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Review

Cardio-Renal Syndrome: Review and New Perspectives

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Abstract

Cardio-renal syndrome (CRS) is a term referring to a bidirectional group of disorders in which there is a concomitant compromise of both organs, the heart and the kidney, leading to a significant increase in morbidity and mortality. In recent years, numerous publications have addressed this complex entity from different points of view. For better understanding, five subtypes have been established: depending on its form of presentation, acute or chronic; the organ initially affected; and whether there is another responsible systemic disease. CRS represents a complex interaction between both organs with several neurohormonal, inflammatory, and hemodynamic pathophysiological mechanisms involved. Because of its heterogeneous presentation and complex management, CRS requires a multidisciplinary approach targeting multiple pathogenic mechanisms. Throughout this review, we will analyze all relevant aspects of CRS from its classification to current diagnosis and treatment. Accordingly, this review provides a holistic overview of cardio-renal syndrome, emphasizing integrated pathophysiological mechanisms, contemporary diagnostic approaches, and their relevance for clinical management.

Keywords: cardio-renal syndrome; heart failure; kidney disease

1. Introduction

A substantial proportion of patients exhibit varying degrees of cardiac and renal dysfunction, where a primary injury in one of these organs may lead to secondary disorder in the other [1–3]. Cardio-renal syndrome (CRS) is characterized by the coexistence of cardiac and renal impairment within a bidirectional and dynamic interaction, in which heart failure (HF) precipitates or exacerbates renal functional decline and vice versa [3–5]. In this process, dysfunction of either organ can initiate or exacerbate injury in the other through complex neurohormonal feedback mechanisms [2,6]. The lack of a clear definition has contributed to uncertainty in the diagnosis and management of this syndrome for a long time. For this reason, a subdivision of CRS into five subtypes has been proposed to allow a more specific approach for each case [2]. However, identifying the initial injury and subsequent events is often challenging in clinical practice, as phenotypic overlap frequently occurs during disease progression [7]. In this context, the present review addresses cardio-renal syndrome as a complex and heterogeneous clinical entity, integrating current knowledge on pathophysiology and diagnostic evaluation to support a more comprehensive and clinically oriented approach to patient management. An integrated overview of the different cardio-renal syndrome subtypes and their clinical implications is provided in Figure 1.

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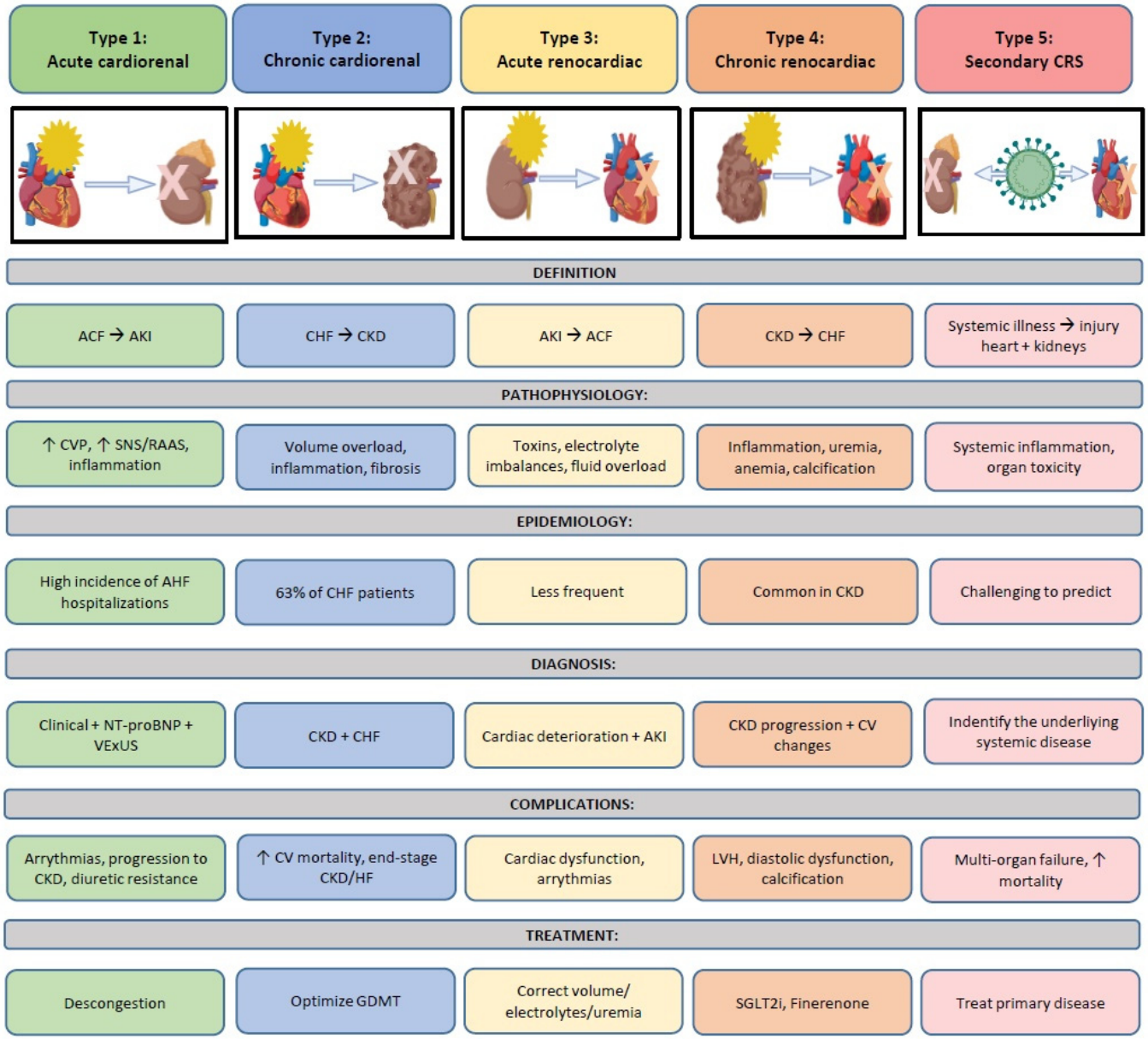


Figure 1. Global management of CRS from subtypes to treatment. This central figure summarizes the five types of cardio-renal syndrome, illustrating their definitions, underlying pathophysiological mechanisms, epidemiology, diagnostic features, major complications, and therapeutic principles. The figure provides an integrated and clinically oriented overview of the bidirectional interactions between the heart and the kidneys across acute and chronic settings, reflecting the conceptual framework developed throughout the manuscript. ACF: Acute cardiac failure; AKI: Acute kidney injury; CHF: Chronic heart failure; CKD: Chronic kidney disease; CRS: Cardio-renal syndrome; CV: Cardiovascular; CVP: Central venous pressure; GDMT: guideline-directed medical therapy; HF: Heart failure; NT-ProBNP: *N*-terminal brain natriuretic peptide; SGLT2i. SGLT2 inhibitors; SNS: Sympathetic nervous system, AVP: Arginine–vasopressin; VExUS: Venous Excess Ultrasound Score.

2. Classification of Cardio-Renal Syndrome and Phenotypes: What Are We Talking About

First description of CRS is attributed to the English physician Robert Bright, who in 1836 described the relationship between the kidney and the heart in his classic paper published in Volume 1 *Guy's Hospital Reports entitled "Cases and observations illustrative of*

renal disease accompanied by the secretion of albuminous urine", in which the significant cardiac structural changes seen in patients with advanced kidney disease were revealed [8].

Years later and, as we have previously mentioned, the pioneering definition of CRS was established by the Working Group of the National Heart, Lung, and Blood Institute in 2004, defining the CRS as the result of interactions between the kidneys and other circulatory compartments that increase circulating volume, which exacerbates the symptoms of heart failure (HF) and disease progression [9,10].

Therefore, it represents the confluence of heart–kidney interactions across several interfaces. Later, in September 2008, a consensus conference was held in Venice, sponsored by the Acute Dialysis Quality Initiative (ADQI), with experts and leaders in the fields of nephrology, critical care, cardiac surgery, and cardiology. This meeting resulted in a consensus document that established the definition and classification of CRS into five phenotypes as we know it today, depending on the organ initially injured and the acute or chronic nature of the damage [11]. The definitions, pathophysiological mechanisms, diagnostic features, and therapeutic principles of the different CRS subtypes are summarized in Figure 1.

The relevance of CRS lies in the fact that the coexistence of heart and kidney disease has been linked to a worse medium and long-term prognosis, due to a higher risk of readmissions and mortality in patients [12]. Understanding the symbiosis between both organs and the early recognition of damage to one of them can help to stop the deterioration in the other one earlier [11].

According to the proposed classification, the five types of CRS are defined as follows.

2.1. Acute Cardio-Renal Syndrome (CRS1)

Acute cardio-renal syndrome, also known as CRS type 1, is defined as an abrupt worsening of cardiac function that occurs in at least 30% of patients with acute decompensated heart failure and can lead to the development of acute kidney injury. Traditionally, acute kidney injury (AKI) in acute heart failure (AHF) patients is defined by worsening renal function (WRF) during hospitalization, which has been broadly defined as serum creatinine changes ranging from 0.3 to 0.5 mg/dL. However, there is a great disagreement between heart failure and nephrology guidelines on the best criteria for WRF [13].

We summarize in Table S1 RIFLE (Risk, Injury, Failure, Loss of Kidney, Function, and End-Stage Kidney Disease), AKIN (Acute Kidney Injury Network), KDIGO (Kidney Disease: Improving Global Outcomes), and WRF (Worsening Renal Function) criteria for the definition of acute kidney injury [14–16].

2.2. Chronic Cardio-Renal Syndrome (CRS2)

Cardio-renal syndrome type 2 is described by chronic cardiac abnormalities resulting in renal damage and or dysfunction. This syndrome is common and has been reported in 63% of patients hospitalized with congestive heart failure (CHF) [17,18].

Two conditions have been proposed to make a diagnosis of CRS type 2: that CHF and chronic kidney disease (CKD) coexist in the patient and that CHF causally provokes the CKD. Sometimes it results in difficulty in determining which of the two pathologies is primary versus secondary; for this reason, the term CRS type 2/4 has been suggested [19].

2.3. Acute Reno-Cardiac Syndrome (CRS3)

This subtype refers to heart injury and/or dysfunction secondary to acute worsening of kidney function. There are a number of potential contributing causes for AKI that may predispose to the development of CRS type 3, such as fluid overload, metabolic acidosis, retention of uremic toxins, electrolyte disturbances, accumulation of myocardial depressant factors, neurohormonal activation, and systemic inflammation. All of them

have been postulated to lead to cardiac dysfunction [13]. The development of AKI may also adversely impact cardiac function by contributing to alterations in drug pharmacokinetics and pharmacodynamics [20,21].

2.4. Chronic Reno-Cardiac Syndrome (CRS4)

It is the result of chronic kidney disease (CKD) leading to heart injury, disease, and/or dysfunction. This subtype refers to a disease or dysfunction of the heart occurring secondary to CKD. Different examples of this subtype are: diabetic nephropathy, chronic glomerular disease, or autosomal dominant polycystic kidney disease. They all can promote the progression of chronic HF (with preserved or reduced ejection fraction [EF]) [22], ventricular hypertrophy, diastolic dysfunction, and increased risk of adverse cardiovascular events [23,24].

Type 4 of CRS is associated with high morbidity and mortality, and its incidence is increasing with population aging.

2.5. Secondary Cardio-Renal Syndrome (CRS5)

It refers to systemic conditions leading to simultaneous injury and/or dysfunction of the heart and kidney, for example, sepsis, lupus, amyloidosis, or inflammatory conditions [23].

2.6. Cardiovascular–Kidney–Metabolic Syndrome

Cardiovascular–kidney–metabolic syndrome represents a novel conceptual framework that integrates metabolic, renal, and cardiovascular dysfunction into a single systemic disorder. Unlike traditional approaches that consider these conditions separately, this syndrome emphasizes the interconnected pathophysiology linking excess or dysfunctional adiposity, chronic kidney disease, and cardiovascular damage. Adiposity acts as a central driver, promoting inflammation, insulin resistance, and organ injury [25].

In Table 1, we summarize the current 5 CRS subtypes.

Table 1. Subtypes of cardio-renal syndrome.

Nomenclature	Phenotype/Syndrome	Primary Event	Clinical Example
Acute cardio-renal syndrome	Type 1	Worsening heart function	Acute heart failure. Cardiogenic shock
Chronic cardio-renal syndrome	Type 2	Chronic heart abnormalities	Chronic heart failure
Acute renal cardiac syndrome	Type 3	Rapid worsening of kidney function	Acute kidney injury: Uremia, hyperkalemia, volume overload
Chronic renal cardiac syndrome	Type 4	Chronic kidney disease	Chronic kidney disease: Left ventricular hypertrophy, diastolic dysfunction
Secondary cardio-renal syndrome	Type 5	Acute or chronic systemic illnesses	Diabetes mellitus, amyloidosis, sepsis, vasculitis, noncardiogenic shock

3. Epidemiology: A Syndrome with High Incidence and Prevalence

The estimated prevalence of chronic kidney disease (CKD) is around 10–20% in many countries. It is well established that these patients carry a high cardiovascular (CV) risk, resulting in an increased incidence of CV events, including CV mortality [2,5]. Data from the United States show that over 60% of patients with CKD have CV disease, and the degree of CV disease is closely correlated with the severity of CKD. Moreover, the impact of CKD on CV disease becomes even more pronounced in patients requiring dialysis [3].

Additionally, it is estimated that the prevalence of HF reaches approximately 64 million adults worldwide, among whom CKD is present in more than 50% [1,5]. Furthermore, the *National Registry of Acute Decompensated Heart Failure* has shown that 30% of patients hospitalized because of HF decompensation exhibit impaired renal function [3,4,6].

Acute kidney injury (AKI) is an ominous predictor of mortality in cardiogenic shock and has been associated with in-hospital mortality rates of approximately 50% across several observational studies [10].

Regarding each subtype of CRS, type 1 precipitates the need for hospitalization in over one million people per year in the United States, with an estimated incidence between 27% and 45%. In addition, the prevalence of type 2 CRS is approximately 25% [2].

Type 3 CRS appears to be less frequent than type 1, probably due to limited research on this subtype and, as referred in the consensus document, the challenge in understanding the epidemiology of type 3 CRS is that its incidence and associated risk factors fail to consider the inciting event for CSA-AKI as either primarily AKI-related or heart-related [2]. Regarding chronic reno-cardiac syndrome (type 4), as we have previously mentioned, cardiac disease is common in patients with CKD, and this is associated with a high increase in both cardiovascular morbidity and mortality. Finally, epidemiological data on type 5 CRS, secondary to other diseases, are difficult to obtain precisely due to the wide range of systemic illnesses involved.

4. Pathophysiological Mechanism in Cardio-Renal Syndrome: Complex and Multifactorial

Pathophysiology of CRS is complex and multifactorial; different processes are involved, and each of them contributes to a different extent depending on the patient's clinical situation [26]. We briefly review these mechanisms:

4.1. Cardiac Output and Cardiac Index: Low Cardiac Output-Renal Hypoperfusion

Among hospitalized patients, worsening renal failure (WRF) is common, and it is associated with increased risk of death and prolonged hospitalization, as proven in different studies [22]. Hemodynamic factors like hypotension play a role, but it is not the only one. Low cardiac output and central fluid redistribution with renal hypoperfusion activate compensatory mechanisms such as stimulation of the sympathetic nervous system, renin–angiotensin–aldosterone system (RAAS), and vasopressin secretion, which lead to enhanced water and sodium reabsorption. As a result of the renal afferent arteriolar vasoconstriction and decrease in glomerular perfusion, renal function finally worsens [27]. This response also induces fibrosis, apoptosis, and ventricular remodeling [26]. In this context, one might think that increasing cardiac output and blood pressure with inotropes would be sufficient to improve renal and other organ perfusion. However, the results of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) found no correlation between renal function and cardiac output, and improvements in cardiac output did not translate into better renal function, reduced mortality, or fewer hospitalizations. Therefore, these results suggest that decreased cardiac output and hemodynamic failure are not solely responsible for the progressive decline in renal function in patients with heart failure [28]. As a conclusion, pathophysiology and management are far more complicated than previously thought.

4.2. Increase in Central Venous Pressure

Carl Ludwig, the first scientist to describe the process of glomerular filtration, and F. R. Winton, in 1931, reached the same conclusion: the increase in venous pressure was responsible for a reduction in urine flow. Although the mechanisms are not clearly established,

the increase in central venous pressure affects the kidney by increasing its afterload and intra-renal pressure [29,30]. This increase leads to a decrease in glomerular filtration rate (GFR) and an increase in water and sodium retention; therefore, relieving decongestion is clearly relevant in the management of patients with heart failure and CRS [27]. Otherwise, and also related to venous congestion, the study published by Maeder et al. showed that patients with at least a moderate tricuspid regurgitation had lower estimated GFR and that a linear relationship existed between the severity of tricuspid regurgitation and the degree of GFR impairment, probably secondary to elevation of central and renal venous pressure [31].

4.3. Neurohormonal Dysregulation and Sympathetic Activity

The sympathetic nervous system (SNS) is activated in both acute kidney injury and heart failure. The direct effects of catecholamines on cardiac myocytes can contribute to both normal physiological adaptation and pathological remodeling, and may be associated with cellular hypertrophy, apoptosis, and alterations in contractile function. Furthermore, stimulation of the SNS involves stimulation of the RAAS. Angiotensin II (AT II) induces apoptosis and fibrosis of myocytes and is also involved in oxidative stress, inflammation, and extracellular matrix regulation, which ultimately lead to renal parenchymal damage [32,33]. RAAS inhibition is a cornerstone of heart failure treatment, offering benefits through reduced adrenergic tone, improved endothelial function, and prevention of myocardial fibrosis. Furthermore, ACE inhibitors and angiotensin receptor blockers also have a renoprotective effect in hypertensive and diabetic patients with nephropathy [27].

4.4. Stress Oxidative and Endothelial Dysfunction

There is growing evidence supporting the link between oxidative stress and progressive cardiac and renal damage. ATII plays a significant role in this process, exerting a deleterious effect by activating NADPH oxidase and NADH oxidase [28]. The activation of these two enzymes is responsible for oxidative stress in renal tubule cells and cardiac myocytes. Since both primary cardiac failure and primary renal failure lead to the development of the RAAS, activation of oxidases by AT-II in one organ has the potential to lead to progressive dysfunction in the other one through the generation of reactive oxygen species [27].

4.5. Inflammatory Response

All the aforementioned factors, such as activation of the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS), venous congestion, and oxidative stress, act as triggers for the initiation and propagation of the inflammatory cascade. Thus, both heart failure and chronic kidney disease are inflammatory states that lead to the generation of pro-inflammatory biomarkers, resulting in damage to both organs with cell death and fibrosis. Several cytokines are involved, such as tumor necrosis factor-α (TNF-α), members of the interleukin-1 (IL-1) family, and interleukin-6 (IL-6), all of which have been associated with heart failure as well as chronic kidney disease (CKD). Otherwise, inflammation seems to be largely associated with inadequate renal perfusion pressures, peritubular edema, pathological reduction in glomerular filtration, and tubular damage [26,34]. Some of these inflammatory biomarkers also have prognostic implications, such as IL-6, which independently predicted overall and cardiovascular mortality in patients at different stages of chronic kidney disease and soluble ST2, a member of the IL-1 family [35]. Moreover, chronic inflammation associated with chronic kidney disease predicts all-cause and cardiovascular mortality in hemodialysis patients. In the same way, high C-Reactive protein (CRP) in hemodialysis patients also predicts left ventricular dysfunction, cardiac hypertrophy, and mortality [35,36].

4.6. Renal Failure and Anemia: The Cardio-Renal Anemia Syndrome

Anemia, as defined by hemoglobin levels < 13 g/dL in men and <12 g/dL in women, plays an important role in the pathogenesis of CRS. It is common in congestive heart failure (CHF) and is associated with increased mortality, morbidity, and progressive kidney failure. The most common causes of anemia in CHF include chronic kidney disease (CKD), which reduces erythropoietin production (EPO), and systemic inflammation, which impairs both erythropoietin synthesis and bone marrow response. This set of interactions is called cardio-renal–anemia syndrome [37].

In patients with CKD, anemia is associated with poor quality of life, progression of kidney disease, cardiovascular comorbidities, and higher mortality. There are several mechanisms by which anemia is involved in the pathogenesis of CRS. Ischemic insult secondary to lack of oxygen in both heart and kidney can result in progressive cell death in both organs, with myocardial necrosis and tubular damage. Anemia can also cause ischemia in other organs and tissues with peripheral vasodilatation and activation of SNS and RAAS, which finally leads to chronic renal venous congestion and progressive nephron loss and fibrosis [26]. Managing anemia is a complex therapeutic target. There are no definitive guidelines, and treatment should address HF, CKD, and anemia concurrently. A proposed algorithm includes correcting iron deficiency, initiating sodium–glucose co-transporter inhibitors, and considering erythropoiesis-stimulating agents if hemoglobin remains <10 g/dL [38].

4.7. Adiposity and Renal Failure: Cardio-Renal–Metabolic Syndrome

Excess visceral and ectopic fat promotes chronic low-grade inflammation, insulin resistance, and dyslipidemia. Adipokines and inflammatory cytokines contribute to endothelial dysfunction, oxidative stress, and organ injury, as previously described. Moreover, hyperglycemia, hypertension, and systemic inflammation impair renal hemodynamics and promote glomerular and tubular injury [25].

5. Diagnosis: Integrated Approach, Testing, and Expected Results

5.1. General Principles of Diagnosis

Diagnosis begins with clinical suspicion: acute or subacute worsening of renal function in the context of heart failure, or cardiac deterioration in a patient with chronic kidney disease without another evident explanation. Worsening renal function is commonly defined as an increase in serum creatinine of $\geq$0.3 mg/dL within 48 h or a $\geq$25% decline in estimated glomerular filtration rate (eGFR) from baseline, while persistent increases in albumin-to-creatinine ratio (ACR) may reflect structural renal injury. Because creatinine and eGFR are late and volume-dependent markers, CRS diagnosis requires a multimodal approach integrating clinical assessment, biomarkers, imaging, and functional testing. In most clinical studies, WRF has been defined as a change in serum creatinine or eGFR over time, but there is great variability in the specific markers used (serum creatinine vs. eGFR vs. cystatin C) and in the thresholds considered significant. Some studies use an absolute rise in creatinine, while others use a relative change in eGFR or different cutoffs, and there is no single consensus definition adopted across international heart failure or nephrology guidelines. This heterogeneity makes it difficult to compare results between studies and generate consistent clinical interpretations. Another source of controversy is that similar changes in serum creatinine may reflect different underlying processes. Because serum creatinine levels can also be influenced by factors such as baseline renal function, muscle mass, inflammation, or fluid shifts, the same numeric change can have different clinical implications in different patients [39–41].

5.2. Clinical and Biomarker Assessment in CRS

Diagnostic evaluation should distinguish between acute (CRS type 1) and chronic (CRS type 2) cardiac patients, and CRS type 3–4, which primarily affect the kidney.

- CRS1 and CRS2 (acute/chronic cardiac):

History and physical examination: monitor diuretics, weight changes, nephrotoxic drugs, signs of congestion (Figure 2, pathway 2: jugular venous distention, edema, and hepatomegaly), and hypoperfusion (Figure 2, pathway 1: oliguria and hypotension). Systemic congestion predicts renal deterioration [42,43].

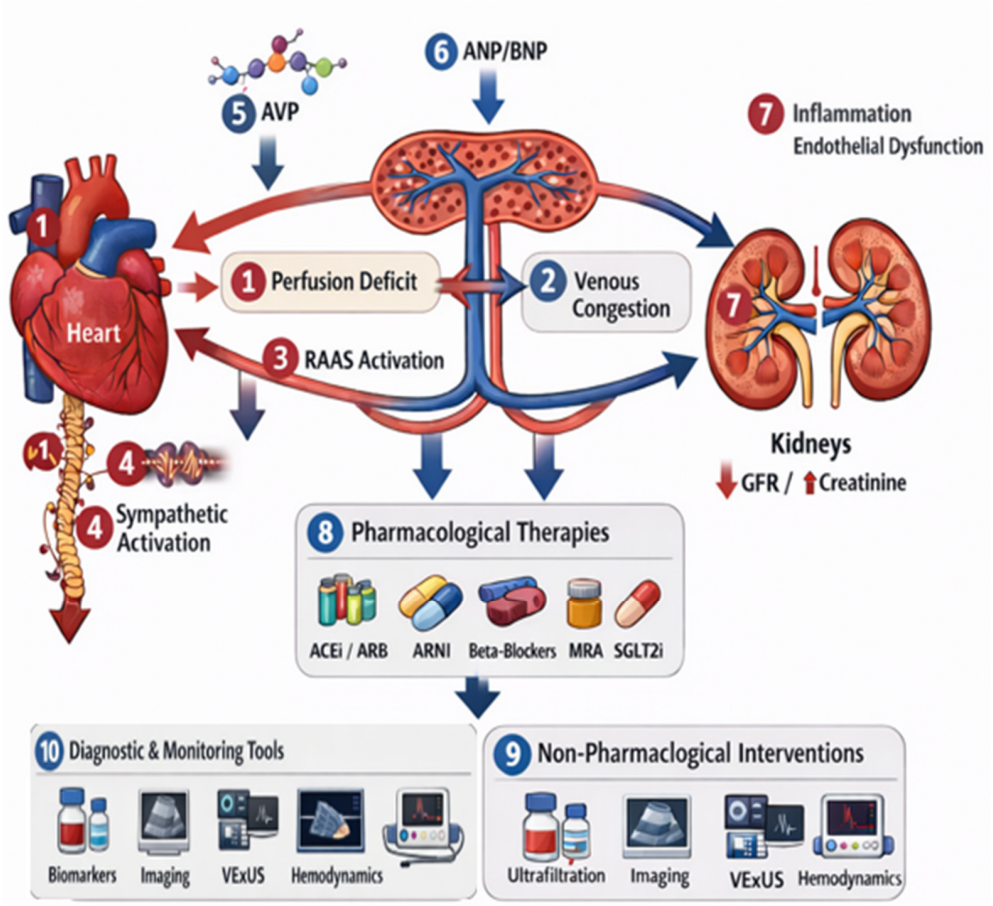


Figure 2. Pathophysiological mechanisms, diagnostic tools, and therapeutic targets in CRS. Numbered pathways correspond to mechanisms or interventions discussed in the text: (1) reduced cardiac output; (2) venous congestion; (3) RAAS activation; (4) sympathetic nervous system activation; (5) AVP release; (6) natriuretic peptides (ANP/BNP); (7) inflammation and endothelial dysfunction; (8) pharmacological therapies (ACEi, ARB, ARNI, beta-blockers, MRA, SGLT2 inhibitors, and diuretics); (9) non-pharmacological interventions (ultrafiltration, peritoneal dialysis, and inotropes); and (10) diagnostic tools (biomarkers, imaging, VExUS, and hemodynamic assessment). A detailed explanation of each pathway is provided in the main text. CRS: Cardio-renal syndrome; RAAS: Renin–angiotensin–aldosterone system; AVP: Arginine–vasopressin; ANP/BNP: Atrial/brain natriuretic peptide; ARBs: Angiotensin receptor blockers; ACEi: Angiotensin-converting enzyme inhibitor; ARNI: Angiotensin receptor–neprilysin inhibitor; MRAs: Mineralocorticoid receptor antagonists; VExUS: Venous Excess Ultrasound Score.

Basic monitoring: Creatinine, urea, electrolytes, hourly diuresis, fluid balance, and sodium/potassium; use an ECG to rule out ischemia/arrhythmias [44].
Biomarkers: BNP/NT-proBNP indicate congestion (Figure 2, pathway 6) [44]; NGAL, KIM-1, cystatin C, and TIMP-2·IGFBP7 detect early tubular injury (Figure 2, pathway 10) [45–47].

Natriuresis: urine sodium after IV diuretics predicts diuretic response; low values indicate need for escalation (Figure 2, pathways 8–9) [48,49].

- CRS3 and CRS4 (primary kidney):

Patients are at risk of heart failure and coronary artery disease due to shared risk factors (hypertension, diabetes, and vascular calcification) and endothelial dysfunction (Figure 2, pathways 1–2, 7) [42–44].

Assessment includes renal function (creatinine and eGFR), electrolytes, and cardiac evaluation (ECG, troponin, and imaging) to detect subclinical CAD and guide therapy (Figure 2, pathways 1–2, 10).
Biomarkers and natriuresis remain critical to identify tubular injury and guide therapy (Figure 2, pathways 8–10) [46–50].

- Interpretation guide (all CRS types):

Elevated NT-proBNP + congestion → predominant venous component (Figure 2, pathways 2,6).

Low natriuresis + abnormal VExUS → renal congestion and diuretic resistance (Figure 2, pathways 2,10).

Positive renal biomarkers + stable creatinine → early tubular injury (Figure 2, pathway 10).

5.3. Imaging and Hemodynamic Testing

- Lung ultrasound (B-lines): Correlates with interstitial edema and lung fluid. Monitors response to diuretics (Figure 2, pathway 10) [51].
- Echocardiography (2D/3D + strain): Evaluates systolic/diastolic function, filling pressures, pericardial effusion, and cardiopathies. Reduced ejection fraction or severe diastolic dysfunction increases CRS risk (Figure 2, pathway 1) [52].
- Global longitudinal strain (GLS): Detects subclinical dysfunction preceding biomarkers and renal deterioration (Figure 2, pathway 1).
- Venous Doppler and VExUS: Quantifies systemic venous congestion. High scores correlate with AKI risk, poor diuretic response, and rehospitalization (Figure 2, pathway 2) [53].
- Intrarenal Doppler/RVSI: Pulsatile/monophasic renal venous flow indicates significant renal congestion. It correlates with reduced diuresis and worse prognosis (Figure 2, pathway 2) [54].
- Right-heart catheterization: In selected patients, measures fill pressures to confirm predominant venous congestion. It guides ultrafiltration or advanced therapy (Figure 2, pathways 2, 10) [55].

5.4. Functional Evaluation and Applied Diagnostic Algorithms

An efficient diagnostic algorithm typically integrates: clinical assessment, natriuresis/biomarkers, POCUS/VExUS, and transthoracic echocardiography. The goal is to classify CRS into subphenotypes (predominant venous congestion, predominant hypoperfusion, primary tubular injury, or mixed forms) (Figure 2, pathways 1–2, 10) that determine the intervention (aggressive decongestion, hemodynamic adjustment, or specific renal-protective therapy) (Figure 2, pathways 8–9) [2,7,56].

6. Complications of Cardio-Renal Syndrome: Pathophysiological Mechanisms

CRS complications (arrhythmias, worsening ventricular function, progression to CKD, diuretic resistance, and electrolyte disturbances) arise from intertwined hemodynamic,

neurohormonal, inflammatory, and structural mechanisms (Figure 2, pathways 1–7). Understanding the "why" behind each complication guides preventive and therapeutic strategies. Figure 1 represents mechanisms and treatment for CRS.

6.1. Arrhythmias: Why They Increase in CRS

Arrhythmias (atrial fibrillation, ventricular tachycardias, and bradyarrhythmias) are frequent and have multiple converging causes:

- Pressure and volume overload: Atrial and ventricular dilation from overload increases reentrant substrate and electrical heterogeneity [57,58]. Venous congestion and elevated left atrial pressure favor atrial fibrillation through anatomical and electrical remodeling.
- Myocardial fibrosis and remodeling: Chronic inflammation, neurohormonal activation (RAAS, norepinephrine), and oxidative stress induce interstitial fibrosis, creating areas of slow conduction and conduction block [59,60].
- Ionic and electrolyte disturbances: Hypokalemia (diuretics), hypomagnesemia, or hyperkalemia (renal failure or RAAS inhibition) alter repolarization and predispose to both tachyarrhythmias and bradyarrhythmias; hyponatremia is also associated with poor prognosis [61].
- Myocardial ischemia and cellular injury: Coronary hypoperfusion in hypotension or coexisting coronary disease can generate irritative foci and elevated troponin with arrhythmic risk [62].
- Pharmacologic effects and drug accumulation.
- Systemic inflammation and sympathetic stress [63].

6.2. Worsening Ventricular Function and Progression to Heart Failure

- Reduced output from systolic or diastolic dysfunction leads to renal hypoperfusion; lower renal perfusion worsens sodium/water retention, increasing congestion [64].
- Chronic neurohormonal activation (RAAS, aldosterone, sympathetic tone) causes vasoconstriction, fibrosis, and remodeling that perpetuate HF and renal injury [65].
- Myocardial injury from uremia and uremic toxins: In advanced CKD, accumulation of metabolites promotes myocardial dysfunction (uremic cardiomyopathy) [66].
- Inflammation and oxidative stress accelerate myocyte loss and replacement with fibrotic tissue [67].

6.3. Diuretic Resistance and Failure of Depletive Therapy

- Pharmacokinetic mechanisms: Reduced renal perfusion may diminish diuretic delivery to the tubule [68].
- Shift in reabsorption site: RAAS and aldosterone activation increase distal sodium reabsorption, counteracting loop inhibition [69].
- Proximal sodium recovery and tubular adaptation (braking phenomenon) [70].
- Intrarenal congestion (elevated renal venous pressure) reduces filtration gradient, and volume depletion fails to produce natriuresis; correcting venous congestion is often more effective than intensifying diuretics [46,48].

6.4. Electrolyte Disorders and Therapeutic Limitations

Hyperkalemia from reduced GFR or RAAS inhibitor use limits evidence-based HF therapies; hyponatremia reflects severe neurohormonal activation and correlates with poor prognosis [52,71].

6.5. Thrombotic Risk and Other Systemic Complications

Venous stasis, chronic inflammation–associated hypercoagulability, and endothelial dysfunction increase thrombotic risk (deep vein thrombosis and pulmonary embolism) [72].

7. Practical Implications and How to Translate Diagnosis into Prevention of Complications

Early diagnosis and subphenotyping: Implementing protocols that combine early natriuresis, renal biomarkers, and VExUS allows identification of patients with intrarenal congestion and intervention before established AKI develops [46,49,53].

Prioritized correction of venous congestion when present: Guided decongestion (natriuresis, VExUS) is more effective than indiscriminate increases in diuretics; consider sequential nephron blockade and, in refractory cases, advanced therapies [2,50].

Management of arrhythmias and correction of precipitants: Strict electrolyte control, review of accumulated drugs, optimization of hemodynamics, and ischemia prevention are recommended [57,61,62].

Preservation of guideline-directed medical therapies: When possible, use strategies (closer monitoring, adjunctive treatments) that allow maintaining RAAS inhibitors, beta-blockers, and SGLT2 inhibitors while protecting renal function [55,65,73].

Integrated care models: Cardiology, nephrology, clinical pharmacy, and specialized nursing improve adherence to diagnostic and therapeutic strategies and enable proactive follow-up [56].

8. Prevention of Cardio-Renal Syndromes

Before addressing the treatment of CRS, it is essential to highlight the importance of prevention. The first step is to identify patients at risk of developing the different types of cardio-renal syndrome and initiate preventive measures early as a strategy to reduce the likelihood of occurrence and improve outcomes should they develop.

8.1. Acute Cardio-Renal Syndrome (CRS1)

Predisposing risk factors for CRS 1 include [23,74,75]:

- Non-modifiable risk factors:
  - History of diabetes mellitus;
  - Previous hospitalizations for heart failure;
  - History of acute myocardial infarction;
  - Severe ventricular dysfunction;
  - Baseline renal impairment.
- Modifiable risk factors:
  - Use of high doses of diuretics;
  - Vasodilator therapy;
  - Drugs promoting sodium and volume retention, such as NSAIDs, thiazolidinediones, and corticosteroids;
  - Radiographic contrast agents.

Several risk-prediction tools exist for estimating the likelihood of acute kidney injury in specific contexts, such as heart failure [22] (exposure to iodinated contrast during interventional procedures [76–78]) or after cardiac surgery [79–81]. These tools incorporate clinical variables [22,77,79,80], procedural characteristics [76–81], and novel approaches including machine learning [82,83], enabling accurate identification of at-risk patients and facilitating preventive and early diagnostic strategies for CRS.

Key preventive measures for CRS type 1 include [6,23,74,75]:

- Comprehensive control of cardiovascular risk factors: smoking cessation, blood pressure optimization, lipid management, intensified glycemic control, and weight management.
- Avoidance of excessive or unnecessary use of radiographic contrast and application of renal protection protocols when contrast is required. Risk factors for contrast-induced nephropathy include pre-existing CKD, diabetes, chronic heart failure, hypotension, advanced age, and high contrast volumes. Evidence supports the use of isotonic fluid administration as the most effective preventive measure, along with low-osmolar, non-ionic contrast agents such as iopamidol [84].
  Additional strategies include statins, which reduce the risk of contrast-induced nephropathy and slow CKD progression in select populations, although heterogeneity in study designs limits generalizability [85], and *N*-acetylcysteine, which in recent meta-analyses has shown benefit in reducing contrast nephropathy but without impact on dialysis or mortality [86].
- Avoidance of nephrotoxic medications, or use at the minimum necessary dose and duration.
- Avoidance of sodium-retaining drugs.
- Implementation of cardiovascular therapies, pharmacological and invasive, appropriate for the underlying cardiac disease, with the aim of improving cardiac function and preventing heart failure decompensation: optimization of hemodynamic and volume status; modulators of neurohormonal and stress responses; treatment of anemia or malnutrition; cardiac resynchronization therapy or defibrillator implantation when indicated; mechanical circulatory support or transplantation in end-stage HF or end stage renal disease (ESRD); optimal renal replacement therapy; and disease-specific therapies for CVD, CKD, or HF.
- Close monitoring of renal function and electrolytes in patients with cardiac decompensation.

8.2. Chronic Cardio-Renal Syndrome (CRS2)

All patients with chronic heart disease, particularly those with chronic heart failure, carry a potential risk of CRS2, especially individuals older than 75 years, those with diabetes, or those with baseline renal dysfunction [23,74]. In this setting, therapies proven to improve the natural history of heart failure with preserved ejection fraction (SGLT2 inhibitors (SGLT2i)) or reduced ejection fraction (renin–angiotensin system inhibitors (RASis), beta-blockers, SGLT2i, mineralocorticoid receptor antagonists (MRAs), cardiac resynchronization therapy, or defibrillator therapy in indicated cases, wherein mechanical circulatory support or transplantation in patients with end-stage HF and other specific therapies for CVD serve as preventive strategies for CRS2 [6,7,23,87].

8.3. Acute Reno-Cardiac Syndrome (CRS3)

Predisposing factors for CRS3 include [74,88,89]:

- Non-modifiable risk factors:
  - Age > 75 years;
  - History of diabetes mellitus;
  - Chronic heart failure;
  - Peripheral vascular disease;
  - Liver disease;
  - Sepsis.
- Modifiable risk factors:
  - Use of nephrotoxic and cardiotoxic medications;
  - Hypotension;

- Electrolyte and fluid imbalances.

Preventive measures for CRS3 focus on avoiding or minimizing the use of potentially nephrotoxic or cardiotoxic drugs, ensuring adequate organ perfusion, and maintaining appropriate hydration while avoiding hypervolemia to prevent cardiac decompensation. Additionally, careful management of uremic changes, hyperkalemia, and pro-inflammatory mediators with adverse cardiac consequences is essential [23,74,88,89].

8.4. Chronic Reno-Cardiac Syndrome (CRS4)

CRS4 is a common manifestation in the natural history of CKD progression. Preventive strategies, therefore, aim at optimizing control of factors associated with CKD progression, such as proteinuria, diabetes, hypertension, atherosclerosis, left ventricular hypertrophy, systolic and diastolic dysfunction, and prothrombotic or proinflammatory states. Slowing CKD progression may reduce the incidence of CRS type 4 [6,7,14,23,74].

8.5. Secondary Cardio-Renal Syndrome (CRS5)

Finally, prevention of CRS5 relies on the early and appropriate management of the primary multisystem disease responsible for simultaneous cardiac and renal involvement [7,23].

9. Treatment of Cardio-Renal Syndrome

Management of CRS is challenging due to its pathophysiological heterogeneity, five subtypes, and frequent comorbidities influencing treatment response. Therefore, therapy should be individualized, focused on the dominant pathology, and often multidisciplinary [1,23]. Specific evidence is limited, as most drugs have not been tested in CRS-specific trials, and patients with reduced glomerular filtration were typically excluded. No dedicated CRS guidelines exist, so management relies on HF and acute or chronic kidney disease recommendations [7,44,90,91]. Drugs improving HF prognosis and slowing renal progression are central. Optimal treatment of underlying cardiac disease is key in CRS types 1 and 2, while controlling baseline nephropathy is critical in types 3 and 4. In CRS type 5, focus is on the primary systemic disease [2]. To facilitate interpretation of the evidence discussed in this section, Table 2 summarizes the major randomized clinical trials supporting the pharmacological treatment of cardio-renal syndrome, including kidney exclusion criteria, key findings, and clinical implications for each therapeutic class across different CRS subtypes.

9.1. Acute Cardio-Renal Syndrome (CRS1)

In CRS1, associated with acute HF, persistent congestion and renal deterioration worsen prognosis, making effective decongestion while preserving renal perfusion the main goal [1,23]. Management includes oxygen therapy, congestion control, hemodynamic support, discontinuation of nephrotoxics, and arrhythmia management [74].

Loop diuretics are first-line; high-dose IV accelerates decongestion, with transient renal impairment generally considered hemodynamic without prognostic impact [50,74]. Dose should be adjusted early according to urine output or urinary sodium [1,44,90,91]. If response is insufficient, combinations with thiazides, acetazolamide, high-dose MRA, or tolvaptan may be used safely, though without additional cardio-renal prognostic benefit. In contrast, iSGLT2 provides provencardio-renall benefit [5,92]. Ultrafiltration shows heterogeneous results. While some studies demonstrated effective decongestion [93,94], others reported greater renal deterioration and adverse effects [95]; these mixed findings highlight that the effectiveness, safety, and optimal use of ultrafiltration remain unsettled, particularly in differing clinical contexts and CRS subtypes. Therefore, current guidelines reserve this technique for volume overload refractory to optimal medical therapy [44,74,90]. Peritoneal

dialysis may be considered in selected patients with advanced CKD and refractory HF, with good hemodynamic tolerance [1].

Vasodilators may help with normal or high blood pressure but carry a risk of hypotension [23,74]. In hypotension or cardiogenic shock, inotropes and mechanical circulatory support are critical [1,23,74].

After stabilization, early initiation and optimization of therapies with proven HF benefit is essential, with close outpatient follow-up for titration and monitoring of volume status and renal function [5,91].

9.2. Chronic Cardio- Renal Syndrome (CRS2)

Management of chronic HF in CRS2 targets underlying etiology and symptom control to prevent progression and decompensation of HF and CKD, requiring a comprehensive patient-centered approach including adherence, lifestyle, and guideline-directed drugs and devices [2,5–7,23].

In LVEF < 40%, RASi (ACEi, ARBs, sacubitril/valsartan), beta-blockers, MRA, and iSGLT2 are first-line, reducing morbidity and mortality. In diabetic or obese patients, aGLP-1 adds cardiovascular benefit. In patients with LVEF > 40%, only iSGLT2 and, in diabetic or obese patients, aGLP-1 have demonstrated significant cardiovascular benefit. Diuretics improve symptoms without affecting mortality. Finerenone reduces HF hospitalizations in CKD with diabetes [5,6,23,44,74,90,91]. CRS2 patients often exhibit hypervolemia, requiring intensive loop diuretics, often combined. Initiation and titration of RASi and MRA may cause transient renal impairment or hyperkalemia, requiring close monitoring and sometimes new potassium binders. RASi, iSGLT2, finerenone, and aGLP-1 reduce proteinuria, and iSGLT2 slows CKD progression. The correction of anemia and iron deficiency improves symptoms and prognosis [1,7,23,74].

Devices such as cardiac resynchronization therapy, implantable defibrillators, and advanced therapies should be considered in selected patients, though less effective in advanced CRS [1,7,23,74].

In patients with CRS type 2, evidence supporting cardio-renal protection derives from multiple clinical settings, including patients with cardiovascular disease and diabetes, as well as those with HF with reduced ejection fraction, HF with preserved ejection fraction, and HF with mildly reduced ejection fraction. In these populations, renin–angiotensin system inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and non-steroidal mineralocorticoid receptor antagonists such as finerenone have demonstrated beneficial effects on cardiovascular and renal outcomes across different randomized trials. While the magnitude of benefit may vary according to the underlying phenotype, these therapies collectively represent the cornerstone of an integrated cardio-renal protective strategy. Key supporting trials are summarized in Table 2.

9.3. Acute Cardio-Renal Syndrome (CRS3)

Prevention is key, particularly in CRS3 associated with contrast nephrotoxicity or cardiac surgery. Once established, management focuses on treating AKI, controlling systemic complications, and close hemodynamic monitoring. Proper volume management, avoiding hypo- or hypervolemia, and correcting uremia, acid-base, and electrolyte disturbances are critical, as these can exacerbate cardiac dysfunction, arrhythmias, hemodynamic compromise, and catecholamine resistance. If conventional therapy fails, renal replacement therapy should be considered early [23,74,89].

9.4. Chronic Reno-Cardiac Syndrome (CRS4)

Management focuses on comprehensive CKD care and mitigating cardiovascular impact. Lifestyle measures (sodium, potassium, and protein restriction) and glycemic

control are essential. Blood pressure should be managed with RASi (ACEi or ARBs) and beta-blockers for cardio- and renoprotection, though use is limited in renal replacement therapy [14,74].

iSGLT2 improves renal and cardiovascular outcomes even in non-diabetic CKD [96]. Finerenone reduces renal progression and CV events in CKD with type 2 diabetes [97], and aGLP-1 improves metabolic control and cardiovascular risk, potentially benefiting renal outcomes in diabetic or obese patients [98].

Metabolic acidosis should be corrected with bicarbonate or citrate, associated with slower CKD progression and improved survival. Anemia management is controversial: iron and erythropoiesis-stimulating agents improve cardiac and renal function, but over-correction increases CV events; target Hb 11–12 g/dL, avoiding > 13 g/dL and excluding iron deficiency. Calcium phosphate metabolism control is crucial to prevent vascular calcification [14,23,74].

9.5. Secondary Cardio-Renal Syndrome (CRS5)

Management is based on treating the primary disease and supporting renal and cardiovascular function. Early hypotension correction with volume resuscitation and, if needed, inotropes or vasopressors is critical to prevent organ dysfunction. Hemodynamic monitoring guides interventions. Persistent renal deterioration may require continuous renal replacement therapy to maintain function and modulate inflammation via cytokine removal. Avoid nephrotoxics and adjust medications according to perfusion and renal function, using an early multidisciplinary approach to optimize outcomes [2,23,74].

Table 2. Evidence table of clinical outcomes with therapeutic interventions in cardio-renal syndromes.

Class of Drug/ Intervention	Drug or Strategy	Mechanism of Action	Trial (Year)	No. of Patients	Intervention	Kidney Exclusion Criteria	Key Findings	Clinical Use in Cardio-Renal Syndrome
ACE inhibitor	Enalapril	RAAS inhibition	SOLVD-Treatment (1991) [99]	2569	Enalapril vs. placebo	Creatinine > 2.5 mg/dL	Reduced mortality and HF hospitalization	Core therapy in CRS type 2 with HFrEF
			SOLVD-Prevention (1992) [100]	4228	Enalapril vs. placebo	Creatinine > 2.5 mg/dL	Delayed HF development	Early CRS type 2 with HFrEF
ARB	Valsartan	AT1 receptor blockade	Val-HeFT (2001) [101]	5010	Valsartan vs. placebo	Creatinine > 2.5 mg/dL	Reduced HF hospitalization	ACEi intolerance in CRS type 2 and CRS type 4
	Candesartan		CHARM (2003) [102]	7601	Candesartan vs. placebo	Creatinine ≥ 3.0 mg/dL	Reduced CV death and HF hospitalization	CRS type 2 with HFrEF and CRS type 4
			CHARM-Preserved (2003) [103]	3023	Candesartan vs. placebo	Creatinine ≥ 3.0 mg/dL	Reduced HF hospitalization	Selected CRS with HFpEF
ARNI	Sacubitril/ valsartan	Neprilysin inhibition + ARB	PARADIGM-HF (2014) [104]	8442	ARNI vs. enalapril	eGFR < 30 mL/min	Reduced CV death and HF hospitalization	Preferred RAAS therapy in CRS type 2 with HFrEF
			PARAGON-HF (2019) [105]	4822	ARNI vs. valsartan	eGFR < 30 mL/min	Trend toward fewer HF hospitalizations	Selected CRS type 2 with HFpEF

Table 2. *Cont.*

Class of Drug/ Intervention	Drug or Strategy	Mechanism of Action	Trial (Year)	No. of Patients	Intervention	Kidney Exclusion Criteria	Key Findings	Clinical Use in Cardio-Renal Syndrome
Beta-blocker	Bisoprolol	β1-adrenergic blockade	CIBIS-II (1999) [106]	2647	Bisoprolol vs. placebo	Severe CKD excluded	Reduced all-cause mortality	Stable CRS type 2 with HFrEF
	Metoprolol CR/XL		MERIT-HF (1999) [107]	3991	Metoprolol vs. placebo	Severe CKD excluded	Reduced mortality and HF hospitalization	CRS type 2 with stable hemodynamics
	Carvedilol		COPERNICUS (2002) [108]	2289	Carvedilol vs. placebo	Creatinine > 2.8 mg/dL	Improved survival	Advanced CRS type 2 with careful titration
	Various		J-DHF (2013) [109]	245	Beta-blocker vs. standard care	Advanced CKD excluded	No mortality benefit	Limited role in CRS type 2 with HFpEF
MRA	Eplerenone	Selective aldosterone blockade	EPHESUS (2003) [110]	6632	Eplerenone post-MI	Creatinine > 2.5 mg/dL	Reduced mortality	CRS type 2 with HFrEF with potassium monitoring
			EMPHASIS-HF (2011) [111]	2737	Eplerenone vs. placebo	eGFR < 30 mL/min	Reduced CV death and HF hospitalization	Early CRS type 2 with HFrEF
	Spironolactone	Aldosterone receptor antagonism	RALES (1999) [112]	1663	Spironolactone vs. placebo	Creatinine > 2.5 mg/dL	Reduced mortality	CRS type 2 with HFrEF with potassium monitoring
		Aldosterone receptor antagonism	TOPCAT (2014) [113]	3445	Spironolactone vs. placebo	Creatinine ≥ 2.5 mg/dL	Reduced HF hospitalization	Selected CRS type 2 with HFpEF
			ATHENA-HF (2017) [114]	360	High-dose spironolactone (100 mg/day) vs. usual care in acute decompensated HF	eGFR < 30 mL/min/1.73 m^2 or serum potassium > 5.0 mmol/L	No improvement in NT-proBNP levels or clinical congestion at 96 h	Limited role for early high-dose spironolactone in acute CRS type 1
Non-steroidal MRA	Finerenone	Selective mineralocorticoid receptor antagonism	FIDELITY (2022) [115]	13,171	Finerenone vs. placebo	eGFR < 25 mL/min	Reduced renal and CV outcomes	CRS type 2 and 4 with diabetic CKD
			FINEARTS-HF (2024) [116]	~6000	Finerenone vs. placebo	eGFR < 25 mL/min	Reduced HF events	CRS type 2 with HFpEF
Loop diuretics	Furosemide	Na-K-2Cl cotransporter inhibition	DOSE (2011) [50]	308	High vs. low IV dose	Creatinine > 3.0 mg/dL	Similar efficacy, transient renal dysfunction	First-line decongestion in CRS type 1
Thiazides	Hydrochlorothiazide	Distal NaCl cotransporter inhibition	CLOROTIC (2023) [117]	230	Add-on thiazide	eGFR < 20 mL/min	Improved decongestion	Diuretic resistance in CRS type 1
Carbonic anhydrase inhibitor	Acetazolamide	Proximal bicarbonate reabsorption inhibition	ADVOR (2022) [92]	519	Add-on acetazolamide	eGFR < 20 mL/min	Faster and more complete decongestion	CRS type 1 with volume overload
Vasopressin antagonist	Tolvaptan	V2 receptor antagonism	EVEREST (2007) [118]	4133	Tolvaptan vs. placebo	Severe CKD excluded	Improved congestion, no mortality benefit	Hyponatremic or refractory CRS type 1

Table 2. *Cont.*

Class of Drug/ Intervention	Drug or Strategy	Mechanism of Action	Trial (Year)	No. of Patients	Intervention	Kidney Exclusion Criteria	Key Findings	Clinical Use in Cardio-Renal Syndrome
SGLT2 inhibitor	Dapagliflozin		DECLARE-TIMI 58 (2019) [119]	17,160	Dapagliflozin vs. placebo	eGFR < 60 mL/min/ 1.73 m^2 at entry	Reduced hospitalization for heart failure; renal composite benefit, including reduced sustained eGFR decline	Diabetic CRS type 2
			DAPA-HF (2019) [73]	4744	Dapagliflozin vs. placebo	eGFR < 30 mL/min	Reduced CV death and HF hospitalization	CRS type 2 with HFrEF and CRS type 4
			DAPA-CKD (2020) [120]	4304	Dapagliflozin vs. placebo	eGFR < 25 mL/min/ 1.73 m^2	Reduced progression to kidney failure and cardiovascular death in patients with and without diabetes	CRS type 4 regardless of diabetic status
		Proximal sodium–glucose cotransport inhibition	DAPA ACT HF–TIMI 68 (2025) [121]	~2400	Early dapagliflozin vs. placebo in hospitalized HF	eGFR < 25 mL/min	Not significantly reduce the risk of cardiovascular death or worsening HF	CRS type 1 during HF hospitalization
	Empagliflozin		EMPA-REG OUTCOME (2015) [122]	7020	mpagliflozin vs. placebo	eGFR < 30 mL/min/ 1.73 m^2	Reduced cardiovascular mortality; slower progression of kidney disease, and reduced incidence or worsening nephropathy	Diabetic CRS type 2 and CRS type 4 with established cardiovascular disease
			EMPEROR-Reduced (2020) [123]	3730	Empagliflozin vs. placebo	eGFR < 20 mL/min	Reduced CV death or HF hospitalization. Slower eGFR decline	CRS type 2 with HFrEF and CRS type 4
			EMPEROR-Preserved (2021) [124]	5988	Empagliflozin vs. placebo	eGFR < 20 mL/min	Reduced HF hospitalization	CRS type 2 with HFpEF
			EMPA-KIDNEY (2022) [125]	6609	Empagliflozin vs. placebo	eGFR < 20 mL/min/ 1.73 m^2	Reduced risk of kidney disease progression or cardiovascular death in CKD patients with and without diabetes	CRS type 4 independent of diabetes
			EMPULSE (2022) [126]	530	Empagliflozin vs. placebo during AHF	eGFR < 20 mL/min	Improved clinical composite outcome	CRS type 1

Table 2. *Cont.*

Class of Drug/ Intervention	Drug or Strategy	Mechanism of Action	Trial (Year)	No. of Patients	Intervention	Kidney Exclusion Criteria	Key Findings	Clinical Use in Cardio-Renal Syndrome
GLP-1 receptor agonist	Semaglutide	GLP-1 receptor activation	STEP-HFpEF (2023) [127]	529	Semaglutide vs. placebo	eGFR < 30 mL/min	Improved symptoms and weight loss	Obese CRS type 2 with HFpEF
			SUSTAIN-6 (2016) [128]	3297	Semaglutide vs. placebo	eGFR < 30 mL/min	Reduced CV events	Diabetic CRS type 2
			FLOW (2024) [129]	3533	Semaglutide vs. placebo	eGFR < 25 mL/min	Reduced kidney failure and CV events	CRS type 4 with diabetic CKD
Ultrafiltration	Mechanical ultrafiltration	Extracorporeal fluid removal	UNLOAD (2007) [94]	200	Ultrafiltration vs. IV diuretics	Severe CKD excluded	Greater weight loss	Refractory CRS type 1
			RAPID-CHF (2005) [93]	40	Early ultrafiltration vs. standard diuretic therapy	Severe CKD excluded	Greater early fluid and weight loss without worsening renal function	Refractory CRS type 1
			CARRESS-HF (2012) [95]	188	Ultrafiltration vs. stepped pharmacologic care	Advanced CKD excluded	Worse renal outcomes	Refractory CRS type 1
			AVOID-HF (2016) [130]	224	Adjustable ultrafiltration vs. adjustable IV diuretics	Advanced CKD excluded	Trend toward fewer HF rehospitalizations; higher catheter-related adverse events	Refractory CRS type 1
Peritoneal dialysis	Chronic peritoneal dialysis	Continuous volume control	Courivaud et al. (2014) [131]	126	PD in refractory HF	ESRD	Reduced HF hospitalizations	End-stage CRS type 2 and 4
			Bertoli et al. (2014) [132]	48	PD	ESRD	Symptom improvement	End-stage CRS type 2 and 4
Cardiac resynchronization	CRT-D	Biventricular pacing	MADIT-CRT (2009) [133]	1820	CRT-D vs. ICD	Severe CKD excluded	Reduced HF events	CRS type 2 with HFrEF and electrical dyssynchrony
			RAFT (2010) [134]	1798	CRT-D vs. ICD	Severe CKD excluded	Reduced mortality and HF hospitalization	CRS type 2 with HFrEF and electrical dyssynchrony
Implantable defibrillator	ICD	Sudden cardiac death prevention	SCD-HeFT (2005) [135]	2521	ICD vs. placebo/ amiodarone	Advanced CKD excluded	Reduced all-cause mortality	CRS type 2 with HFrEF
Inotropes	Dopamine/ Nesiritide	Increased cardiac output	ROSE-AHF (2014) [136]	360	Inotropes vs. placebo	Advanced CKD excluded	No renal benefit	Refractory CRS type 1
	Levosimendan	Calcium sensitization	REVIVE (2013) [137]	600	Levosimendan vs. placebo	Severe CKD excluded	Rapid and sustained symptomatic improvement; increased cardiovascular adverse events	Refractory CRS type 1

Table 2. *Cont.*

Class of Drug/ Intervention	Drug or Strategy	Mechanism of Action	Trial (Year)	No. of Patients	Intervention	Kidney Exclusion Criteria	Key Findings	Clinical Use in Cardio-Renal Syndrome
Anemia and iron therapy	Ferric carboxymaltose	Iron repletion	FAIR-HF (2009) [138]	459	IV iron vs. placebo	Severe CKD excluded	Improved symptoms and exercise capacity	CRS type 2 and 4 with iron deficiency
			AFFIRM-AHF (2020) [139]	1132	IV iron vs. placebo	Severe CKD excluded	Reduced HF re-hospitalization	CRS type 2 and 4 with iron deficiency
	Darbepoetin alfa	Erythropoiesis stimulation	RED-HF (2013) [140]	2278	Darbepoetin vs. placebo	Severe CKD excluded	No CV benefit	Not recommended in CRS

ACEi: Angiotensin-converting enzyme inhibitor; AHF: Acute heart failure; ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor–neprilysin inhibitor; β1: Beta-1 adrenergic receptor; CKD: Chronic kidney disease; CRS: Cardio-renal syndrome; CRT-D: Cardiac resynchronization therapy with defibrillator; CV: Cardiovascular; DAPA-HF: Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; ICD: Implantable cardioverter–defibrillator; IV: Intravenous; MRA: Mineralocorticoid receptor antagonist; NT-proBNP: *N*-terminal pro-B-type natriuretic peptide; PD: Peritoneal dialysis; RAAS: Renin–angiotensin–aldosterone system; SGLT2 inhibitor: Sodium–glucose cotransporter 2 inhibitor; GLP-1 receptor agonist: Glucagon-like peptide-1 receptor agonist; V2 receptor: Vasopressin type 2 receptor.

9.6. Innovative Treatments in CRS

In recent years, basic and translational research has increasingly focused on emerging and experimental therapeutic pathways targeting the complex pathophysiology of CRS. These include strategies aimed at reducing oxidative stress and inflammation through targeted modulation of the inhibitor of kappa B (IκB)/nuclear factor kappa B (NF-κB) pathway, the Kelch-like ECH-associated protein 1 (Keap1)/nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, and their downstream genes. Other approaches focus on remodeling the gut microbiota. Linaclotide, a guanylate cyclase C agonist, has been shown to restore microbial dysbiosis in murine models of chronic kidney disease. In addition, modulation of non-coding RNAs has emerged as a potential therapeutic strategy. Clofibrate, a peroxisome proliferator-activated receptor alpha (PPARα) agonist, improves left ventricular function in rats with type 4 CRS [87]. Overall, this is a rapidly expanding field, and advances in translational medicine may enable the incorporation of novel therapeutic strategies for CRS in the coming years.

Numerous studies are currently evaluating new agents for the treatment of CRS. These include pharmacological therapies designed to induce vasodilation and monoclonal antibodies targeting inflammatory cytokines. Other strategies aim to enhance innate and humoral immunity to mitigate inflammation and endothelial dysfunction. Diuretic resistance represents another major area of investigation. Ongoing trials are assessing pharmacological agents that increase diuretic responsiveness, such as lysine chloride, as well as non-diuretic approaches to remove salt and water, including sodium-free peritoneal dialysate. Finally, several device-based therapies are under investigation. These devices aim to reduce cardiac preload and afterload, increase renal preload by improving renal artery perfusion, and decrease renal afterload either by facilitating renal venous outflow or by reducing intracapsular renal pressure [1].

10. Conclusions

CRS management poses multiple clinical challenges. Classification into five types is not always straightforward, and distinguishing true AKI from hemoconcentration-

related functional changes can be difficult [1,2,7,23,74]. Assessing fluid overload, individualizing diuretic therapy, and determining optimal decongestion rates remain challenging, though controlled rapid decongestion does not worsen renal prognosis or increase mortality [1,2,23,74].

Patient evaluation should integrate renal function with symptoms, vital signs, urine output, and CKD history, while excluding secondary causes such as persistent hypotension, nephrotoxics, or renovascular disease [1,2,23,74]. Multidisciplinary cardio-renal units and bedside echocardiography are key tools for prevention, early detection, and timely management of CRS [99–117,120,122,123,125–140].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcrm2010004/s1, Table S1: RIFLE, AKIN, KDIGO, and WRF classification.

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Abbreviations

The following abbreviations are used in this manuscript

CRS	Cardio-Renal Syndrome
HF	Heart Failure
CKD	Chronic Kidney Disease
ADQI	Acute Dialysis Quality Initiative
CV	Cardiovascular
AKI	Acute Kidney Injury
AHF	Acute Heart Failure
WRF	Worsening Renal Function
RIFLE	Risk Injury Failure Loss of Kidney Function and End-Stage Kidney Disease
AKIN	Acute Kidney Injury Network
KDIGO	Kidney Disease: Improving Global Outcomes
CHF	Congestive Heart Failure
EF	Ejection Fraction
RAAS	Renin–Angiotensin–Aldosterone System
GFR	Glomerular Filtration Rate
SNS	Sympathetic Nervous System
ATII	Angiotensin II
ACE	Angiontensin-Converting Enzyme
TNF-α	Tumor necrosis factor-α
ILE-1	Interleukin-1
ILE-6	Interleukin-6
CRP	C- Reactive protein
EPO	Erythropoietin
eGFR	Estimated Glomerular Filtration Rate
ECG	Electrocardiogram
GLS	Global Longitudinal Strain
PCPW	Pulmonary Capillary Wedge Pressure

IVC	Inferior Vena Cava
RVSI	Renal Venous Stasis Index
AVP	Arginin–Vasopresin
ANP	Atrial Natriuretic Peptide
BNP	Brain Natriuretic Peptide
VExUS	Venous Excess Ultrasound Score
POCUS	Point of Care Ultrasound
ESRD	End Stage Renal Disease
iSGLT2s	SGLT 2 Inhibitors
RASis	Renin–Angiotensin System Inhibitors
ACEis	Angiotensin-Converting Enzyme Inhibitors
ARBs	Angiotensin Receptor Blockers
MRAs	Mineralocorticoid Receptor Antagonists
aGLP-1s	Glucagon-Like Peptide 1 Agonists
RRRT	Renal Replacement Therapy
NSAiDs	Non Steroidal Antiinflamatory Drugs
LVEF	Left Ventricle Ejection Fraction

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