

Article information

DOI: 10.63475/yjm.v5i1.0282

Article history:

Received: 23 February 2026

Accepted: 04 March 2026

Published: 05 April 2026

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How to cite this article

Habas E, Habas A, Bhagi M, Habas E, Rayani A. Chronic renocardiac syndrome (type 4 cardiorenal syndrome): A comprehensive review. *Yemen J Med.* Published online April 05, 2026. doi: 10.63475/yjm.v5i1.0282:1-8.

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Review Article

Chronic Renocardiac Syndrome (Type 4 Cardiorenal Syndrome): A Comprehensive Review

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ABSTRACT

The five-subtype classification of cardiorenal syndrome (CRS), established a decade ago, provides a crucial framework for understanding the interdependent relationship between the heart and kidneys. Chronic renal cardiac syndrome (cRCS), categorized as type 4 CRS, is characterized by primary chronic kidney disease (CKD) that leads to persistent cardiac dysfunction, associated with markedly increased morbidity and mortality rates. The elevated risk is attributed to a multifaceted pathophysiological mechanism wherein advancing renal dysfunction induces metabolic anomalies, persistent inflammation, neurohormonal stimulation, and expedited vascular pathology, culminating in considerable structural harm to the heart. CKD has diverse cardiac effects, including systolic heart failure, diastolic dysfunction, arrhythmias, valvular calcification, and sudden cardiac death. Historically, management focused on support via volume control, dialytic optimization, and neurohormonal blockade. The therapeutic landscape for cRCS has undergone a notable paradigm shift. The use of sodium-glucose cotransporter-2 (SGLT2) inhibitors and non-steroidal mineralocorticoid receptor antagonists (MRAs) as critical, disease-modifying therapies offers a substantial opportunity to improve cardiovascular and renal outcomes. This review, current through December 2025, synthesizes contemporary epidemiology, pathophysiology, and evolving diagnostic approaches for cRCS, with an emphasis on evidence-based treatment strategies. An early and integrated cardiorenal management strategy is crucial for addressing the substantial and growing public health challenge posed by CKD.

Key words: Cardiorenal syndrome, type 4 CRS, chronic kidney disease, heart failure, SGLT2 inhibitors, finerenone, mineralocorticoid receptor antagonist, cardiorenal protection, biomarkers

INTRODUCTION

The intricate and bidirectional connection between the cardiovascular and renal systems is a fundamental concept in medicine. [1, 2] Chronic kidney disease (CKD) is not merely a comorbidity but a powerful and independent risk multiplier for cardiovascular disease (CVD), a relationship formalized as chronic renocardiac syndrome (cRCS), or type 4 cardiorenal syndrome (CRS). [2, 3] Consensus definitions classify CRS into five subtypes according to the primary organ affected and the duration of the condition, with cRCS specifically characterized as chronic cardiac dysfunction resulting from primary CKD. The clinical burden is significant; individuals with CKD experience a mortality risk that is up to ten times greater than that of the general population, with CVD responsible for more

than half of these fatalities. [2, 4] The increased CVD risk appears early in the continuum of CKD, frequently occurring before the onset of end-stage kidney disease (ESKD). [5] The spectrum of CVD in CKD is extensive, including heart failure, coronary artery disease, arrhythmias, valvular calcification, and sudden cardiac death. [4, 6, 7] Historically, management has predominantly been reactive, emphasizing the control of conventional risk factors and the management of complex complications.

This review seeks to offer a current synthesis of cRCS. This discussion will address the evolving epidemiology, the intricate pathophysiological mechanisms connecting renal decline to cardiac injury, contemporary diagnostic and prognostic methods, and, importantly, the revised, evidence-based therapeutic strategies that constitute the foundation of proactive cardiorenal protection. A comprehensive literature search was conducted using PubMed, EMBASE, and Google Scholar for original research, reviews, and guideline statements published between January 2010 and December 2025, utilizing key terms including "type 4 CRS," "chronic renocardiac syndrome," "CKD and heart failure," "SGLT2 inhibitors," "finerenone," and "cardiorenal biomarkers."

EPIDEMIOLOGY

CKD constitutes a significant global public health issue, impacting around 10% of the global population. The prevalence is anticipated to increase, driven by aging populations and the rising incidence of diabetes mellitus (DM) and hypertension. The 2024 International Society of Nephrology Global Kidney Health Atlas highlights significant disparities in care, indicating that access to kidney replacement therapy differs by a factor of 200 between high-income and low-income countries. [8]

Data from the 2023 US Renal Data System Annual Data Report indicate that the prevalence of CKD stages 1–4 in the United States has plateaued at approximately 14%. The total number of affected individuals remains significantly elevated. The convergence of CKD and CVD delineates the significant burden of cardiorenal syndrome (cRCS). The prevalence of CVD (including acute myocardial infarction, stroke, and HF) is 66.6% in adults with CKD, compared to 37.5% in those without. [9] Heart failure demonstrates a powerful graded relationship with CKD severity, with a prevalence nearing 28% in advanced CKD—approximately four-fold higher than in non-CKD populations. [9, 10] This synergistic relationship leads to increased risks of hospitalization, intensive care admission, and mortality, establishing cRCS as a critical factor in healthcare utilization, costs, and adverse patient outcomes. [11]

CKD EFFECTS ON THE HEART

The cardiac effects of CKD are systemic, complex, and initiate early in the progression of the disease. Pathological left ventricular (LV) remodeling, which includes hypertrophy, interstitial fibrosis, diastolic dysfunction, and subsequent systolic impairment, is a key characteristic of cRCS. [12] A combination of pressure and volume overload, neurohormonal activation, and direct uremic and pro-fibrotic stimuli drives this process. In addition to classical LV failure, CKD independently increases the risk for various cardiac pathologies.

Right Ventricular (RV) Dysfunction and Pulmonary Hypertension

CKD is an established contributor to group 5 pulmonary hypertension, resulting in RV pressure overload, RV-pulmonary artery uncoupling, and RV systolic dysfunction, which serves as a significant independent predictor of mortality. [13, 14]

Coronary Microvascular Dysfunction

Alterations in the coronary microcirculation are significant contributors to angina and ischemia in the absence of obstructive epicardial disease, and they are strong predictors of adverse cardiovascular events. [15, 16]

Valvular Heart Disease

Calcific aortic and mitral valve disease manifests more frequently and at an earlier stage in CKD, primarily due to dysregulated mineral bone metabolism. Tricuspid regurgitation frequently occurs, typically as a consequence of pulmonary hypertension. [17, 18] The 2023 ESC Guidelines for Cardiovascular Disease in CKD offer targeted recommendations for the management of valve disease within this intricate population. [19]

Arrhythmias and Sudden Cardiac Death

The prevalence of atrial fibrillation is 2 to 4 times higher in CKD patients, presenting unique challenges for stroke prevention. [20] The risk of sudden cardiac death escalates steeply with declining renal function, reaching an annual incidence of up to 7% in dialysis patients. The etiology is multifactorial, involving electrolyte shifts, autonomic dysfunction, and structural heart disease, with recent data highlighting a prominent role for bradyarrhythmias. [21, 22] Emerging insights from wearable continuous ECG monitors are refining our understanding of the arrhythmic burden in this group. [23]

PATHOPHYSIOLOGY OF CHRONIC RENOCARDIAC SYNDROME

The pathogenesis of cRCS involves a self-sustaining, detrimental loop that begins with renal failure (**Figure 1**). As the glomerular filtration rate (GFR) drops below roughly 60 mL/min/1.73 m², a series of interrelated pathogenic events is initiated.

Neurohormonal Activation

Sustained and maladaptive activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) promotes systemic vasoconstriction, sodium retention, inflammation, and direct myocardial fibrosis.

Metabolic and Biochemical Derangements

- **Fluid Overload and Hypertension:** Contribute to both pressure and volume overload, directly driving concentric and eccentric LV hypertrophy.
- **Disordered Mineral Bone Metabolism:** Hyperphosphatemia, increased fibroblast growth factor 23 (FGF-23), and a lack of the renoprotective protein Klotho directly induce vascular and valvular calcification, cardiomyocyte hypertrophy, and interstitial fibrosis. [24]

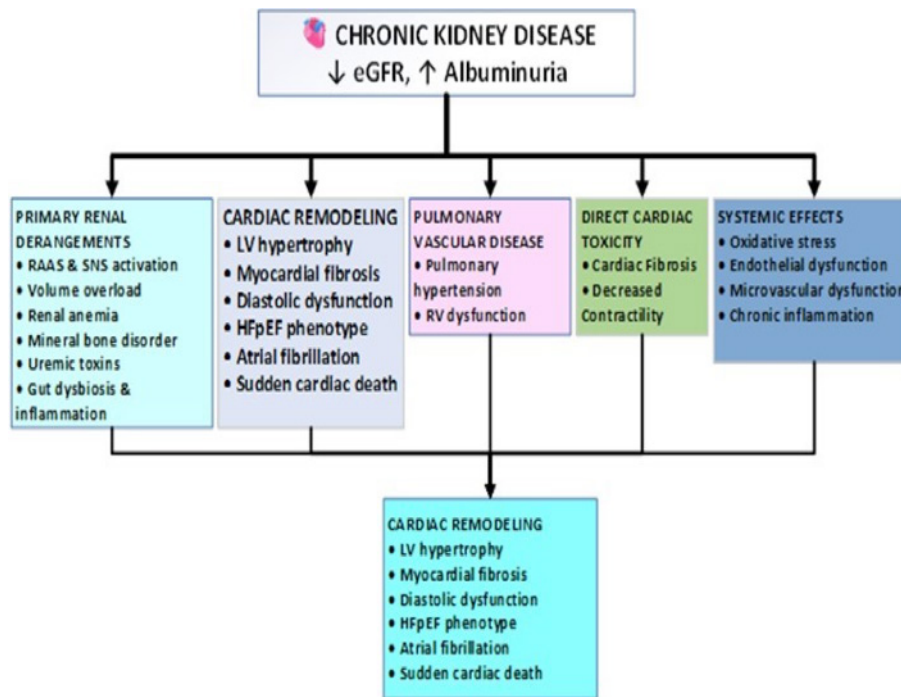


Figure 1: Pathophysiological mechanisms of chronic renal-cardiac syndrome. A conceptual diagram illustrating the central role of CKD. Arrows depict how declining renal function activates key pathophysiological drivers: RAAS/SNS Activation, Fluid Overload/hypertension, Uremic Toxins & Oxidative Stress, Chronic Inflammation, and Disordered Mineral Bone Metabolism (FGF-23/ \uparrow PO₄/Klotho deficiency). These drivers converge to cause “Cardiac Structural & Functional Remodeling” (hypertrophy, fibrosis, dysfunction), leading to the clinical syndromes of Heart Failure, Arrhythmias, and Ischemia. Contemporary therapeutic pillars (SGLT2 inhibitors, Finerenone) are shown to exert inhibitory effects across multiple pathways.

Anemia of Chronic Disease

Decreases systemic oxygen transport capacity, prompting compensatory high-output cardiac remodeling and elevating myocardial workload.

Uremic Toxemia and Oxidative Stress

The buildup of retained solutes, especially protein-bound uremic toxins (such as indoxyl sulfate and p-cresyl sulfate), leads to significant endothelial dysfunction, oxidative stress, and increased inflammation. [25]

Chronic Inflammation

A condition of chronic, low-grade inflammation is a defining characteristic of CKD, caused by diminished clearance of pro-inflammatory cytokines, endotoxin exposure due to gut dysbiosis, and, in dialysis patients, recurrent blood-membrane contact. This inflammatory environment hastens atherosclerosis, fosters myocardial fibrosis, and exacerbates insulin resistance.

The interplay of these variables results in the distinctive cardiac structural phenotype of cRCS: LV hypertrophy, diastolic dysfunction, microvascular rarefaction, and widespread interstitial fibrosis. This pathological substrate predisposes individuals to the clinical signs of heart failure, arrhythmia, and sudden death.

PRESENTATION AND DIAGNOSIS OF CHRONIC RENOCARDIAC SYNDROME

The clinical presentation of cRCS is frequently insidious and non-specific, characterized by symptoms of progressive CKD—such as fatigue, anorexia, pruritus, and fluid overload—that overlap

with and are worsened by concurrent cardiac decompensation (exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema). Diagnosis necessitates a strong index of suspicion and relies on the synthesis of clinical evaluation, specific laboratory tests, and thorough imaging studies.

Essential Diagnostic Workup

This involves evaluating renal function (serum creatinine, estimated GFR, urinalysis for albuminuria), electrolytes, complete blood count, and cardiac assessment. Transthoracic echocardiography serves as the primary imaging technique essential for evaluating LV mass and geometry, systolic and diastolic function, valvular disorders, pulmonary artery pressures, and pericardial conditions.

Evolving Role of Biomarkers

Biomarkers are increasingly important for risk stratification and prognostication.

Established Prognostic Markers

Cardiac troponin T (cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are significant predictors of cardiovascular mortality in CKD, irrespective of their diagnostic constraints for acute coronary syndromes in this demographic. [26, 27] Serial measurements can monitor disease activity and therapeutic response.

Emerging Biomarkers

Novel markers less influenced by renal clearance are gaining clinical traction.

Soluble ST2 and Growth Differentiation Factor-15 (GDF-15)

These biomarkers indicate myocardial fibrosis and cellular stress or inflammation, respectively. They offer significant independent prognostic insights for heart failure hospitalization and mortality in CKD, potentially aiding in the determination of therapeutic intensity. [28]

Cystatin C

Cystatin C serves not only as a sensitive marker of GFR but is also independently linked to cardiovascular risk and LV mass.

The future of risk assessment in cRCS is likely to involve integrated multi-marker panels and possibly novel proteomic or metabolomic signatures.

THERAPY OF CHRONIC RENOCARDIAC SYNDROME

The management of cRCS has transitioned decisively from passive, complication-focused support to active, guideline-directed disease modification and cardiorenal protection.

Foundation of Pharmacotherapy: The New Pillars

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

Empagliflozin and dapagliflozin signify a significant advancement in therapy. Recent landmark outcome trials (CREDESCENCE, DAPA-CKD, EMPEROR-Preserved/Reduced) have demonstrated that these agents significantly reduce the risk of cardiovascular death and hospitalization for heart failure, while also slowing the progression of CKD in patients, regardless of ejection fraction or diabetes status. [29, 30] The benefits are ascribed to pleiotropic effects, which encompass modest diuresis, enhanced myocardial energetics, diminished inflammation and fibrosis, and lowered intraglomerular pressure. SGLT2 inhibitors are regarded as the primary treatment for cRCS and should be commenced promptly in eligible patients.

Non-Steroidal Mineralocorticoid Receptor Antagonists (MRAs)

Finerenone, a selective non-steroidal MRA, has shown substantial reductions in cardiovascular events and CKD progression among patients with CKD and type 2 diabetes in the FIDELIO-DKD and FIGARO-DKD trials, exhibiting a more advantageous hyperkalemia profile compared to conventional steroidal MRAs such as spironolactone. [31] This therapy is essential for achieving comprehensive cardiorenal protection. To facilitate comparison of the evidence supporting these foundational therapies, **Table 1** summarizes the key landmark trials, including populations, outcomes, benefits, and notable limitations.

Limitations of Key Trial Evidence and Remaining Knowledge Gaps

Citations of the major trials supporting SGLT2 inhibitors, such as DAPA-CKD (eGFR 25–75 mL/min/1.73 m² with albuminuria, including notable non-diabetic subgroups) and EMPA-KIDNEY (eGFR ≥20 to <45 or ≥45 to <90 with high albuminuria, approximately 54% non-diabetic), as well as finerenone (FIDELIO-DKD and FIGARO-DKD, primarily focused on type 2 diabetes, eGFR 25–90 ranges with

albuminuria), are substantial. Earlier studies, however, have underrepresented non-diabetic patients and those with advanced chronic CKD, as evidenced by limited enrollment of individuals with an eGFR below 25 to 30 mL/min/1.73 m² in certain cohorts. This limitation may diminish the generalizability of findings to severe stages or non-diabetic etiologies. Recent meta-analyses and real-world data from 2024 to 2025 confirm significant benefits in non-diabetic CKD, while noting lower initiation rates in advanced stages due to concerns such as initial declines in eGFR or volume effects. However, chronic benefits frequently endure. Significant gaps exist in the research concerning underrepresented subgroups in advanced CKD/ESKD, the long-term safety profile in non-diabetic lean patients, and the necessity for additional data on combination therapies or extended indications. For instance, the CONFIDENCE trial, scheduled for 2025, aims to demonstrate the additive reduction in urinary albumin-to-creatinine ratio with the combination of finerenone and empagliflozin in patients with type 2 diabetes and CKD. Future research should address these factors to enhance application across various cRCS populations.

Renin-Angiotensin System Inhibitors (RASi)

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are fundamental treatments for hypertension management, proteinuria reduction, and adverse remodeling mitigation. The introduction of new potassium binders, such as patiromer and sodium zirconium cyclosilicate, enables the safe and sustained uptitration of RAS inhibitors and MRAs by effectively managing hyperkalemia.

Beta-Blockers

Beta-blockers, such as carvedilol, bisoprolol, and metoprolol succinate, are recommended for patients with reduced ejection fraction (HFrEF) and chronic heart failure with reduced ejection fraction (cRCS), as they enhance survival rates and decrease hospitalizations due to heart failure.

Dialysis and Precision Volume Management

Achieving and sustaining true euvoemia is a fundamental treatment objective that directly influences cardiac load. This requires advancing from subjective clinical evaluation to the integration of objective instruments such as bioimpedance spectroscopy and lung ultrasound.

Hemodialysis

The CONVINCe trial (2023) showed a survival advantage for high-dose hemodiafiltration (HDF) over high-flux hemodialysis, endorsing its preferential application when accessible. [32] The continuous emphasis is on enhancing hemodynamic tolerance via individualized dialysate sodium and temperature profiling, alongside sophisticated biofeedback systems.

Peritoneal Dialysis (PD)

PD offers continuous, gradual ultrafiltration, which may promote greater hemodynamic stability and preserve residual renal function longer. The choice of dialysis modality should be individualized based on patient preferences, lifestyle, and specific cardiorenal physiology.

Table 1: Summary of landmark trials for disease-modifying therapies in cRCS.

Drug/class	Key trials (year)	Population (key inclusion)	eGFR range (mL/min/1.73 m ²)	Primary/composite outcomes (key results)	Key benefits (HR or reduction)	Main limitations/notes
SGLT2 inhibitors (Canagliflozin)	CREDESCENCE (2019)	T2DM + CKD with albuminuria	30-90	Composite: ESKD, sustained $\geq 57\%$ eGFR decline, renal/cardiovascular death (30% relative risk reduction)	Kidney progression $\downarrow 30\%$; cardiovascular events $\downarrow 20\%$; HF hospitalization $\downarrow 39\%$	T2DM only; limited non-diabetic; eGFR ≥ 30 (no < 30 inclusion)
SGLT2 inhibitors (Dapagliflozin)	DAPA-CKD (2020)	CKD \pm T2DM, albuminuria ≥ 200 mg/g	25-75	Composite: $\geq 50\%$ eGFR decline, ESKD, renal/cardiovascular death (39% reduction); cardiovascular death/HHF (29% reduction)	Kidney outcomes $\downarrow 39\%$; all-cause mortality $\downarrow 31\%$ benefits in non-diabetic ($\sim 32\%$)	Limited advances CKD (< 25 underrepresented); initial eGFR dip concern in real-world use
SGLT2 inhibitors (Empagliflozin)	EMPA-KIDNEY (2022)	CKD \pm T2DM, broad albuminuria criteria	≥ 20 to < 45 (or ≥ 45 to < 90 with high uACR)	Kidney progression or cardiovascular death (28% reduction); board benefits across eGFR/albuminuria	Kidney progression $\downarrow 28\%$ - 29% ; consistent in non-diabetic ($\sim 54\%$); eGFR < 30 subgroup benefit	Fewer cardiovascular death/HHF events; lower albuminuria subgroups had slower progression
Non-steroidal MRA (Finerone)	FIDELIO-DKD (2020)	T2DM + CKD with albuminuria	25-75 (dose-adjusted)	Composite: $\geq 40\%$ eGFR decline, ESKD, renal death (18% reduction); cardiovascular composite (14% reduction)	Kidney progression $\downarrow 18\%$ cardiovascular events $\downarrow 14\%$; Hyperkalemia manageable	T2DM only; Advanced CKD limited; hyperkalemia risk (higher discontinuation)
Non-steroidal MRA (Finerone)	FIGARO-DKD (2021)	T2DM + earlier CKD (broader albuminuria)	25-90	Cardiovascular composite (13% reduction, driven by HF hospitalization $\downarrow 29\%$); kidney composite (non-significant)	Cardiovascular events $\downarrow 13\%$; HF hospitalization $\downarrow 29\%$; ESKD $\downarrow 36\%$ in exploratory analyses	Kidney primary not significant; T2DM only; higher eGFR focus
Combination (Finerone empagliflozin)	CONFIDNECE (2025)	T2DM + CKD with albuminuria	30-90	Relative UACR change at 180 days (additive reduction vs. monotherapy)	UACR $\downarrow 29\%$ - 32% greater than monotherapy; consistent safety	Surrogate endpoint (UACR); short-term (180 days); additive hyperkalemia risk possible

CKD, chronic kidney disease; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; T2DM, type 2 diabetes mellitus; UACR, urine albumin/creatinine ratio.

Imperative of Integrated Care

The effective management of cRCS requires a multidisciplinary approach involving both cardiology and nephrology. Specialized cardiorenal clinics or integrated care pathways facilitate prompt initiation and adjustment of protective therapies, effective management of complex comorbidities (such as arrhythmias and valvular disease), and ongoing patient education, ultimately enhancing outcomes and quality of life. [19]

PREVENTION

The prevention of cRCS relies on early intervention within the cardiorenal continuum, shifting the focus of management from treating established disease to preserving organ function.

Early Detection of CKD and Proactive Management of Primary Diseases

Implement systematic screening for albuminuria and estimate GFR in high-risk populations, alongside rigorous management of diabetes, hypertension, and glomerulonephritis.

Proactive Pharmacologic CRS

Early initiation of SGLT2 inhibitors and/or finerenone in eligible patients with CKD, before the development of overt cardiac dysfunction or advanced renal failure, aims to alter the underlying disease trajectory.

Comprehensive Lifestyle Modification

Encouragement of heart-healthy dietary patterns (e.g., Mediterranean, DASH, plant-based), regular physical activity as tolerated, smoking cessation, and weight management.

Structured Multidisciplinary Care Models

Establishing specialized cardiorenal clinics or virtual care coordination to systematically implement preventive strategies and ensure effective follow-up.

CONCLUSIONS

Chronic renal-cardiac syndrome poses a significant clinical challenge at the intersection of nephrology and cardiology. The pathophysiology is characterized by a complex cycle of neurohormonal, metabolic, and inflammatory interactions between the failing kidney and the heart. The diagnostic strategy should be integrative, utilizing clinical evaluation, advanced imaging, and developing biomarker panels. The therapeutic paradigm has undergone a fundamental transformation. The introduction of SGLT2 inhibitors and non-steroidal MRAs marks a significant advancement, offering agents that demonstrate efficacy in simultaneously safeguarding both cardiac and renal functions, thereby modifying the previously unchangeable prognosis of cRCS. An early and sustained proactive management strategy, integrated through collaborative cardio-nephrology care, is now essential to mitigate the significant personal and societal burden of CKD. Future research will concentrate on innovative anti-inflammatory and anti-fibrotic targets, senolytic

therapies, and precision medicine strategies to enhance personalization and outcomes for this high-risk population.

AUTHORS' CONTRIBUTION

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

SOURCE OF FUNDING

None.

CONFLICT OF INTEREST

None.

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