal oxygenation, and anti-inflammatory effects.	• Benefits both HFrEF and HFpEF. • Safe across CKD stages (eGFR down to 20). • Start early upon diagnosis.
RAAS inhibitors (ACEi, ARB, ARNI)	Cornerstone for HFrEF. Improves survival and cardiac function by blocking maladaptive neurohormonal activation.	• Monitor for an initial rise in creatinine (often hemodynamic, not injury) and hyperkalemia. • Use with caution with high-dose diuretics to avoid pre-renal AKI.
Diuretics (loop ± thiazide)	Symptom control for congestion. Essential for managing fluid overload and relieving symptoms.	• Use the lowest effective dose to avoid diuretic resistance, electrolyte imbalances, and worsening renal function. • IV administration may be needed for resistance.
Mineralocorticoid receptor antagonists (MRAs) (e.g., Spironolactone, Eplerenone)	Mortality benefit in HFrEF. Counteracts aldosterone-mediated fibrosis and sodium retention.	• High risk of hyperkalemia, especially in advanced CKD. • Monitor potassium and renal function closely.
Intravenous iron (for Iron Deficiency)	Improves functional status and symptoms. Corrects anemia and iron deficiency, improving quality of life and exercise capacity.	• Preferred over ESAs (which increase thromboembolic risk). • Effective with or without anemia.
Ultrafiltration (UF)	Rescue therapy for refractory congestion. Mechanically removes fluid when diuretics fail.	• Not a first-line treatment for congestion. • Avoid in patients with significant baseline CKD; may worsen renal outcomes.

ACEi: angiotensin-converting enzyme inhibitor; AKI: acute kidney injury; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESA: erythropoiesis-stimulating agent; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; IV: intravenous; RAAS: renin-angiotensin-aldosterone system; SGLT2i: sodium-glucose cotransporter-2 inhibitor.

CCRS PREVENTION

The main act for the prevention of chronic CRS is the prevention and proper active treatment of CHF. The usual strategies for CHF prevention are diet modification, lifestyle modification, smoking cessation, and reasonable control of DM and hypertension. Other measures, such as prophylactic aspirin use, are questionable. The standard treatment for CHF, such as fluid restriction, diuretics, beta-blockers, ARB, ACEi, and SGLT2 inhibitors, is indicated for the improvement and prevention of HF and CKD progression.

CONCLUSIONS

cCRS (CRS Type 2) is a multifaceted interaction of cardiac and renal impairment influenced by neurohormonal stimulation, persistent inflammation, and venous congestion, resulting in progressive organ fibrosis. Effective management of cCRS necessitates a meticulous equilibrium; foundational therapies such as RAAS inhibitors and diuretics are crucial yet pose a risk of iatrogenic renal impairment if not precisely dosed.

SGLT2 inhibitors have revolutionized the therapy paradigm by offering substantial cardiorenal protection and should be commenced promptly. In cases of refractory congestion, intravenous diuretic approaches and selective ultrafiltration are essential, but intravenous iron is the preferred therapy for concomitant anemia, as opposed to more hazardous erythropoiesis-stimulating agents.

Future endeavors should concentrate on identifying precise biomarkers for early diagnosis and formulating medicines that directly address the fundamental inflammatory and fibrotic pathways to enhance patient outcomes.

Key takeaways for the clinician

Pathophysiology is complex: cCRS goes beyond decreased blood flow. Venous congestion, neurohormonal activation, inflammation, and fibrosis all accelerate heart and kidney damage.

Foundational: SGLT2 inhibitors are the first-line treatment for cCRS in HFrEF and HFpEF, delivering cardiorenal benefits regardless of diabetes status.

Carefully manage RAASi with diuretics: Although life-saving, RAAS inhibitors can raise creatinine. This differs from renal damage. High-dose diuretics, especially with RAASi, can cause WRF; use the lowest effective dose.

Ultrafiltration is not a first-line congestion treatment: Only diuretic-resistant patients without significant renal impairment can use it. Using it in advanced CKD can worsen outcomes.

IV iron therapy: Improves symptoms and function in CRS patients with iron deficiency or anemia**.**

Erythropoiesis-stimulating agents: Enhance thrombotic risk and should be avoided.

AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by conducting literature searches, drafting, revising, or critically reviewing the article. They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Expansion of Medical and Clinical Trial Terms

Abbreviation	Expansion
EU	European Union
RIFLE	Risk, Injury, Failure, Loss, End-stage kidney disease
RF	Renal Failure
PWAP	Percutaneous Waltman (or Wire-Assisted) Perfusion
DM	Diabetes Mellitus
KDIGO	Kidney Disease: Improving Global Outcomes
BUN	Blood Urea Nitrogen
CysC	Cystatin C
NGAL	Neutrophil Gelatinase-Associated Lipocalin
KIM-1	Kidney Injury Molecule-1
NAG	N-Acetyl-β-D-Glucosaminidase
TGF-β	Transforming Growth Factor-beta
TNF	Tumor Necrosis Factor
TNF-α	Tumor Necrosis Factor-alpha
IL-1β	Interleukin-1 beta
IL-1α	Interleukin-1 alpha
IL-18	Interleukin-18
IL-6	Interleukin-6
IL-2	Interleukin-2
IL-4	Interleukin-4
IL-10	Interleukin-10
VCAM-1	Vascular Cell Adhesion Molecule-1
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
CD3+	Cluster of Differentiation 3 positive (T-cells)
CD68+	Cluster of Differentiation 68 positive (Macrophages)
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
NT-pro-BNP	N-terminal pro-B-type Natriuretic Peptide
PINP	Procollagen type I N-terminal Propeptide
PICP	Procollagen type I C-terminal Propeptide
PIIINP	Procollagen type III N-terminal Propeptide
SOLVD CHF	Studies Of Left Ventricular Dysfunction (CHF arm)

Abbreviation	Expansion
COPERNICUS	CarvedilOl ProspEctive RaNdomIzed CUmulative Survival
CAPRICORN	CArvedilol Post-infaRct survival COntRol in LV dysfunctioN
CIBIS	Cardiac Insufficiency Bisoprolol Study
GISSI-HF	Gruppo Italiano Studio Sopravvivenza Insufficienza Cardiaca
DHF	Diastolic Heart Failure (now HFpEF)
RALES	Randomized Aldactone Evaluation Study
EPHESUS	Eplerenone Post-AMI Heart Failure Efficacy Survival Study
UNLOAD	Ultrafiltration vs Intravenous Diuretics for ADHF
CARRESS-HF	Cardiorenal Rescue Study in Acute Decompensated HF
CRS2	Chronic Cardio-Renal Syndrome (Type 2)
ALTITUDE	Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints
VA NEPHRON-D	VA Nephropathy in Diabetes study
ATTACH	Anti-TNF Therapy Against Congestive Heart failure
RENAISSANCE	Randomized Etanercept North American Strategy to Study Antagonism of Cytokines
RENEWAL	Research into Etanercept Cytokine Antagonism in Ventricular Dysfunction
RECOVER	Research into Etanercept Cytokine Antagonism in Ventricular Dysfunction
ANCHOR	Efficacy and safety of vaptans in hyponatremia in HF patients
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
ENABLE	Endothelin Antagonist Bosentan for Lowering Cardiac Events in HF
FDA	Food and Drug Administration (USA)
EMEA/EMA	European Medicines Agency (EMEA historical, EMA current)

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