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Cardiorenal Relationship: Current Clinical Issues and Management Strategies for Patients with Chronic Heart Failure

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Abstract This scientific article analyzes the mechanisms of development, clinical manifestations, and major therapeutic challenges of cardiorenal syndrome (CRS) in patients with chronic heart failure (CHF). Cardiorenal syndrome is characterized by a bidirectional pathophysiological interaction between cardiac and renal dysfunction and significantly increases morbidity and mortality in patients with CHF. The article discusses the mechanisms of CRS associated with hemodynamic disturbances—including renal venous hypertension, intrarenal hemodynamic alterations, and tubular sodium avidity—activation of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system, endothelial–glycocalyx dysfunction, inflammation, and oxidative stress based on current scientific evidence [1–6]. The cyclic guanosine monophosphate/natriuretic peptide (cGMP/NP) signaling axis and its cardioprotective and renoprotective roles are examined. All five CRS subtypes are delineated with their clinical implications. Important clinical nuances—including the worsening renal function (WRF) paradox and the primacy of decongestion—are addressed. In addition, clinical challenges such as diuretic resistance, fluid imbalance, and deterioration of renal function are reviewed. The study analyzes modern diagnostic approaches, biomarkers (creatinine, glomerular filtration rate, NT-proBNP), novel biomarkers (cystatin C, NGAL, KIM-1, albuminuria) and congestion-assessment modalities (lung ultrasound, IVC ultrasound, bioimpedance, CardioMEMS), and comprehensive treatment strategies, including individualized diuretic therapy, DOSE trial principles, sequential nephron blockade, ADVOR acetazolamide protocol, urinary sodium-guided escalation, RAAS blockers, and the effectiveness of a multidisciplinary approach. SGLT2 inhibitors (DAPA-HF, EMPEROR-Reduced, DELIVER, DAPA-CKD, EMPA-KIDNEY), finerenone, sacubitril/valsartan, and novel potassium binders enabling RAASi continuation are also reviewed. The potential of data-driven risk stratification, informatics pipelines, and computational hemodynamic modeling to modernize CRS management is discussed.

Keywords Cardiorenal syndrome, Chronic heart failure, Renal failure, Hemodynamic disturbances, Renal venous hypertension, Tubular sodium avidity, Diuretic resistance, Renin–angiotensin–aldosterone system, Biomarkers, Comprehensive treatment, SGLT2 inhibitors, Finerenone, Sacubitril/valsartan, Congestion assessment, Ultrafiltration, Risk stratification

1. Introduction

In recent years, cardiovascular diseases have remained the leading cause of mortality and disability worldwide. In particular, chronic heart failure (CHF) is considered one of the most complex and multifactorial problems in modern medicine. According to data from the World Health Organization and cardiology associations, the prevalence of CHF continues to increase annually due to population aging and the growing incidence of arterial hypertension, diabetes mellitus, and ischemic heart disease. CHF is associated not only with impaired cardiac function but also with dysfunction of other vital organs, especially the kidneys [1,2,3].

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Cardiorenal syndrome (CRS) is a clinical condition that arises as a result of a complex, bidirectional pathophysiological interaction between the heart and the kidneys and is frequently observed in patients with CHF. According to modern classifications, CRS is characterized either by worsening cardiac function leading to renal dysfunction or, conversely, by renal failure exacerbating heart failure. Studies indicate that a significant proportion of patients with CHF exhibit a reduction in glomerular filtration rate (GFR), which markedly worsens prognosis [7,8,9,10].

The pathogenesis of cardiorenal syndrome is closely associated with hemodynamic disturbances, reduced arterial perfusion, venous congestion, and excessive activation of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system. Furthermore, inflammatory mediators, oxidative stress, endothelial–glycocalyx dysfunction,

and disruption of the cGMP/natriuretic peptide axis play an important role in the development of CRS. As a result of these mechanisms, renal blood flow deteriorates, sodium and fluid retention increases, and diuretic resistance develops [4,5,6].

In clinical practice, cardiorenal syndrome poses serious challenges in the management of patients with chronic heart failure. Declining renal function limits pharmacological treatment options, reduces the effectiveness of diuretics, and leads to frequent episodes of decompensation. Scientific studies show that patients with CHF complicated by CRS have significantly higher rates of hospitalization, treatment costs, and mortality. Therefore, CRS is considered an independent prognostic factor in clinical practice. Early identification of cardiorenal syndrome, in-depth understanding of its pathophysiological basis, and the development of modern, comprehensive treatment approaches represent one of the most important scientific and practical tasks today. This article analyzes the clinical challenges of cardiorenal syndrome developing in the setting of chronic heart failure and possible solutions based on scientific literature and current clinical guidelines.

This narrative review synthesizes current evidence from landmark randomized controlled trials, contemporary clinical guidelines (ESC 2021 [2], KDIGO 2023 [8], ACC/AHA 2022), and emerging translational research. Where formal PRISMA methodology was not applied, the scope of evidence is explicitly described and potential for selection bias is acknowledged.

2. Cardiorenal Syndrome and Its Classification

Cardiorenal syndrome (CRS) is a complex of interrelated functional disorders of the heart and kidneys, in which pathological processes in one organ lead to structural and functional damage in the other. The contemporary five-type classification, proposed by Ronco et al. [1] and refined by the ADQI consensus [5], provides an instructive framework with distinct pathophysiological mechanisms and therapeutic implications.

Type 1 CRS: Acute Cardiorenal Syndrome

Type 1 CRS arises from an abrupt deterioration in cardiac function—most commonly acute decompensated heart failure (ADHF) or cardiogenic shock—causing acute kidney injury (AKI). The primary mechanisms include sudden reduction in renal perfusion pressure and a sharp increase in renal venous pressure [1,3]. Therapeutically, prompt hemodynamic stabilization, cautious diuresis with volume optimization, and avoidance of nephrotoxic agents are paramount.

Type 2 CRS: Chronic Cardiorenal Syndrome

Type 2 is the most clinically prevalent subtype and forms the central focus of this review. Chronic cardiac dysfunction—predominantly CHF—leads to progressive chronic kidney disease (CKD) through sustained hemodynamic compromise and neurohormonal activation [4]. A gradual and persistent decline in GFR is characteristic, aggravating CHF course and worsening prognosis. Management requires long-term optimization of cardiac output, RAAS modulation, and renoprotective pharmacotherapy.

Type 3 CRS: Acute Renocardiac Syndrome

Type 3 is defined by an abrupt worsening of renal function (AKI) causing acute cardiac dysfunction through fluid overload, hyperkalemia, uremic toxin accumulation, and inflammatory mediator release [5]. Therapeutic priorities include rapid correction of electrolyte disturbances, fluid removal, and, when indicated, renal replacement therapy to protect cardiac function.

Type 4 CRS: Chronic Renocardiac Syndrome

In type 4, primary CKD contributes to chronic impairment of cardiac function, manifesting as left ventricular hypertrophy, diastolic dysfunction, and increased cardiovascular mortality [6]. The uremic milieu promotes endothelial dysfunction, oxidative stress, and accelerated atherosclerosis. Management focuses on CKD-specific cardiovascular risk reduction, including blood pressure control, anemia management, and phosphate regulation.

Type 5 CRS: Secondary Cardiorenal Syndrome

Type 5 encompasses systemic conditions—such as sepsis, diabetes mellitus, amyloidosis, or systemic lupus erythematosus—that simultaneously damage both the heart and the kidneys [5]. Treatment targets the underlying systemic disease while providing organ-specific supportive care.

3. Pathophysiological Mechanisms of Cardiorenal Syndrome

Hemodynamic Disturbances: Low-Flow and Venous Congestion

The development of cardiorenal syndrome in chronic heart failure is associated with multifactorial pathophysiological mechanisms. One of the primary mechanisms is hemodynamic disturbance. Reduced cardiac pump function leads to decreased renal blood flow, resulting in a decline in glomerular filtration. However, landmark observations demonstrated that low cardiac output alone explains only a minority of CRS cases. Central to the modern understanding of CRS is the critical role of renal venous hypertension. Elevated central venous pressure (CVP) is transmitted to renal interstitial pressure, directly impairing glomerular filtration through increased tubular hydrostatic pressure and reduced net filtration gradient. Damman et al. demonstrated that elevated CVP, rather than reduced cardiac output, was the dominant hemodynamic predictor of impaired renal function in CHF patients [4]. Intrarenal hemodynamics are further disturbed by afferent arteriolar vasoconstriction (mediated by angiotensin II and sympathetic activation) and efferent arteriolar vasoconstriction, which initially preserves GFR but ultimately leads to ischemic tubular injury under sustained low-flow conditions [3,9].

Tubular Sodium Avidity

A key downstream consequence of hemodynamic and neurohormonal activation is exaggerated tubular sodium reabsorption—termed tubular sodium avidity. Angiotensin II stimulates sodium-hydrogen exchangers in the proximal tubule, while aldosterone enhances distal tubular sodium reabsorption. Sympathetic activation further amplifies these effects [3,6]. The result is markedly reduced fractional excretion of sodium and blunted natriuretic response to loop diuretics, contributing directly to diuretic resistance. Monitoring urinary sodium excretion (spot urinary sodium after loop diuretic administration) has emerged as a practical tool to assess tubular sodium avidity and guide diuretic escalation strategies [7].

Endothelial–Glycocalyx Dysfunction

The vascular endothelial glycocalyx—a proteoglycan and glycoprotein layer lining the luminal surface of endothelial cells—plays a critical role in maintaining vascular permeability, mechanotransduction, and inflammatory signaling. In CHF, sustained venous congestion, oxidative stress, and systemic inflammation disrupt the glycocalyx, leading to increased vascular permeability, interstitial edema, and impaired microvascular regulation in the kidney [6,9]. Glycocalyx shedding products, including syndecan-1 and heparan sulfate, are elevated in acute HF and correlate with the severity of congestion and renal impairment, representing emerging biomarkers of endothelial injury in CRS.

Neurohormonal Activation: RAAS, SNS, and ADH

Another key mechanism is the activation of neurohormonal systems. Reduced cardiac output triggers compensatory activation of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system. While this response helps maintain arterial blood pressure in the short term, sustained activation contributes to renal fibrosis, sodium and fluid retention, arterial hypertension, and increased cardiac workload [1,3]. Arginine vasopressin (ADH) release contributes to free-water retention, hyponatremia, and further neurohormonal dysregulation [9].

The cGMP/Natriuretic Peptide Axis

The natriuretic peptide system—comprising atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and their shared second messenger cyclic guanosine monophosphate (cGMP)—forms a critical counter-regulatory axis against RAAS and SNS overactivation [10]. In the kidney, cGMP signaling mediates natriuresis, diuresis, and renoprotection through inhibition of tubular sodium reabsorption and suppression of renin secretion. In CHF, the natriuretic peptide system is upregulated but functionally impaired ('natriuretic peptide resistance'), partly attributable to reduced particulate guanylate cyclase receptor sensitivity, accelerated neprilysin-mediated NP degradation, and competing RAAS activation. Sacubitril/valsartan (an ARNI) directly addresses this axis by inhibiting neprilysin, thereby augmenting endogenous NP levels and cGMP signaling—providing both hemodynamic and direct renoprotective effects [17]. Additionally, SGLT2 inhibitors may enhance tubular cGMP signaling through osmotic and tubuloglomerular feedback mechanisms [11,12].

Inflammation and Oxidative Stress

Moreover, recent studies have demonstrated that inflammatory processes and oxidative stress play an important role in the pathogenesis of cardiorenal syndrome. Proinflammatory cytokines (TNF-alpha, IL-6, IL-1beta), reactive oxygen species, and endothelial dysfunction impair renal microcirculation and promote structural changes in both cardiac and renal tissues [4,9]. The NLRP3 inflammasome pathway has been identified as a convergence point linking congestion, metabolic stress, and fibrotic remodeling in CRS [6].

Computational hemodynamic modeling approaches—analogous to those used in forward-looking hemodynamic simulation studies—offer the potential to quantify the relative contributions of renal venous congestion, perfusion pressure, and tubular pressure to GFR decline in CRS, helping to identify patient-specific therapeutic targets [9,10].

4. Clinical Challenges of Cardiorenal Syndrome in Chronic Heart Failure

Diuretic Resistance

One of the major challenges in CRS management is diuretic resistance. Reduced renal perfusion, tubular sodium avidity, and increased RAAS activity lead to a diminished natriuretic response to loop diuretic therapy, resulting in persistent edema and fluid overload [4,6]. Clinically, diuretic resistance is defined as inadequate decongestion despite loop diuretic doses equivalent to furosemide ≥160 mg/day or equivalent. Urinary sodium measurement (spot urine sodium <50–70 mmol/L at 2 hours post-loop diuretic) is a practical marker of suboptimal tubular response and should prompt dose escalation or addition of a second diuretic agent [7,18].

The WRF Paradox and Primacy of Decongestion

A clinically critical and historically underappreciated concept in CRS management is the worsening renal function (WRF) paradox. WRF—conventionally defined as an increase in serum creatinine ≥0.3 mg/dL or ≥25% from baseline during hospitalization—occurs in 20–30% of acute HF admissions and has traditionally been viewed as a harbinger of poor outcomes [4].

However, contemporary data challenge this binary interpretation. The DOSE [18] and CARRESS-HF [19] analyses demonstrated that WRF occurring in the context of effective decongestion (negative fluid balance, symptom relief, natriuretic peptide reduction) does not uniformly translate into worse long-term outcomes. In contrast, WRF driven by hemodynamic compromise or over-aggressive diuresis without adequate decongestion carries an adverse prognosis. This distinction underscores the clinical maxim that 'congestion is king'—residual congestion at discharge is the dominant predictor of 90-day readmission and mortality,

outweighing modest elevations in creatinine occurring during decongestion [7,18,19]. Clinicians should therefore resist premature discontinuation of diuretic therapy in response to modest creatinine rises during active decongestion. The functional trajectory—assessed by urinary output, spot urinary sodium, daily weight, and congestion markers—must guide therapeutic decisions rather than creatinine dynamics in isolation.

Pharmacological Limitations

Worsening renal function also imposes limitations on pharmacological treatment in CRS. In particular, the use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor antagonists may be associated with an increased risk of elevated creatinine levels and hyperkalemia—particularly when GFR falls below 30 mL/min/1.73 m². This requires an individualized approach and continuous laboratory monitoring [2,3]. Contemporary hyperkalemia mitigation strategies (discussed in the management section) have substantially expanded the ability to maintain guideline-directed medical therapy (GDMT) in CRS patients with advanced renal impairment [24,25].

According to scientific evidence, cardiorenal syndrome is directly associated with increased rates of rehospitalization, reduced treatment efficacy, and higher mortality in patients with CHF. Therefore, CRS is considered an independent prognostic factor in clinical practice.

5. Modern Approaches to the Diagnosis of Cardiorenal Syndrome

Traditional Laboratory Parameters

Serum creatinine, estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), and urinalysis remain the main indicators for assessing renal function in CRS [8]. However, their limitations are well recognized: creatinine is influenced by muscle mass, volume of distribution, and tubular secretion, and may not reflect GFR accurately in patients with sarcopenia or marked fluid overload. Dynamic changes in these parameters are often more informative than single absolute values [4,9].

In recent years, combined analysis of cardiac biomarkers such as NT-proBNP and BNP together with renal function markers has demonstrated high diagnostic value in identifying cardiorenal syndrome [2,10]. Assessment of dynamic changes in these parameters plays an important role in predicting disease progression and selecting appropriate treatment strategies.

Novel Renal Biomarkers

Recent years have seen validation of several kidney-injury biomarkers that detect tubular damage earlier and more specifically than creatinine-based metrics [8,9]:

Cystatin C: A low-molecular-weight protein freely filtered by glomeruli and completely reabsorbed and catabolized by proximal tubular cells without secretion. Cystatin C-based eGFR equations (CKD-EPI Cys) provide more accurate GFR estimation in CHF patients and detect earlier GFR decline than creatinine-based formulas, particularly in sarcopenic patients [8,9].

Albuminuria/UACR: Urinary albumin-to-creatinine ratio (UACR) reflects glomerular permeability and tubular dysfunction and carries independent prognostic value in both CHF and CKD. Albuminuria provides incremental risk stratification beyond eGFR alone and is a key target for SGLT2 inhibitor [15,16] and finerenone therapy [21,22].

NGAL (Neutrophil Gelatinase-Associated Lipocalin): Both serum and urinary NGAL rise within 2–4 hours of acute tubular injury, well before creatinine elevation. In acute decompensated HF, urinary NGAL predicts WRF and adverse outcomes. High urinary NGAL in the context of normal creatinine signals subclinical tubular stress [9].

KIM-1 (Kidney Injury Molecule-1): A proximal tubular injury marker that is elevated in AKI and CKD progression. In CRS, KIM-1 reflects ischemic and inflammatory tubular damage. Combined panels of NGAL + KIM-1 improve prediction of persistent AKI over creatinine alone [9].

NT-proBNP and BNP: Combined analysis of cardiac biomarkers (NT-proBNP, BNP) with renal biomarkers (cystatin C, NGAL) demonstrates high diagnostic and prognostic value in CRS. The trajectory of NT-proBNP during hospitalization informs decongestion adequacy, while the BUN-to-creatinine ratio reflects prerenal hemodynamic stress [2,10].

Congestion Assessment Tools

Contemporary management of CRS requires multimodal, point-of-care congestion assessment beyond clinical signs alone (peripheral edema, orthopnea, raised JVP) [2,7]:

Lung Ultrasound (LUS): Identification of B-lines (comet-tail artifacts) on bedside lung ultrasound provides a reliable, real-time, and reproducible measure of pulmonary congestion. The number of B-lines correlates with pulmonary capillary wedge pressure and NT-proBNP levels, and serial LUS monitoring can guide diuretic titration during hospitalization [2,7].

IVC Ultrasound: Measurement of inferior vena cava (IVC) diameter and its collapsibility with respiration provides a non-invasive estimate of right atrial pressure and volume status. Dilated, non-collapsible IVC (>2.1 cm with <50% collapse) correlates with elevated CVP and persistent congestion [2].

Bioimpedance Analysis: Multi-frequency bioimpedance (e.g., Body Composition Monitor, BCM) quantifies extracellular fluid excess and provides an objective measure of fluid overload complementary to clinical assessment. It can identify subclinical fluid excess not yet clinically apparent as peripheral oedema [7].

CardioMEMS (Pulmonary Artery Pressure Monitoring): The CardioMEMS HF system allows ambulatory wireless monitoring of pulmonary artery pressures. The CHAMPION trial [23] demonstrated that PA pressure-guided therapy

significantly reduced HF hospitalizations compared with standard care. Remote haemodynamic monitoring enables earlier detection of rising filling pressures before overt decompensation, providing direct guidance for diuretic and GDMT adjustments in CRS patients.

6. Modern Management and Treatment Strategies for Cardiorenal Syndrome

The management of cardiorenal syndrome requires a comprehensive and multidisciplinary approach. The primary goals are stabilization of cardiac function, optimization of fluid balance ('congestion is king'), and maximal preservation of renal function [2,3]. The following sections present an evidence-based framework organized by therapeutic category.

Structured Diuretic Strategy

Diuretic therapy is the cornerstone of decongestion in CRS but must be systematically individualised according to diuretic response and tubular sodium avidity [7,18]:

Loop Diuretic Dosing (DOSE Trial [18]): The DOSE trial (Diuretic Optimization Strategies Evaluation; N=308, ADHF) compared low-dose (equivalent to patient's oral dose) versus high-dose IV furosemide (2.5× oral dose) and bolus versus continuous infusion. High-dose strategy produced greater symptom relief and fluid removal with transient creatinine elevation that did not translate into worse 60-day outcomes—supporting the primacy of decongestion. Continuous infusion showed no significant advantage over bolus dosing for the primary endpoint [18].

Sequential Nephron Blockade: In cases of loop diuretic resistance, addition of a thiazide or thiazide-like diuretic (hydrochlorothiazide, metolazone) blocks sodium reabsorption at the distal convoluted tubule, overcoming compensatory distal sodium reabsorption and synergistically enhancing natriuresis. Metolazone (2.5–10 mg) 30 minutes prior to loop diuretic is a commonly used regimen, requiring close electrolyte monitoring due to risk of hypokalemia and hyponatremia [7].

Acetazolamide: ADVOR Trial [7]: The ADVOR trial (Acetazolamide in Acute Decompensated Heart Failure with Volume Overload; N=519) demonstrated that intravenous acetazolamide (500 mg/day) added to standard loop diuretics significantly increased the rate of successful decongestion at 3 days (42.2% vs 30.5%; RR 1.46; 95% CI 1.17–1.82) without increasing rates of WRF or adverse 3-month outcomes. Acetazolamide inhibits proximal tubular carbonic anhydrase, blocking sodium bicarbonate reabsorption and counteracting the metabolic alkalosis that impairs loop diuretic response. This represents an evidence-based escalation option in diuretic-resistant CRS [7].

Urinary Sodium-Guided Escalation: Spot urinary sodium measured at 2 hours post-loop diuretic (threshold <50–70 mmol/L) indicates insufficient tubular response and should trigger dose escalation or addition of a second agent. This pragmatic strategy—supported by observational data and incorporated in contemporary ESC guidance [2]—operationalizes tubular sodium avidity assessment at the bedside and reduces guesswork in diuretic titration.

RAAS Blockade: ACEi/ARB, Thresholds, and STOP-ACEi

ACE inhibitors and ARBs remain foundational in CHF management, reducing mortality and hospitalization across all EF categories. In CRS, their use requires individualized risk-benefit assessment [2,3]. The STOP-ACEi trial (N=411, advanced CKD stages 4–5) randomized patients to discontinuation versus continuation of ACEi/ARB. Discontinuation did not significantly improve eGFR at 3 years compared with continuation, while contributing to potential cardiovascular risk—supporting maintenance of ACEi/ARB unless clear clinical contraindications exist. Practical thresholds for dose holding include: acute rise in creatinine >30% from baseline, serum potassium >5.5 mmol/L, or symptomatic hypotension. Temporary withholding—with close reassessment within 1–2 weeks rather than permanent discontinuation—is preferred whenever possible [3,8].

ARNI: Sacubitril/Valsartan [17]

Sacubitril/valsartan (PARADIGM-HF [17]: N=8,442; HFrEF, EF ≤40%) demonstrated 20% relative risk reduction in the composite of cardiovascular death or HF hospitalization versus enalapril (HR 0.80; 95% CI 0.73–0.87), with additional renoprotective effects: slower eGFR decline, lower incidence of CKD progression, and reduced albuminuria. These benefits are mediated through augmentation of natriuretic peptides and cGMP signaling, in addition to RAAS blockade. Sacubitril/valsartan should be initiated after haemodynamic stabilisation, with a mandatory 36-hour washout from ACEi to avoid angioedema. The starting dose is 24/26 mg twice daily, with uptitration to the target dose of 97/103 mg twice daily as tolerated. In CRS patients with eGFR 20–30 mL/min /1.73 m^2, initiation at the lowest dose with gradual uptitration and close renal/electrolyte monitoring is recommended by contemporary guidelines [2,17].

Contemporary MRAs: Spironolactone, Eplerenone, and Finerenone [21,22]

Mineralocorticoid receptor antagonists (MRAs) reduce mortality and hospitalization in HFrEF but carry risk of hyperkalemia and AKI, limiting use when eGFR <30 mL/min/1.73 m^2 or baseline potassium >5.0 mmol/L [2]. Finerenone, a novel non-steroidal, highly selective MRA, has demonstrated a distinct profile in the cardiorenal continuum. In the FIDELIO-DKD [22] and FIGARO-DKD [21] trials (CKD with diabetes; combined FIDELITY analysis: N>13,000), finerenone reduced kidney failure, cardiovascular death, and HF hospitalizations with a significantly lower rate of hyperkalemia and kidney function deterioration compared with steroidal MRAs. Finerenone's favorable pharmacokinetics (no active metabolites, balanced cardiac/renal distribution) may make it an attractive option for CRS patients requiring MRA therapy with advanced

CKD [21,22].

SGLT2 Inhibitors: Evidence Across HFrEF, HFpEF, and CKD [11–16]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors represent the most transformative pharmacological advance in CRS management in the past decade, with benefits independent of glycemic effects [11–16]:

HFrEF: DAPA-HF [11] (dapagliflozin; N=4,744; EF ≤40%; 45% non-diabetic) demonstrated 26% relative risk reduction in worsening HF or cardiovascular death (HR 0.74; 95% CI 0.65–0.85). EMPEROR-Reduced [12] (empagliflozin; N=3,730; EF ≤40%) showed 25% reduction (HR 0.75; 95% CI 0.65–0.86), with a 50% reduction in the rate of eGFR decline—a direct renoprotective signal relevant to CRS.

HFpEF: DELIVER [13] (dapagliflozin; N=6,263; EF >40%) demonstrated 18% relative risk reduction in the primary endpoint (HR 0.82; 95% CI 0.73–0.92). EMPEROR -Preserved [14] (empagliflozin; N=5,988; EF >40%) showed 21% reduction (HR 0.79; 95% CI 0.69–0.90). These results establish SGLT2 inhibitors as the first class to demonstrate outcomes benefit across the full EF spectrum.

CKD (Non-HF): DAPA-CKD [15] (dapagliflozin; N=4,304; eGFR 25–75 mL/min/1.73 m²; 33% without diabetes) demonstrated 39% relative risk reduction in composite kidney endpoint (HR 0.61; 95% CI 0.51–0.72). EMPA-KIDNEY [16] (empagliflozin; N=6,609; broad CKD spectrum) showed 28% relative risk reduction in kidney disease progression or cardiovascular death (HR 0.72; 95% CI 0.64–0.82), with benefits extending to patients with eGFR as low as 20 mL/min/1.73 m².

The renoprotective mechanisms of SGLT2 inhibitors in CRS include: (1) restoration of tubuloglomerular feedback via macula densa sodium delivery, reducing intraglomerular hypertension; (2) reduction of proximal tubular metabolic demand and oxygen consumption; (3) natriuresis and osmotic diuresis reducing tubular sodium avidity; (4) direct anti-inflammatory and anti-fibrotic effects; and (5) potential cGMP-enhancing actions [11–16]. SGLT2 inhibitors should be initiated at stable baseline (eGFR ≥20 mL/min/1.73 m ²for dapagliflozin in HF) and continued through hospitalization unless hemodynamic instability or significant volume depletion contraindicates use.

Hyperkalemia Mitigation: Patiromer and Sodium Zirconium Cyclosilicate [24,25]

Hyperkalemia remains the principal barrier to maintaining guideline-directed RAASi therapy in CRS. Novel potassium binders have substantially changed this therapeutic landscape:

Patiromer (OPAL-HK trial [24]): A non-absorbed polymer binding potassium in the colon demonstrated effective potassium reduction in CKD patients on RAASi, enabling continuation of spironolactone in 91% of patients during an 8-week correction phase. Onset of action is 7–12 hours, making it suitable for chronic maintenance.

Sodium Zirconium Cyclosilicate (ZS-9; HARMONIZE trial): A highly selective inorganic cation exchanger with rapid onset (within 1 hour), enabling use in both acute and chronic settings. HARMONIZE demonstrated rapid potassium normalization and sustained maintenance over 28 days.

The DIAMOND trial [25] evaluated patiromer specifically to enable spironolactone optimization in HFrEF with hyperkalemia or prior RAASi intolerance—demonstrating that potassium binder use significantly increased the proportion of patients able to receive and uptitrate spironolactone. Contemporary guidelines recommend considering novel potassium binders to facilitate RAASi continuation rather than default discontinuation, particularly in CRS patients with CKD where RAASi benefits are greatest [2,8,24,25].

Ultrafiltration: UNLOAD and CARRESS-HF [19,20]

Extracorporeal ultrafiltration (UF) mechanically removes isotonic fluid from plasma across a semipermeable membrane, bypassing the tubular sodium avidity that limits diuretic efficacy [19,20]. Two landmark randomised trials define the current evidence base:

UNLOAD Trial [20] (N=200, ADHF): UF versus standard IV diuretic therapy demonstrated greater fluid and weight removal at 48 hours with UF, and significantly lower 90-day rehospitalization rates (18% vs 32%; p=0.037), without significant differences in serum creatinine at 48 hours or 90 days.

CARRESS-HF Trial [19] (N=188, ADHF with WRF): In patients with worsening renal function during acute decompensated HF, UF was compared with stepped pharmacologic diuretic therapy (including high-dose IV furosemide, metolazone, and low-dose dopamine). Stepped pharmacologic therapy achieved superior renal function preservation (creatinine change: +0.04 vs +0.23 mg/dL; p=0.003) with similar fluid removal and without significant differences in 60-day mortality or rehospitalization. The UF arm had significantly higher rates of adverse events.

Based on this evidence, the recommended approach is: (1) stepped pharmacologic diuretic therapy (high-dose loop ± sequential nephron blockade ± acetazolamide, guided by urinary sodium [7,18]) as the preferred first-line strategy for diuretic-resistant CRS; (2) UF reserved for patients with true refractory fluid overload despite optimized stepped pharmacologic therapy; (3) renal replacement therapy indicated when AKI with volume overload is refractory to medical therapy, or when uremia, severe hyperkalemia, or metabolic acidosis supervene [8,19,20].

Reconciling Cardiology and Nephrology Guidelines in Multimorbidity

Management of CRS inherently spans the boundary between cardiology and nephrology, and specialty guidelines do not always converge. Cardiology guidelines (ESC 2021 [2], ACC/AHA 2022) prioritize HF outcomes and recommend initiation of SGLT2 inhibitors and MRAs down to lower eGFR thresholds than historically recognized in nephrology guidelines. Conversely, nephrology guidelines (KDIGO 2023 [8]) place greater emphasis on proteinuria monitoring, CKD staging, and renal endpoint protection. Contemporary evidence—particularly the SGLT2 inhibitor trials in both HF

[11–14] and CKD populations [15,16]—increasingly supports a unified cardiorenal approach where agents such as SGLT2 inhibitors and finerenone are recommended regardless of specialty perspective. Neuro-symbolic approaches to guideline reconciliation highlight that managing patients with CHF and CKD simultaneously requires explicit conflict resolution between recommendations—particularly around RAASi dosing thresholds, MRA initiation, and diuretic targets. Integrated cardionephrology clinics and formal multidisciplinary case conferences represent the most effective structural approach to resolving these conflicts in complex CRS patients [3].

Data-Driven Risk Stratification and Emerging Informatics Approaches

Beyond traditional clinical parameters, the integration of electronic health record (EHR) data with machine learning approaches holds substantial promise for earlier CRS identification and personalized management. Data-driven EHR analyses have demonstrated scalable discovery of risk factors for cardiorenal impairment that may not be individually apparent in routine clinical care but emerge at population scale. Risk models incorporating eGFR trajectory, NT-proBNP dynamics, UACR, and medication adherence patterns can identify patients at imminent risk of CRS decompensation [9,10].

Parallel advances in wearable and remote monitoring technologies—including continuous cardiac rhythm monitoring, remote weight and impedance sensors, and implantable hemodynamic monitors (CardioMEMS [23])—enable multi-system phenotyping of CRS patients in the ambulatory setting. Integrating such data streams with biomarker panels could enable risk stratification approaches analogous to those proposed in the cardiovascular-kidney-metabolic (CKM) syndrome framework, where subtype-specific management pathways are informed by multi-system biomarker and sensor data. Although synthetic EHR technologies and large language model-based decision-support tools represent emerging methodological frontiers in CRS research, their direct clinical translation remains investigational and will require prospective validation [9].

7. Conclusions

Cardiorenal syndrome developing in the setting of chronic heart failure is recognized as a complex and multifactorial clinical problem in modern medicine. This syndrome arises from disrupted pathophysiological interactions between the heart and kidneys, leading to disease progression, reduced treatment efficacy, and a negative impact on patients' quality of life and prognosis. Studies show that patients with CHF complicated by cardiorenal syndrome have significantly higher rates of rehospitalization and mortality [1,2,3].

In conclusion, early detection of cardiorenal syndrome, integrated assessment of cardiac and renal function, and the application of comprehensive, individualized, and multidisciplinary treatment approaches are crucial for improving outcomes in patients with chronic heart failure [2,3]. Renal venous hypertension, tubular sodium avidity, endothelial–glycocalyx dysfunction, and impaired cGMP/natriuretic peptide signaling emerge as mechanistic drivers that extend well beyond the traditional hemodynamic model [4,6,9]. A full five-type CRS classification framework provides clinically actionable distinctions in therapeutic approach. The WRF paradox highlights that modest creatinine rises during effective decongestion should not trigger premature diuretic withdrawal—decongestion remains the paramount therapeutic goal [7,18,19]. Diagnostically, the integration of novel biomarkers (cystatin C, NGAL, KIM-1, UACR) with multimodal congestion assessment tools (lung ultrasound, IVC ultrasound, bioimpedance, CardioMEMS) substantially enhances the precision of CRS evaluation [9,23]. Therapeutically, the evidence landscape has been transformed by SGLT2 inhibitors—with consistent benefits across HFrEF (DAPA-HF [11], EMPEROR-Reduced [12]), HFpEF (DELIVER [13], EMPEROR-Preserved [14]), and CKD (DAPA-CKD [15], EMPA-KIDNEY [16])—and by finerenone [21,22], sacubitril/valsartan [17], and novel potassium binders enabling RAASi continuation [24,25]. A structured diuretic strategy incorporating DOSE trial principles [18], sequential nephron blockade, ADVOR acetazolamide protocol [7], and urinary sodium monitoring provides a systematic approach to diuretic resistance. Ultrafiltration, guided by CARRESS-HF evidence [19], is appropriately positioned as a rescue strategy after optimized pharmacologic decongestion. Continued investigation and the development of novel diagnostic and therapeutic strategies will further expand the opportunities for effective, patient-centred management of cardiorenal syndrome.

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