Review Article

The Interplay between Chronic Kidney Disease and Cardiovascular Disease: Mechanisms, Biomarkers, and Management

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ABSTRACT

Chronic kidney disease (CKD) and cardiovascular disease (CVD) share a bidirectional relationship that accelerates global morbidity and mortality. This review synthesizes the mechanisms underlying cardiorenal syndrome, highlights advance in diagnostic biomarkers and evaluates both established and emerging therapeutic strategies for managing the CKD–CVD interplay. Literature from PubMed, Scopus, and Google Scholar databases (2000-2025) was systematically searched for human studies on heart–kidney physiology, CKD-driven cardiovascular complications, biomarker development, and therapeutic interventions. CKD significantly increases cardiovascular risk via pathophysiological processes including persistent hypertension, oxidative stress, systemic inflammation, endothelial dysfunction, vascular calcification, and uremic toxin accumulation. The spectrum of cardiorenal syndrome (types 1–5) underscores the intricacy of cardiorenal crosstalk. Advances in biomarker research, notably serum creatinine, cystatin C (CysC), neutrophil gelatinase-associated lipocalin (NGAL), and metabolomic profiling have enabled more precise risk assessment and early detection. Traditional approaches focus on blood pressure control and proteinuria reduction through renin–angiotensin–aldosterone system (RAAS) blockade, mineralocorticoid antagonism, and diuretic use. Novel therapies seek to target disease drivers including fibrotic transformation, inflammation, and gut–kidney axis disruption. The reciprocal relationship between CKD and CVD demands early recognition, adoption of innovative biomarkers, and application of integrative management strategies. Enhancing disease awareness and fostering multidisciplinary care are vital to alleviating the global impact of cardiorenal syndrome.

Key words: Chronic kidney disease, cardiovascular disease, cardiorenal syndrome, inflammation, biomarkers, management

The kidneys and heart are interconnected, with the kidneys filter the waste and extra fluid from the blood to create urine, control blood pressure, and maintain electrolyte balance. This interdependence is crucial for overall health, as the failure of one organ can have a determined effect on the others [1]. Chronic kidney disease (CKD) and cardiovascular disease (CVD) are significantly increasing the risk of heart attacks, heart failure, and death. CKD can lead to arterial calcification and fibrosis, increasing the burden of cardiovascular events and developing CVD-related comorbidities like anemia [2].

Urine formation occurs through three fundamental processes: tubular secretion, tubular reabsorption, and glomerular filtration in the nephron [3]. Kidneys regulate extracellular fluid volume (ECFV) homeostasis, which is essential for blood pressure control [4]. Renin, angiotensin I, and angiotensin II are key components of kidney function, and when one organ malfunctions, another develops chronic affection, such as CVD and CKD [5] CKD-specific changes, such as oxidative stress, chronic inflammation, and uremic toxin accumulation, raise cardiovascular risk. Vascular changes, including atherosclerosis and vascular calcification, have significant impacts on the relationship between CKD and cardiovascular mortality. Endothelial dysfunction, characterized by decreased synthesis of vasodilators and increased production of vasoconstrictors, directly affects CV morbidity and death in CKD patients [6].

In CKD, hypertension is caused by fluid overload linked to salt retention and sympathetic hyperactivity, while kidney impairment puts the heart under stress, increasing the risk of heart disease. Cardiorenal syndrome is a harmful feedback loop that occurs when an issue with either the heart or the kidneys interferes with the other's normal function [7].

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Cardiorenal syndrome (CRS) can be classified into five forms: acute, chronic, acute, chronic, and secondary [8]. Chronic CRS is a long-term heart condition that gradually impairs kidney function over time, while acute CRS occurs suddenly and may be curable [8]. To reduce mortality due to CKD the early diagnosis is crucial [8]. Diagnostic biomarkers, such as uromodulin, kidney injury molecule-1, and metabolomics, help identify the disease and predict future clinical events. Treatment strategies focus on reducing disease progression, controlling its consequences, and enhancing quality of life [9]. CKD and CVD are interrelated, with one affecting the other and raising the death risk. In 2017, 1.2 million people died due to CKD and is expected to rise by 2040 to the fifth most common cause of death [10].

METHODOLOGY

A systematic search of PubMed, Scopus, and Google Scholar covered January 2000 to August 2025 using terms: "chronic kidney disease," "cardiorenal syndrome," "cardiovascular disease," "biomarkers," and "management." English Language human studies (trails, reviews, guidelines) were included; animal/in vitro studies, case reports and abstracts excluded.

Inclusion and Exclusion Criteria

Studies were included if they: (i) involved human participants; (ii) addressed the pathophysiological interaction between CKD and CVD; (iii) evaluated diagnostic or prognostic biomarkers; or (iv) discussed pharmacological, non-pharmacological, or emerging management strategies. Eligible article types comprised randomized controlled trials, observational studies, systematic and narrative reviews, and clinical guidelines.

Studies were excluded if they: (i) were limited exclusively to animal or in vitro models; (ii) consisted of single case reports, editorials, or conference abstracts; or (iii) lacked clinical relevance to cardiorenal disease.

Study Selection and Data Synthesis

Titles and abstracts were initially screened for relevance, followed by full-text evaluation of eligible articles. Reference lists of selected publications were manually searched to identify additional pertinent studies. Data were narratively synthesized and thematically organized into sections addressing disease mechanisms, biomarkers, and current and emerging management strategies.

RESULT AND DISCUSSION

Pathophysiological link between CKD and CVD:

CVD is a leading cause of death among individuals with CKD. The rising prevalence of both conditions worsens patient outcomes and increases healthcare costs. Research indicates that CKD is a separate risk factor for CVD, largely due to oxidative stress, persistent inflammation, and accumulation of uremic toxins. Vascular abnormalities, particularly atherosclerosis and vascular calcification (VC), play a central role in linking CKD with cardiovascular mortality. While VC mainly affects the medial layer of blood vessels, endothelial dysfunction and other risk factors accelerate atherosclerosis, leading to vascular damage. Current research indicates that VC is a complex, cell-mediated process, often triggered by mineral imbalances such as hyperphosphatemia, which drive vascular smooth muscle cells to adopt an osteoblast-like phenotype [11]. Table No. 1 give the pathophysiological elements for CKD and CVD.

Table No 1: Pathophysiological mechanisms linking CKD and CVD.

Mechanism	Description	Key Effects / Outcomes	References
Oxidative Stress	Oxidative stress is a major contributor to CKD-induced vascular injury.	Promotes vascular dysfunction and CVD progression.	[11]
Endothelial Dysfunction (ED)	ED is an early and critical step in atherosclerosis. Endothelium releases relaxing factors like nitric oxide (NO).	↓ NO due to L-arginine deficiency, reduced eNOS activity, cofactors shortage, ↑ ADMA → impaired vascular tone, loss of homeostasis → arteriosclerosis.	[13], [14]. [15]
RAAS Activation	Overactivation of RAAS increases blood pressure and induces cardiac/renal damage.	Causes vasoconstriction, sodium retention, LVH, myocardial remodeling → ↑ risk of CHF, arrhythmias, sudden death.	[16], [17]
Fluid Overload & Hypertension	Sodium retention + sympathetic hyperactivity in CKD lead to volume overload and high BP.	Stimulates renin release, ↑ Ang II → vasoconstriction, sodium reabsorption, impaired sodium excretion → persistent hypertension and CV risk.	[18]
Uremic Toxins & Vascular Calcification	Accumulation of solutes normally cleared by kidneys (middle molecules, protein-bound, small water-soluble).	UTs (Pi, PCS, IS, FGF23, hippuric acid, TMAO, ADMA, TNF-α, IL-6) induce VSMCs → osteoblast-like phenotype → Ca/PO_4 deposition → vascular calcification → arteriosclerosis.	[19], [20], [21], [22]

Oxidative Stress:

Oxidative stress denotes an imbalance between the generation and removal of reactive oxygen species (ROS). In mammalian cells, ROS are mainly generated in mitochondria during aerobic respiration, but additional sources include enzymes such as NAD(P)H oxidase, xanthine oxidase, lipoxygenases, and cyclooxygenases, as well as non-enzymatic pathways in vascular tissues. While ROS play a role in normal defence mechanisms, excessive levels damage proteins, lipids, and nucleic acids, impairing tissue function. Elevated oxidative stress is frequently observed in renal disorders, with markers such as malondialdehyde and plasma F2-isoprostanes often elevated in those with compromised renal function. Oxidative modification of lipoproteins, particularly LDL, results in higher oxidized LDL levels, which contribute to atherosclerosis and ultimately raise the risk of CVD [11, 12].

Endothelial Dysfunction:

Endothelial dysfunction (ED) is an early and key event in atherosclerosis and serves as a major pathophysiological link between CKD and the heightened cardiovascular risk seen in these patients [13]. The endothelium generates several relaxing factors, including nitric oxide (NO), that have a crucial function in preserving vascular tone, structural integrity, and overall vascular homeostasis [14]. Endothelial cells synthesize nitric oxide (NO) through the activity of endothelial nitric oxide synthase (eNOS) on L-arginine, producing NO and L-citrulline. Impaired NO production can result from L-arginine deficiency, reduced eNOS activity, limited cofactors, or increased concentrations of endogenous NOS inhibitors.

Among these, asymmetric dimethylarginine (ADMA) acts as a strong competitive inhibitor, significantly lowering NO availability [13], [15]. Even in the early stages of CKD, patients show reduced nitric oxide (NO) levels. This deficiency arises from limited L-arginine availability and increased asymmetric dimethylarginine (ADMA), an endogenous NOS inhibitor. Reduced NO disrupts vascular tone, homeostasis, and structural integrity, leading to endothelial dysfunction and progression to arteriosclerosis [13].

Activation of the Renin-Angiotensin-Aldosterone System (RAAS):

The renin–angiotensin–aldosterone system (RAAS) is vital for regulating blood pressure. However, under certain conditions, its overactivation can cause cardiovascular injury, including coronary heart disease (CHD), and may progress to chronic heart failure (CHF). Excessive RAS activity is now recognized as a pathogenic factor in several clinical conditions, such as coronary atherosclerosis, myocardial infarction, CHF, left ventricular hypertrophy, diabetic and non-diabetic nephropathies, renal artery stenosis, and hypertension [16]. The RAAS influences kidney function to regulate blood pressure and intravascular volume. Activation of renal AT1 receptors initiates several responses, most notably increased blood pressure through vasoconstriction of systemic arteries.

RAAS activity also impacts sodium reabsorption and renal hemodynamics. Stimulation of the angiotensin II (AII) signaling pathway induces major changes in the myocardium, leading to left ventricular hypertrophy (LVH). LVH is a significant risk factor for congestive heart failure (CHF), resulting from impaired diastolic filling or reduced systolic function, and it heightens the likelihood of life-threatening arrhythmias and sudden cardiac death [17].

Fluid overload and hypertension:

In CKD, hypertension arises from fluid overload due to sodium retention and heightened sympathetic activity. Persistent high blood pressure increases cardiovascular morbidity and mortality. CKD is strongly associated with overactivation of the RAAS. decreased blood flow downstream of sclerosed glomeruli in capillaries that pertubule stimulates renin release, elevating angiotensin II levels. Angiotensin II raises blood pressure through vasoconstriction, enhances sodium reabsorption in the PCT and collecting duct via aldosterone, and maintains glomerular filtration by increasing systemic arterial pressure. Impaired sodium excretion, coupled with reduced total GFR, further promotes fluid overload and hypertension [18].

Uremic toxins and vascular calcification:

Uremia, a hallmark of CKD, results from the buildup of solutes normally eliminated by the kidneys. As renal function progressively declines, these toxins accumulate. Uremic toxins are generally divided into three groups: middle molecules, protein-bound compounds, and freely water-soluble low–molecular-weight solutes [19].

Common uremic toxins (UTs) include inorganic phosphate (Pi), para-cresyl sulfate (PCS), indoxyl sulfate (IS), fibroblast growth factor-23 (FGF23), hippuric acid, trimethylamine N-oxide (TMAO), ADMA, as well as inflammatory mediators like TNF-α and IL-6 [19], [20]. Uremic toxins play a key role in vascular calcification by driving vascular smooth muscle cells to adopt an osteoblast-like phenotype, leading to calcium and phosphate deposition in the vessel wall [21]. This calcification is the major cause for arteriosclerosis [22].

Gut–Kidney Axis in Cardiorenal Syndrome (CRS)

The gut–kidney axis represents a two-way interaction between intestinal microbiota and the kidneys, significantly influencing cardiovascular and renal health. In CKD and heart failure, intestinal dysbiosis occurs—marked by loss of beneficial microbes and overgrowth of pathogenic bacteria. This imbalance disrupts the gut barrier, allowing microbial toxins and uremic metabolites to enter circulation, thereby worsening kidney and heart injury.

Molecular Mechanisms

1. Inflammation: TMAO (Trimethylamine N-oxide) and uremic toxins activate TLRs, NF-κB, and the NLRP3 inflammasome, elevating cytokines like IL-6 and TNF-α.
2. Oxidative stress & endothelial dysfunction: Reduced nitric oxide and enhanced NADPH oxidase activity contribute to vascular aging.
3. Fibrosis: TGF-β/Smad3 signaling promotes renal and cardiac fibrosis.
4. Mitochondrial dysfunction: Microbial toxins impair ATP production and increase ROS.
5. Vascular calcification: TMAO and indoxyl sulfate trigger osteogenic transformation in vascular smooth muscle cells.
6. Energy metabolism disruption: TMAVA (Trimethyl-5-aminovaleric acid) alters carnitine metabolism, leading to cardiac hypertrophy.

Therapeutic Strategies

Modulating the gut microbiota offers promising new therapeutic opportunities for managing Reno cardiac syndrome. Dietary interventions, particularly adherence to Mediterranean or DASH diets, have been shown to restore microbial balance and reduce the production of harmful uremic toxins and other toxic metabolites. In addition, probiotics and prebiotics can promote the growth of beneficial bacterial strains and enhance short-chain fatty acid (SCFA) synthesis, thereby supporting intestinal barrier integrity and systemic metabolic health. Emerging therapeutic agents, including berberine, indole-3-propionic acid, and quinic acid, as well as fecal microbiota transplantation, are being explored for their potential to rebalance gut flora and mitigate cardiorenal dysfunction. Furthermore, precision microbiome medicine aims to tailor therapeutic strategies according to individual microbial profiles, optimizing treatment efficacy and clinical outcomes [23]. Figure 1 illustrates the pathogenesis of Reno cardiac syndrome [23].

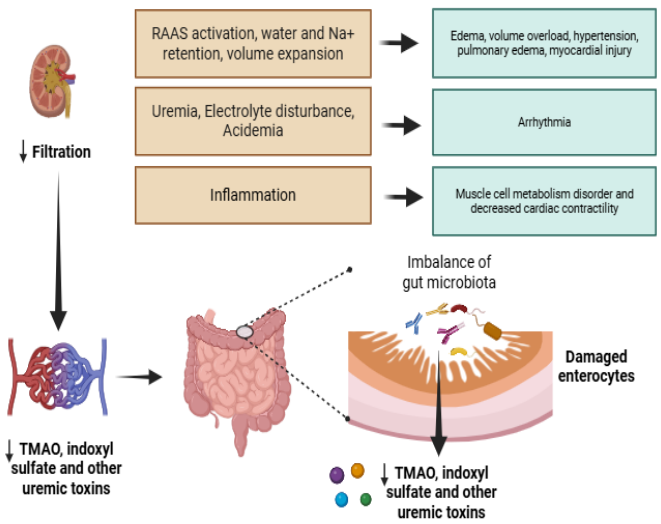

Fig 1: Gut Microbiota Metabolites as Key Mediators in the Pathogenesis of Reno cardiac Syndrome

Cardiorenal syndrome (CRS):

CRS is a pathophysiological disorder involving the heart and kidneys, wherein dysfunction in one organ may precipitate or exacerbate either acute or chronic impairment in the other [24]. CRS refers to the bidirectional mechanism between the heart and kidneys; wherein acute or chronic dysfunction of one organ contributes to impairment of the other. Based on the primary organ involved and the temporal pattern of dysfunction, CRS is classified into five distinct types. The syndrome encompasses complex mechanisms, including reduced renal perfusion because of heart failure, neurohormonal dysregulation, and systemic conditions that concurrently compromise both cardiac and renal function [25]. Cardiorenal syndrome is classified into five subtypes, each characterized by distinct pathogenic mechanisms, therapeutic strategies, and prognostic implications.

Type 1: Acute Cardiorenal Syndrome (CRS-1)

CRS-1 is characterized by an abrupt decline in heart function that precipitates acute kidney injury (AKI). It commonly occurs in the condition of acute decompensated heart failure (ADHF), often following ischemic events such as acute coronary syndrome or cardiac surgery complications, as well as non-ischemic conditions including valvular disease or pulmonary embolism. Approximately 25% of patients hospitalized with ADHF develop CRS-1, frequently in association with pre-existing renal dysfunction [26].

Type 2: Chronic Cardiorenal Syndrome (CRS-2)

CRS-2 arises from sustained cardiac dysfunction leading to progressive renal impairment. CHF and CKD frequently coexist, with literature indicating a bidirectional relationship. Many studies have shown that the onset of chronic heart failure significantly increases the prevalence and progression of CKD.

Type 3: Acute Reno cardiac Syndrome (CRS-3)

CRS-3 involves acute kidney injury that triggers or exacerbates acute cardiac dysfunction. Renal injury may precipitate acute cardiac events directly or indirectly through mechanisms such as electrolyte imbalances (such as hyperkalemia and hypocalcemia), fluid overload, and metabolic acidosis. Patients with AKI are also predisposed to coronary artery disease, left ventricular dysfunction, and myocardial fibrosis, all of which negatively impact cardiovascular outcomes.

Type 4: Chronic Reno cardiac Syndrome (CRS-4)

CRS-4 refers to CKD contributing to the development and progression of CVD. Cardiovascular morbidity and mortality account for nearly 50% of deaths among CKD patients, largely due to shared risk factors such as aging, diabetes, dyslipidemia, and hypertension. This underscores the strong association between CKD and increased susceptibility to adverse cardiac events.

Type 5: Secondary Cardiorenal Syndrome (CRS-5)

CRS-5 is defined by simultaneous cardiac and renal dysfunction caused by systemic conditions such as sepsis, Fabry's disease, or hepatorenal syndrome. In sepsis, inflammatory cascades, microvascular alterations, and cellular ultrastructural damage contribute to combined renal and cardiac impairment [25]. The classification of cardiorenal syndrome is give in Table No.2 [27].

Table No.2: Classification of Cardiorenal syndrome: Types, nomenclature and underlying mechanism [27]

Type	Nomenclature	Mechanism
Type 1	Acute cardiorenal syndrome	A worsening in renal function that frequently complicates hospitalized patients with acute decompensated heart failure and acute coronary syndrome
Type 2	Chronic cardiorenal syndrome	Chronic heart disease leading to a chronic state of kidney disease complicating chronic heart disease
Type 3	Acute renocardiac syndrome	Cardiac dysfunction and complication developed secondary to acute kidney injury
Type 4	Chronic renocardiac syndrome	Patients with chronic kidney disease and evidence of cardiac disease that cannot be attributed to other conditions and where chronic kidney disease is the main contributor to the cardiovascular disorder
Type 5	Secondary cardiorenal syndrome	In this subtype, it is not possible to identify a primary and secondary renal or cardiac dysfunction: both organs are simultaneously targeted by either acute or chronic systemic disease (eg, sepsis, systemic lupus erythematosus, amyloidosis, diabetes mellitus)

CRS encompasses distinct subtypes classified according to their severity and underlying etiology. Accurate identification of each subtype is essential, as it guides therapeutic decision-making. CRS is broadly categorized into acute and chronic forms, depending on the initiating organ dysfunction and its temporal pattern. In type 1 CRS, acute cardiac failure precipitates AKI, whereas type 2 CRS involves chronic heart failure leading to progressive CKD. Conversely, type 3 CRS arises from AKI that induces acute cardiac dysfunction, while type 4 CRS represents CKD contributing to long-term deterioration of cardiac function [28].

Acute CRS is characterized by a sudden decline in cardiac performance resulting in rapid impairment of renal function, often reversible with timely intervention. In contrast, chronic CRS reflects a persistent pathological state in which long-standing cardiac or renal dysfunction progressively worsens the other organ, often culminating in irreversible damage [29].

The bidirectional interplay between the heart and kidneys makes CRS clinically significant, as it is independently related with negative outcomes, including higher morbidity, mortality, and rehospitalization rates. Despite advances in biomarkers and imaging modalities, challenges remain in early diagnosis, risk stratification, and therapeutic management. The limited availability of effective pharmacological interventions underscores the urgent need for improved treatment strategies in CRS [30].

Biomarkers in CKD and CVD:

Chronic kidney disease (CKD) can directly or indirectly contribute to the development and progression of cardiac dysfunction, substantially increasing morbidity and mortality. Early detection of CKD is therefore essential for timely intervention and improved clinical outcomes. Biomarkers—defined as measurable indicators of biological or pathological processes—play a central role in the diagnosis, monitoring, and prognostication of CKD and its associated cardiovascular complications [31].

Traditional Biomarkers of Renal and Cardiac Dysfunction

Traditional biomarkers remain the cornerstone of CKD diagnosis and clinical staging due to their wide availability and established clinical relevance [32].

Serum creatinine is one of the most used indicators of renal function. It is derived from the continuous catabolism of skeletal muscle creatine and is predominantly eliminated by glomerular filtration. Because of its relatively stable production rate and renal clearance, serum creatinine serves as a surrogate marker for estimating glomerular filtration rate (GFR) and overall kidney function [33].

The estimated glomerular filtration rate (eGFR) is calculated using serum creatinine in combination with patient-specific variables such as age, sex, and, in some equations, ethnicity. eGFR is a key clinical parameter used to stage CKD, monitor disease progression, and predict outcomes such as the need for dialysis or kidney replacement therapy [34][35].

Cystatin C (CysC), a low–molecular weight cysteine protease inhibitor produced by all nucleated cells, is freely filtered by the glomeruli and neither secreted nor reabsorbed by renal tubules. These characteristics make cystatin C a more sensitive and accurate marker of GFR than creatinine, particularly for the early detection of CKD and timely therapeutic intervention [36][37].

From a cardiovascular perspective, B-type natriuretic peptide (BNP) is a well-established biomarker synthesized and released by cardiac myocytes in response to ventricular stretch. Produced initially as proBNP and subsequently cleaved into active BNP, elevated circulating levels (typically >20 pg/mL) are associated with left ventricular dysfunction and an increased risk of heart failure, particularly in patients with CKD [39][40].

Imaging and Functional Biomarkers

Imaging biomarkers are quantifiable parameters derived from medical imaging that reflect structural or physiological changes associated with disease. Modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and renal ultrasonography are considered first-line tools in CKD evaluation, providing information on renal morphology, size, cortical thickness, and perfusion. However, their sensitivity for detecting early renal injury remains limited [41][42].

Functional biomarkers assess the performance of specific physiological processes, offering insight into how well various bodily functions are operating. These biomarkers are often derived from advanced imaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). For example, alterations in brain activity in response to stimuli, as detected by fMRI, can serve as indicators of disease progression [43].

Novel and Emerging Biomarkers

Recent advances have led to the identification of novel biomarkers that enhance early diagnosis, risk stratification, and prognostication in CKD and cardiorenal syndrome. Protein-based biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and uromodulin have shown promise for detecting subclinical renal injury and predicting disease progression. NGAL is considered a troponin-like biomarker measurable in both plasma and urine and is widely investigated for early prediction of acute kidney injury and therapeutic monitoring [44].

Functional molecular markers, including asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA), reflect endothelial dysfunction and impaired nitric oxide metabolism, linking renal dysfunction with cardiovascular risk. In addition, soluble urokinase plasminogen activator receptor (suPAR) and soluble tumor necrosis factor receptor-1 (sTNFR1) have emerged as powerful inflammatory biomarkers associated with adverse renal and cardiovascular outcomes.

At the molecular level, microRNAs (miRNAs), non-coding RNAs (ncRNAs), and long intergenic non-coding RNAs (lincRNAs) represent a rapidly expanding class of biomarkers that regulate gene expression and reflect disease-specific signaling pathways. Furthermore, proteomic and metabolomic signatures provide comprehensive insights into altered biochemical networks in CKD, offering potential tools for precision medicine approaches

Clinical Consequences of CKD on cardiovascular outcomes:

Recent epidemiological data from a large German multicenter study (2024) show that among 174,829 hospitalized heart failure patients, 55% had coexisting CKD. CKD patients were older and had worse symptoms, higher comorbidity burden, increased in-hospital mortality (5.5% vs. 3.9%), and more frequent, earlier readmissions compared to those without CKD. Higher CKD stages were linked to even greater in-hospital mortality. CKD independently increased risks of readmission, heart failure events, and all-cause and cardiovascular death, highlighting the substantial burden and need for improved care strategies in cardiorenal syndrome [45]. The risk of cardiovascular morbidity and mortality increases significantly with the progression of CKD.

Even during the early stages (1–3), renal impairment predisposes patients to complications such as heart failure, arrhythmias, and stroke. A common cardiac abnormality observed in CKD is left ventricular (LV) diastolic dysfunction, which is influenced by elevated LV preload as kidney function declines. Additionally, factors such as LV hypertrophy, coronary artery disease (CAD), microvascular dysfunction, interstitial fibrosis, disturbances in fluid and electrolyte balance, and neurohumoral alterations contribute to the development and progression of LV diastolic dysfunction in this population [46]. Heart failure (HF) is significantly aggravated by CKD, which accelerates disease progression, increases complications, and elevates the risk of hospitalization and mortality.

The relationship between HF and CKD is bidirectional and self-perpetuating: HF impairs renal perfusion, leading to further kidney injury, while CKD imposes additional stress on the heart through increased workload and maladaptive neurohumoral activation. This interdependence complicates management strategies and contributes to poor clinical outcomes [47]. Declining kidney function leads to sodium and fluid retention, resulting in increased blood volume and elevated cardiac workload. This volume overload not only raises blood pressure but also imposes additional strain on the heart. Moreover, CKD disrupts the regulation of key minerals such as calcium and phosphorus. These imbalances contribute to vascular calcification, arterial stiffness, and may precipitate

arrhythmias, thereby increasing the risk of adverse cardiovascular events, including myocardial infarction [48]. Chronic kidney disease (CKD) accelerates atherosclerosis and vascular injury through mechanisms involving uremic toxin accumulation, oxidative stress, and disturbances in mineral and bone metabolism.

As a result, patients with CKD face a markedly increased risk of cerebrovascular events, including stroke. Owing to this strong association, CKD is now recognized as an independent risk factor for CVD. The progressive decline in renal function further exacerbates cardiovascular complications, and notably, many individuals with advanced CKD (stages 4–5) succumb to cardiovascular disease rather than to end-stage renal failure itself [49]. Advanced stages of CKD are strongly associated with increased mortality. As CKD progresses from stage 1 to stage 5, recovery potential diminishes while mortality rates per patient-year rise substantially, with the highest risk observed in stages 4 and 5. In these advanced stages, the leading causes of death include cardiovascular disease, infectious complications, and, in cases of profound renal impairment, renal failure itself [49].

Risk assessment tools for chronic kidney disease and cardiorenal syndrome often lack robust validation in these vulnerable groups and can inaccurately estimate disease risk, particularly with widely used scoring systems like H2FPEF and HFA-PEFF. Kidney dysfunction frequently necessitates adjusting biomarker thresholds, while many individuals are categorized as having intermediate risk or present nonspecific symptoms, contributing to diagnostic uncertainty and delayed recognition. Underdiagnosis is further perpetuated by infrequent routine albuminuria screening, inadequate medical record-keeping, and limited provider awareness—especially among those without diabetes or heart failure—resulting in postponed treatment and worse clinical outcomes [50], [51].

Current and emerging management strategies

Pharmacological Intervention:

Treatment of CKD focuses on slowing disease progression, managing complications, and improving quality of life through pharmacological therapy and lifestyle modifications [52]. Hypertension and proteinuria are the two most important independent risk factors for CKD progression. Consequently, current therapeutic strategies emphasize strict blood pressure control and reduction of proteinuria to delay disease advancement. RAAS inhibitors not only lower blood pressure but also exert antiproteinuric, anti-inflammatory, and anti-fibrotic effects, thereby preserving renal function [52].

Blood pressure control is central to renal and cardiovascular protection at all stages of CKD. Agents targeting the RAAS are the preferred first-line therapy [53]. As shown in Fig. 2 [54] Angiotensin-converting enzyme (ACE) inhibitors act by disrupting the RAAS. By blocking the conversion of angiotensin I to angiotensin II, they prevent RAAS-mediated vasoconstriction and indirectly reduce sodium and water retention [55].

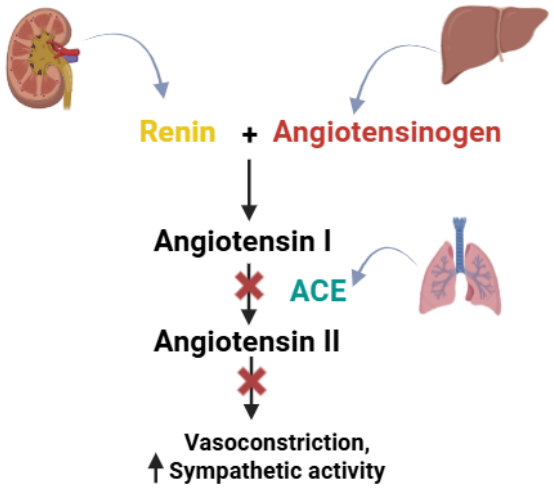

Fig. 2: Schematic representation of the RAAS and the mechanism of action of ACE inhibitors. ACE inhibitors block the conversion of angiotensin I to angiotensin II, reducing vasoconstriction and sympathetic activation.

SGLT2 (sodium-glucose cotransporter-2) inhibitors slow the progression of CKD by reducing glomerular pressure and decreasing albuminuria. Diuretics increase urine output by inhibiting sodium reabsorption in different segments of the nephron, thereby promoting water excretion and reducing blood volume and pressure [56], [57].

Mineralocorticoid Receptor (MR) Antagonists: MR antagonists, such as spironolactone and eplerenone, are used to treat hypertension and slow CKD progression. Aldosterone-mediated MR activation in the kidney promotes inflammation, fibrosis, and oxidative damage. MR antagonists can reduce proteinuria, improve cardiovascular outcomes, and slow CKD progression, especially in diabetic nephropathy. However, they carry a risk of hyperkalemia, requiring careful monitoring [58].

Dialysis Considerations: Hemodialysis is essential for advanced CKD. Early referral, understanding dialysis types, adherence to medications and diet, and open communication with healthcare providers are key to effective management and minimizing complications [59].

Non-Pharmacological Intervention:

Developing dietary guidelines for CKD requires robust evidence. This study evaluated the impact of dietetic interventions, including nutritionist involvement, on patient health, kidney risk factors, nutritional status, and clinical outcomes in CKD [60].

Low-Protein Diet in CKD: Studies focusing on single nutrients or intentional weight loss were excluded, and risk of bias was assessed using a randomized approach, with mean

differences used to summarize outcomes. Adoption of a low-protein diet (LPD) may improve quality of life and slow progression to end-stage renal disease (ESRD), as recommended by KDOQI guidelines. Hahn et al. reported that, after 15 months, a very low-protein diet (VLPD) supplemented with keto-acid analogues (0.28–0.43 g/kg/day) significantly reduced serum urea and uric acid compared to standard LPD, though effects on serum creatinine remain inconclusive [61].

Physical Activity in CKD: The Physical Activity Guidelines for Americans recommend 150 minutes of moderate or 75 minutes of vigorous activity per week for adults. While exercise in CKD is often limited due to concerns about proteinuria and renal function, a meta-analysis by Villanego et al. found that moderate exercise improves quality of life without adversely affecting kidney function [61].

Novel and Experimental Strategies:

Emerging therapies, including endothelin receptor antagonists and anti-fibrotic agents, offer potential in CKD management. The cardiorenal concept emphasizes the bidirectional interplay between heart and kidney failure, guiding more effective therapeutic strategies. Future care will require precision medicine, public health initiatives, multidisciplinary models, and continued research to develop innovative treatments [62]. Physicochemical factors such as pH, shear stress, and pulsatile stretch regulate endothelin synthesis. Exercise increases myocardial ET-1 expression, indicating a potential role for ET-1 in maintaining cardiac function [63]. CHF is Characterized by poor left ventricular function, increased peripheral and pulmonary vascular resistance, decreased exercise tolerance, and dyspnea.

The endothelin (ET) family—ET-1, ET-2, ET-3, and ET-4—induces vasoconstriction, cell proliferation, and myocardial effects primarily via ETA receptor activation [64]. Platform technologies such as low molecular weight proteins, nanoparticles, liposomes, and microparticles are used for kidney-specific drug delivery. Passive targeting exploits carrier size and charge, while active targeting employs ligands (peptides or antibodies) to direct drugs to specific renal compartments or cell types [65]. Since its discovery, BMP7 has been recognized for its role in fibrotic diseases, particularly via its interaction with the profibrotic factor TGF-β. BMP7 binds serine/threonine kinase receptors to activate signaling cascades that regulate organ homeostasis and antifibrotic processes. BMP7/Smad signaling has demonstrated protective effects in cardiac and pulmonary fibrosis [66]. Microcapsules, lipid bilayers, nanocopolymers, and other nanomaterials are engineered to improve renal targeting and biocompatibility, enabling effective delivery of anti-fibrotic agents such as peptides, drugs, and active compounds from traditional medicines. Metal-organic frameworks (MOFs), consist of metal ions or clusters coupled with organic ligands, are particularly promising due to their high porosity, large surface area, stability, and tunability [67].

Precision medicine approaches:

Precision medicine integrates an individual's genetics, lifestyle, and environmental factors to prevent and manage cardiovascular disease. Traditional approaches rely on evidence-based, multi-tiered strategies involving clinicians, patients, and healthcare systems. Advances in panomics—genomics, transcriptomics, epigenomics, metabolomics, proteomics, and microbiomics—highlight the complexity of cardiovascular phenotypes beyond reductionist models. Leveraging comprehensive datasets from clinical, imaging, laboratory, and multi-omics sources enables more precise risk assessment and personalized therapeutic strategies [68]. Advances in genomics and other omics enhance precision medicine, but it also depends on imaging, functional testing, and established biomarkers. Cardiovascular management commonly integrates symptom-based approaches with non-invasive diagnostics [69].

Individualized management of chronic kidney disease (CKD) incorporates environmental and lifestyle factors, including diet, exercise, and stress, tailored to patient preferences, socioeconomic status, and cultural context. Kidney function influences systemic homeostasis, highlighting inter-organ interactions. Genomic medicine plays a key role, as advances in sequencing have identified gene mutations linked to specific renal disorders [70].Personalized Renal Replacement Therapy (RRT): RRT is customized based on age, comorbidities, functional status, and patient goals to maximize benefits and minimize risks. Multidisciplinary teams—including nephrologists, transplant surgeons, nurses, and nutritionists—collaborate to design patient-centered treatment plans that optimize outcomes and quality of life [70].

Advanced metabolomic techniques allow analysis of thousands of metabolites in biofluids or tissues to generate a patient-specific metabolic fingerprint. These profiles can serve as diagnostic or prognostic tools and, when integrated with other omics technologies, enhance personalized therapy and deepen understanding of the interactions between metabolites, proteins, genes, and disease states [71]. The gut microbiota affects systemic health by producing important metabolites such as short-chain fatty acids (SCFA), bile acids (BA), and trimethylamine-N-oxide (TMAO). These metabolites interact with host metabolic pathways and can enter circulation via the intestinal epithelium, impacting the function of distant organs and physiological systems [72]. Metabolomics studies commonly use urine, plasma, or serum to capture systemic biochemical processes. Other sample types include cell lines, saliva, cerebrospinal fluid, and microorganisms. Most metabolomic analyses rely on non-invasive or minimally invasive sample collection [73]. Urinary metabolites can reflect the progression of diabetic kidney disease (DKD). Future studies on aconitic acid and 3-HIBA may help identify patients at high risk of GFR decline, enabling more targeted interventions and improved clinical management [74].

Table No 3: Comparison of Current and Emerging Management Strategies in Chronic Kidney Disease

Category	Current Management Strategies	Emerging / Novel Strategies
Therapeutic Goal	Slow CKD progression, control hypertension and proteinuria, manage complications, improve quality of life	Disease modification, precision targeting of molecular pathways, personalized risk stratification
Pharmacological Agents	RAAS inhibitors (ACE inhibitors, ARBs) for blood pressure and proteinuria control; diuretics for volume management; SGLT2 inhibitors to reduce glomerular pressure and albuminuria	Endothelin receptor antagonists; anti-fibrotic agents (e.g., BMP7 modulators); novel mineralocorticoid receptor antagonists with improved safety profiles
Mechanistic Focus	Hemodynamic control, reduction of intraglomerular pressure, suppression of RAAS-mediated inflammation and fibrosis	Targeting inflammation, fibrosis, endothelial dysfunction, and cardiorenal signaling pathways
Cardiorenal Protection	BNP-guided cardiovascular risk assessment; blood pressure optimization for renal–cardiac protection	Integrated cardiorenal therapies addressing bidirectional heart–kidney interactions; endothelin pathway modulation
Renal Replacement Therapy (RRT)	Conventional hemodialysis initiated in advanced CKD; standardized dialysis protocols	Personalized RRT tailored to age, comorbidities, functional status, and patient goals
Non-Pharmacological Interventions	Low-protein or very low-protein diets (KDOQI-guided); nutritional counselling; moderate physical activity to improve quality of life	Lifestyle interventions informed by individual metabolic and genomic profiles
Drug Delivery Approaches	Systemic drug administration with limited renal specificity	Kidney-targeted drug delivery using nanoparticles, liposomes, microparticles, and metal–organic frameworks (MOFs)
Precision Medicine	Standardized, guideline-driven care using clinical parameters and conventional biomarkers	Integration of genomics, transcriptomics, proteomics, metabolomics, microbiomics, imaging, and functional biomarkers
Metabolomics and Microbiome	Limited routine clinical use	Patient-specific metabolic fingerprinting; targeting gut-derived metabolites (SCFA, bile acids, TMAO) to modify disease progression
Clinical Outlook	Symptom control and slowing progression	Early risk prediction, individualized therapy, and improved long-term renal and cardiovascular outcomes

CONCLUSION

The bidirectional relationship between chronic kidney disease (CKD) and cardiovascular disease (CVD) underscores an urgent need not only for earlier diagnosis and integrated management, but also for a shift toward targeting upstream drivers such as inflammation, oxidative stress, fibrosis, and endothelial dysfunction rather than solely treating downstream complications. Future research should prioritize: (i) robust validation of early, mechanistically relevant biomarkers (including omics-based signatures) in large, multi-ethnic longitudinal cohorts; (ii) randomized trials of kidney- and vasculature-targeted therapies that incorporate these biomarkers for risk stratification and treatment selection; and (iii) systematic evaluation of combination strategies that integrate pharmacologic, device-based, and lifestyle interventions in cardiorenal populations.

To overcome clinical implementation barriers, there is a critical need for cost-effective, scalable diagnostic platforms, pragmatic trial designs embedded within routine care, and interoperable digital tools that can translate complex molecular data into actionable risk scores at the point of care. Finally, multidisciplinary, patient-centered care models that link nephrology, cardiology, primary care, and behavioral health, and that are tailored to resource-limited settings, will be essential to ensure that advances in molecular understanding and precision therapeutics translate into meaningful reductions in the global burden and inequities of cardiorenal disease..

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