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Review

Chronic Kidney Disease-Associated Cardiomyopathy: Mechanisms and Therapeutic Strategies

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Abstract

Chronic kidney disease-associated cardiomyopathy (CKD-CM) is a term that captures the spectrum of myocardial disease that begins early in chronic kidney disease (CKD) and progresses as kidney function declines. Historically described as uremic cardiomyopathy, the condition was associated with severe left ventricular hypertrophy and fibrosis in patients with kidney failure. However, functional abnormalities and myocardial injury have been shown to begin much earlier, with diffuse interstitial fibrosis preceding overt hypertrophy or reduced ejection fraction. Fibrosis drives heart failure with preserved ejection fraction (HFpEF)-like physiology and atrial fibrillation and increases arrhythmic risk. In this review, we describe the multiple interacting mechanisms, including abnormal loading, neurohormonal activation, metabolic and inflammatory stress, mineral bone disorder, and microvascular dysfunction. We summarize imaging findings across CKD stages and describe established and emerging therapeutic strategies. A better understanding of CKD-CM pathogenesis is likely to enable early intervention and prevention, with successful outcomes measured by reduced progression to severe cardiomyopathy and lower cardiovascular mortality in CKD.

Keywords: chronic kidney disease; uremic cardiomyopathy; myocardial fibrosis; left ventricular hypertrophy; heart failure; atrial fibrillation

1. Introduction

Chronic kidney disease (CKD) is a global public health burden, currently affecting more than 10% of adults worldwide, with a further increase in prevalence expected in the next few years [1,2]. CKD is associated with a graded and exponential increase in cardiovascular (CV) morbidity and mortality across all stages of renal dysfunction [3]. CKD is classified by glomerular filtration rate (GFR) into G categories (G1–G5) and by albuminuria into A categories (A1–A3). Both categories can predict adverse CV outcomes either independently or synergistically [3,4]. CV risk is apparent early and rises significantly with worsening kidney function and increasing albuminuria [5,6].

The dominant modes of cardiovascular death in CKD are not primarily related to atherosclerotic events, as heart failure (HF), sudden cardiac death (SCD), and cardiac arrhythmias account for the excess mortality. In dialysis patients, coronary artery disease accounts for only ~6.8% of deaths, whereas arrhythmias and SCD account for ~18–25% [7]. This pattern suggests a distinct myocardial disease process directly linked to CKD that was historically described as uremic cardiomyopathy, characterized by left ventricular hypertrophy (LVH), chamber remodeling, and myocardial fibrosis [8]. However, this terminology does not adequately capture the early onset, progressive pathophysiology, and clinical consequences of cardiac remodeling that begins in the earlier stages of kidney disease.

In this review, we propose reframing uremic cardiomyopathy as CKD-associated cardiomyopathy (CKD-CM), a progressive myocardial disorder that begins in the early stages of CKD and evolves across the entire disease spectrum. In CKD-CM, diffuse interstitial myocardial fibrosis, which precedes overt LVH, serves as the dominant structural substrate for the development of heart failure and

arrhythmias that lead to a heightened susceptibility to SCD [7]. This fibrotic phenotype is driven by a complex combination of hemodynamic stress, neurohormonal activation, inflammation, metabolic dysregulation, and CKD-specific toxins, yet remains largely undetected by conventional cardiac imaging focused on late-stage structural changes [5,7].

The objective of this review is to redefine the pathophysiological framework of CKD-CM and identify gaps in early diagnosis and therapeutic strategies. The novelty of this work lies in repositioning CKD-CM as an integral component of CKD rather than a late complication, thereby emphasizing the need for earlier recognition and intervention to reduce cardiovascular burden. Recognizing CKD-CM as part of the disease provides the necessary conceptual framework for rethinking both research priorities and clinical care.

2. Pathobiological Mechanisms of CKD-CM

The declining kidney function triggers hemodynamic stress, neurohormonal activation, metabolic and toxic exposures, inflammation, and mineral-bone disorders that converge to drive maladaptive myocardial remodeling, leading to CKD-CM. The progression is amplified in advanced CKD and dialysis (Fig. 1).

2.1 Interstitial Fibrosis

Evidence from both human and experimental studies consistently identifies diffuse interstitial myocardial fibrosis as the central structural abnormality in CKD-CM. Autopsy and biopsy studies show greater interstitial collagen deposition in patients with CKD than in non-CKD control groups, with these fibrotic deposits being present in a substantial proportion of patients receiving dialysis [9,10,11]. These changes are associated with increased myocardial stiffness that leads to diastolic dysfunction, atrial remodeling, and arrhythmogenesis [12].

Left ventricular (LV) tissue from patients with kidney failure demonstrates stiffer collagen isoforms, driven predominantly by impaired collagen degradation as reflected by reduced myocardial expression of matrix metalloproteinases (MMPs) [13].

Experimental data support a model in which combined hemodynamic stress, neurohormonal activation, inflammation, and uremic toxicity induce myocardial fibrosis more reliably than isolated changes. These findings position interstitial fibrosis as the dominant pathological structural feature leading to the CKD-CM phenotype [14].

2.2 Abnormal Loading

Pressure and volume overload increase progressively with declining kidney function and trigger myocardial remodeling in CKD.

CKD is characterized by accelerated medial arterial hypertrophy, fibrosis, and calcification, processes that markedly increase pulse wave velocity and lead to early wave reflection during systole [15,16,17]. These changes elevate systolic blood pressure, increase LV wall stress, and reduce coronary perfusion during diastole, promoting hypertrophy and myocardial injury [3]. Coronary artery calcification develops early in CKD, progresses rapidly, and is closely associated with disturbances in mineral and bone metabolism [18]. Calcification of central arteries and cardiac valves further amplifies afterload and is strongly associated with adverse cardiovascular outcomes [3,19].

Impaired pressure–natriuresis drives sodium retention, plasma volume expansion, and increased vascular resistance, leading to hypertension. Sodium excess also contributes to endothelial dysfunction, vascular stiffness, and low-grade inflammation [20].

Chronic anemia, a common feature of CKD, increases cardiac output and LV filling, while volume overload further distends the ventricle and raises wall stress, leading to increased preload [21]. In patients receiving hemodialysis, high-flow arteriovenous fistulae can further exacerbate preload, accelerating chamber remodeling [22]. These hemodynamic stresses contribute to cardiomyocyte hypertrophy and set the stage for fibrotic remodeling, even when systolic function appears preserved.

2.3 Neurohormonal Activation

Neurohormonal activation is a central mechanism that links kidney dysfunction to maladaptive myocardial remodeling in CKD-CM. Both the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system are chronically upregulated in CKD and have direct profibrotic and hypertrophic effects on the myocardium [23,24].

Angiotensin II is a key molecular driver of CKD-CM progression. Signaling through the angiotensin II type 1 receptor activates multiple intracellular cascades, including phospholipase-dependent pathways and downstream Janus kinase (JAK) and mitogen-activated protein kinase (MAPK) signaling that promote cardiomyocyte hypertrophy and fibroblast activation [25]. In preclinical experimental studies, angiotensin II engages calcium (Ca^{2+})-dependent signaling and SMAD pathways, promoting the synthesis and release of transforming growth factor-beta (TGF-β), a key regulator of extracellular matrix production [26]. Additional preclinical models implicate mechanistic target of rapamycin (mTOR) signaling as a mediator of angiotensin II–driven myocardial fibrosis and contractile dysfunction [27]. Early pharmacological blockade of angiotensin signaling in animal models of CKD attenuates myocardial fibrosis, limits hypertrophy, and preserves cardiac structure, supporting a causal role for RAAS activation in CKD-CM [28,29]. Aldosterone contributes independently by promoting inflammatory cell infiltration and increasing profibrotic mediators such as endothelin-1 and galectin-3 [30,31].

Sympathetic overactivity is another hallmark of CKD and contributes independently to fibrotic remodeling [32].

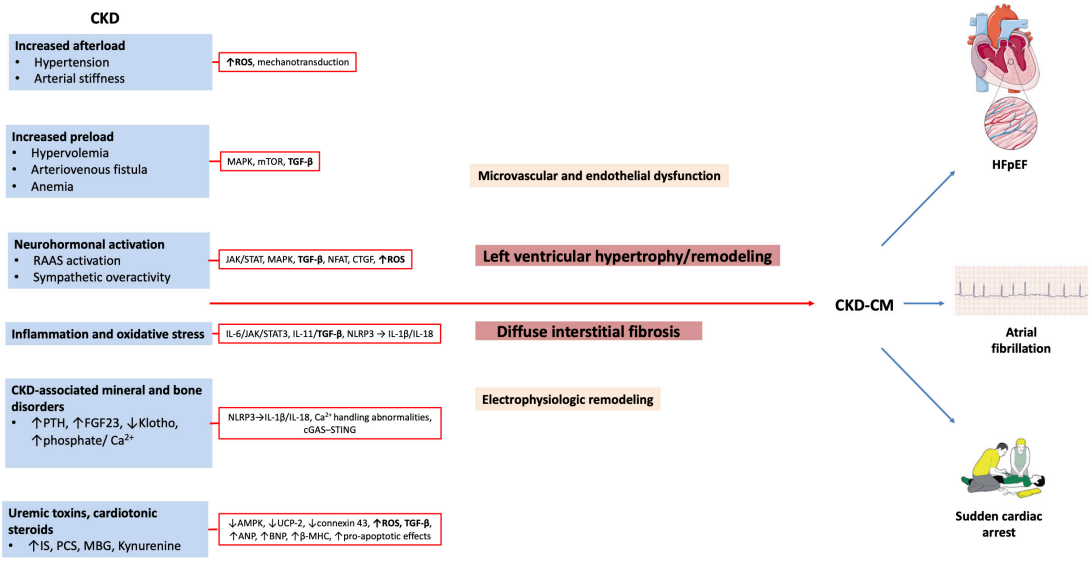

Fig. 1. Pathophysiology of CKD-CM. CKD promotes myocardial remodeling through multiple, interacting mechanisms. Hemodynamic stressors, including increased afterload and preload, together with neurohormonal activation, inflammation, oxidative stress, CKD-associated mineral and bone disorders, uremic toxins, microvascular and endothelial dysfunction, and electrophysiologic remodeling, converge on the myocardium. These processes drive left ventricular hypertrophy and diffuse interstitial fibrosis, the central structural substrates of CKD-CM, which subsequently lead to HFpEF, atrial fibrillation, and sudden cardiac arrest. CKD, chronic kidney disease; ROS, reactive oxygen species; MAPK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; TGF-β, transforming growth factor-beta; RAAS, renin–angiotensin–aldosterone system; JAK/STAT, Janus kinase/signal transducer and activator of transcription; NFAT, nuclear factor of activated T cells; CTGF, connective tissue growth factor; IL-6, interleukin-6; IL-11, interleukin-11; NLRP3, nucleotide-binding oligomerization domain-like receptor protein 3; IL-1β, interleukin-1β; IL-18, interleukin-18; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23; Ca^{2+}, calcium; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; IS, indoxyl sulfate; PCS, p-cresyl sulfate; MBG, marinobufagenin; AMPK, AMP-activated protein kinase; UCP-2, uncoupling protein-2; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; β-MHC, β-myosin heavy chain; CKD-CM, CKD-associated cardiomyopathy; HFpEF, heart failure with preserved ejection fraction. Fig. 1 was created using Microsoft PowerPoint 2021 (Microsoft Corporation, Redmond, WA, USA).

Proposed mechanisms include adrenergic induction of inflammatory cytokines such as interleukin (IL)-6, activation of the calcineurin–nuclear factor of activated T cells (NFAT) signaling pathway, increased expression of the profibrotic mediator connective tissue growth factor (CTGF), and enhanced generation of reactive oxygen species (ROS) [33,34,35,36]. β3-adrenergic receptor signaling appears to exert antifibrotic effects, potentially through nitric oxide–dependent and redox-sensitive paracrine signaling [37]. Together, chronic RAAS and sympathetic activation form a neurohormonal axis that converges on fibroblast activation and interstitial fibrosis in CKD-CM.

2.4 Metabolic and Toxic Milieu

CKD leads to systemic accumulation of uremic solutes that act as both biomarkers and mediators of cardiovascular injury. Key metabolites include indoxyl sulfate (IS), p-cresyl sulfate (PCS), and kynurenine pathway derivatives [38].

IS, a hepatic metabolite of tryptophan, promotes myocardial remodeling primarily through oxidative stress, by enhancing mitochondrial ROS generation after inhibiting AMP-activated protein kinase (AMPK) and reducing uncoupling protein-2 (UCP-2) expression [39]. This imbalance drives cardiomyocyte hypertrophy by promoting the upregulation of hypertrophic markers, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and β-myosin heavy chain (β-MHC) [40]. In addition, IS stimulates cardiac fibrosis via upregulation of micro ribonucleic acid (miR)-21 and suppression of miR-29b, which amplify transforming growth factor-beta (TGF-β) signaling and extracellular matrix deposition [41].

Electrophysiologically, IS predisposes to arrhythmias by reducing the transient outward potassium currents and downregulating connexin 43, impairing electrical coupling. In the vasculature, preclinical studies show that IS activates endothelial cells and vascular smooth muscle cells through oxidative stress, promoting atherosclerosis and vascular calcification [38].

PCS, a gut microbiota–derived metabolite of tyrosine and phenylalanine, similarly contributes to oxidative stress and inflammation by upregulating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits and increasing ROS production. This induces cardiomyocyte apoptosis via Bax/Bcl-2 imbalance and caspase-3 activation [42]. PCS also alters potassium channel function and connexin 43 phosphorylation, affecting action potential duration and intercellular electrical communication [38].

In the vasculature, PCS activates endothelial cells and promotes vascular smooth muscle cell osteogenic differentiation, contributing to vascular calcification. It also impairs insulin signaling through extracellular signal-regulated kinases 1 and 2 (ERK1/2)-mediated Akt inhibition, linking metabolic dysregulation to cardiac dysfunction [38].

CKD-associated alterations in tryptophan metabolism increase circulating kynurenine and kynurenic acid levels. Kynurenine enhances ROS production via aryl hydrocarbon receptor (AhR) activation and exerts pro-apoptotic effects on cardiomyocytes [43]. In preclinical studies using primary human coronary artery endothelial cells, kynurenine also suppresses hypoxia-inducible factor-1α (HIF-1α), impairing adaptive responses to ischemia and promoting a prothrombotic phenotype [44]. *In vivo* evidence from indoleamine 2,3-dioxygenase 1 (IDO1)/IL-10 double-deficient mouse models further demonstrates that kynurenic acid promotes atherothrombosis through suppression of anti-inflammatory IL-10 signaling [45].

Cardiotonic steroids, such as ouabain and marinobufagenin (MBG), are endogenous ligands of the sodium–potassium adenosine triphosphatase (Na^+/K^+-ATPase) [46]. In CKD, circulating levels of these cardiotonic steroids increase in response to stimuli such as volume overload, adrenocorticotropic hormone, and angiotensin II [47,48]. In rats, chronic administration of low-dose MBG reproduced the cardiac phenotype observed after partial nephrectomy, including hypertension, increased cardiac mass, diastolic dysfunction, and myocardial fibrosis [49]. Conversely, pre-immunization against MBG attenuated LVH, diastolic impairment, fibrosis, and systemic oxidative stress in nephrectomized animals, without significantly altering blood pressure [50]. At the cellular level, MBG directly stimulates cardiac fibroblasts, enhancing collagen synthesis and procollagen stabilization through Src-, epidermal growth factor receptor- (EGFR-), tyrosine kinase-, and ROS-dependent signaling pathways [46].

2.5 Inflammation

CKD is characterized by systemic inflammation, which contributes to disease progression, and circulating proinflammatory mediators increase as kidney function declines [51]. Among these, IL-6, IL-11, and tumor necrosis factor-alpha (TNF-α) appear to play particularly important roles in the pathogenesis of CKD-CM.

IL-6 levels increase secondary to oxidative stress, chronic inflammation, and volume overload, together with reduced renal clearance, particularly in end-stage disease [52]. IL-6 promotes cardiac fibrosis and hypertrophy primarily through JAK/signal transducer and activator of transcription 3 (STAT3) activation, stimulating fibroblast proliferation and collagen synthesis [53,54]. Moreover, selective blockage of IL-6 trans-signaling attenuates atrial fibrillation (AF) inducibility [55]. IL-11 acts as a downstream mediator of TGF-β1 in fibroblasts, and its inhibition in experimental models reduces cardiac and renal fibrosis highlighting its importance in cardiorenal remodeling [56,57]. TNF-α also contributes to CKD pathophysiology, as experimental mouse models show that its inhibition reduces renal inflammation and fibrosis, suggesting a potential role in attenuating cardiac fibrotic remodeling as well [58].

In the kidney, activation of nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome amplifies inflammatory responses in both immune and non-immune renal cells, including tubular epithelial and mesangial cells, thereby promoting the progression of renal fibrosis [59]. Beyond renal injury, evidence from murine sham-operated and 5/6 nephrectomy models has demonstrated that CKD can impair cardiac contractile function through activation of the NLRP3 inflammasome and upregulation of the IL-1β and IL-18 signaling pathways induced by uremic toxins [60]. Consistently, another CKD mouse model further revealed that NLRP3–IL-1β signaling plays a pivotal role in the development of AF associated with CKD [61]. Uremic toxin–induced neutrophil extracellular trap (NET) formation further amplifies inflammasome activation and promotes fibroblast pyroptosis, while NET inhibition reduces cardiac inflammation and fibrosis [62].

Mitochondrial dysfunction represents a convergent mechanism, with impaired oxidative phosphorylation and increased ROS production contributing to endothelial dysfunction, microvascular impairment, and increased susceptibility to ischemic injury [63,64,65].

2.6 Coronary Microvascular Dysfunction/Rarefaction

CKD is associated with structural changes, including arteriolar remodeling and capillary rarefaction, as well as functional impairment of endothelial and smooth muscle cells in the coronary microvasculature in both experimental models and humans [66,67,68,69]. These changes are thought to be the direct result of oxidative stress, inflammation, hypertension, and impaired bioavailability of nitric oxide that contribute to myocardial ischemia, subclinical injury, and the development of fibrosis and increase the risk of HF and SCD [69,70]. Notably, the severity of microvascular dysfunction correlates with rising serum urea levels [71].

2.7 Impaired Mineral Metabolism

Disordered mineral metabolism is another mechanistically complex component of CKD-CM. With the decline of glomerular filtration, circulating phosphate, fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) rise, whereas calciferol and soluble α-klotho decrease [72].

PTH contributes to cardiac remodeling in uremia as it is found to promote fibrosis and hypertrophy, whereas parathyroidectomy reduces LVH and inflammation and in some cases does so independently of phosphate levels [73,74]. FGF23 is strongly associated with LV hypertrophy and adverse outcomes, potentially via FGF23 receptor (FGFR4)-mediated activation of hypertrophic signaling and Ca^{2+} handling abnormalities [75]. It also contributes to atrial and ventricular fibrosis through β-catenin- and protein kinase B (AKT)-dependent pathways [75]. In contrast, soluble klotho exerts protective effects, and its deficiency exacerbates cardiac remodeling, whereas restoration improves myocardial structure [76,77,78]. In parallel, hyperphosphatemia and hypercalcemia promote vascular calcification and increased afterload, with inflammatory pathways such as NLRP3 and cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) implicated [75,79,80].

2.8 Electrophysiologic Remodeling

Patients with CKD have a heightened susceptibility to cardiac arrhythmias and an elevated risk of SCD through combined effects of electrolyte disturbances, sympathetic overactivity, fibrosis, and ion channel remodeling [81].

QT interval prolongation in CKD may result from altered cardiomyocyte ion currents, such as reductions in fast voltage-gated sodium channel current (I_{Na}) and transient outward potassium channel current (I_{to}), as well as from elevated FGF23 levels acting through FGFR4-related pathways [82,83]. Moreover, in a genetic CKD rat model, cardiomyocyte action potentials were prolonged, and reduced expression of L-type Ca^{2+} channels, sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2a), Kv1.4, and Kv4.3 likely increased susceptibility to Ca^{2+} alternans and ventricular fibrillation [84].

Taken together, the pathobiology of CKD-CM is best understood as a network of interconnected and mutually reinforcing mechanisms and not as discrete processes. Hemodynamic stress initiates myocardial injury and remodeling. These are further amplified by RAAS activation and the sympathetic pathway, which promote oxidative stress, inflammation, and fibroblast activation. Uremic toxins act as important modulators because they induce mitochondrial dysfunction, ROS generation, and activation of inflammatory pathways, including the NLRP3 inflammasome, thereby linking metabolic disturbance with immune and fibrotic responses. In parallel, coronary microvascular dysfunction, also driven by oxidative stress, inflammation, and endothelial impairment, contributes to ischemia and further promotes fibrosis. Disordered mineral metabolism, particularly the combination of elevated FGF23 and klotho deficiency, exerts synergistic effects on myocardial hypertrophy, fibrosis, and Ca^{2+} handling abnormalities, which contribute to both structural and electrophysiological remodeling. These bidirectional interactions accelerate cardiac dysfunction and underpin the progression of CKD-CM.

3. Main Clinical Associations of CKD-CM

The complex interplay of hemodynamic stress, neurohormonal activation, inflammation, uremic toxicity, microvascular dysfunction, and disordered mineral metabolism ultimately translates into clinically overt CV disease. These overlapping mechanisms drive progressive structural and functional cardiac remodeling and provide the pathophysiological basis for the high burden of HF and arrhythmias observed in patients with CKD-CM.

3.1 Heart Failure

Prospective cohort data consistently indicate that CKD is associated with an increased risk of CV events, including HF [85,86,87,88,89,90]. Men with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 had a 2.2-fold higher risk of developing HF compared to men with eGFR ≥60 mL/min/1.73 m^2 [85]. The prevalence of HF in individuals with CKD varies significantly across populations and study settings, rising progressively with advancing CKD severity [86]. The atherosclerosis risk in communities (ARIC) study reported an incidence of 17.7 per 1000 patient–years among individuals with reduced eGFR and no baseline HF, while the German chronic kidney disease (GCKD) study found a 43% prevalence in patients with moderate CKD. The multinational CaReMe-CKD study observed a 24.5% prevalence of HF [86,89,90].

The prevalence of different HF subtypes (heart failure with reduced ejection fraction [HFrEF] and heart failure with preserved ejection fraction [HFpEF]) and their associated mortality risks in patients with advanced CKD are of considerable epidemiological and clinical significance [91]. Among 76,688 patients with incident CKD, 18.6% had prevalent HF, with 59.2% having HFpEF and 23.3% having HFrEF. Patients with HF had a 1.70-fold higher risk of all-cause mortality over one year, compared to those who had not developed HF, and the hazard ratio for CV-related mortality in HF patients was found to be 6.69 compared to those without HF [91].

The definitive diagnosis of HF in patients with CKD is often challenging, as symptoms frequently overlap. Patients with end-stage renal disease (ESRD), especially those not receiving renal replacement therapy, exhibit signs and symptoms consistent with HF, such as dyspnea and edema, due to the impaired ability of severely damaged kidneys to eliminate sodium and water [92]. Distinguishing the underlying organ source of overhydration is essential in clinical practice, as it provides prognostic information and may influence treatment decisions. This distinction is espe-

cially important because only systemic congestion resulting from cardiac dysfunction, rather than overhydration itself, is linked to increased mortality in ESRD patients undergoing hemodialysis [92,93]. Dyspnea is a symptom that may occur even in the earlier stages of CKD and beyond fluid overload, other potential contributing factors are unrecognized chronic lung disease, pulmonary hypertension, lung fibrosis, microembolism, anemia, sodium imbalances, malnutrition, and muscle wasting [94]. Therefore, although evaluating symptoms is important, clinicians should conduct further diagnostic tests, such as echocardiography, natriuretic peptide measurements, and possibly lung ultrasound, to establish a definitive diagnosis.

The development of HF in CKD-CM reflects the combined effects of structural myocardial remodeling, microvascular dysfunction, and persistent hemodynamic and metabolic stress, which together contribute to progressive and often irreversible cardiac dysfunction.

3.2 Arrhythmogenic Consequences of CKD-CM

AF is one of the most common cardiac arrhythmias, with a notably high prevalence in patients with CKD that can be attributed to the shared risk factors between AF and CKD, such as hypertension, diabetes, and coronary artery disease, as well as CKD-induced diastolic dysfunction and atrial dilation [95,96]. In a large nationwide Korean cohort of 4.8 million individuals without prior AF who underwent biennial health examinations, participants were followed for a median of 8.1 years. After multivariable adjustment, CKD remained independently associated with a higher risk of incident AF, with stepwise increases in hazard ratios across CKD stages and across age and sex subgroups [95].

The presence of AF is linked to reduced quality of life, higher rates of hospitalization, and an elevated risk of HF, stroke, SCD and overall mortality [96,97]. This increased vulnerability is largely driven by electrolyte imbalances and augmented sympathetic activation, which increase myocardial electrical instability and facilitate malignant arrhythmias that may culminate in cardiac arrest [98]. The burden is particularly pronounced in ESRD, where SCD accounts for approximately 24% of deaths over a 5-year follow-up [99]. Recent evidence indicates that even moderate CKD (eGFR 30 to <60 mL/min per 1.73 m^2) is independently associated with an increased risk of SCD in the general population [100]. The underlying arrhythmic mechanisms leading to SCD in patients with CKD are still uncertain. In a cohort of 317 patients receiving hemodialysis who were monitored with implantable loop recorders, 20 SCDs occurred during a mean follow-up of 14–21 months. Most events were linked to bradyarrhythmias, only two were attributed to tachyarrhythmias and three were associated with indeterminate electrocardiographic patterns [101].

4. Imaging and Blood Biomarkers

4.1 Imaging of the CKD-CM Phenotype

Imaging has been central to defining the phenotype of CKD-CM, revealing a continuum of structural, functional, and tissue-level myocardial abnormalities that evolve with declining kidney function. Echocardiography provided the earliest insights, whereas cardiovascular magnetic resonance (CMR) has refined phenotypic characterization through accurate volumetric assessment and myocardial tissue characterization. Importantly, contemporary imaging studies demonstrate that many features of CKD-CM emerge in early-stage CKD, before the development of overt LVH or reductions in ejection fraction.

Echocardiography remains the cornerstone imaging modality for the assessment of cardiac structure and function. Even in early studies, LVH was highly prevalent and LV dilatation was frequently observed, whereas overt systolic dysfunction was comparatively uncommon among patients initiating dialysis [102]. Moreover, in a study of CKD patients receiving hemodialysis, LVH emerged as the most prevalent structural abnormality, while LV diastolic dysfunction was the most common functional impairment, especially in those with concomitant hypertension [103]. A subsequent study extended these observations across the spectrum of kidney disease, demonstrating a graded inverse relationship between kidney function and LV mass [104].

Given that LVH in CKD patients is linked to increased mortality and adverse outcomes, accurate detection is clinically important [102,105,106]. While echocardiography is widely used, studies have shown that mean LV mass index (LVMi) values from echocardiography are significantly higher than those measured by CMR, indicating potential overestimation, which highlights the need for more precise imaging modalities [105,106,107].

CMR has emerged as the reference non-invasive modality for phenotyping CKD-CM, offering reproducible quantification of LV mass and volumes independent of loading conditions, along with myocardial tissue characterization. Late gadolinium enhancement (LGE) studies in dialysis populations show that over 70% of patients exhibit LVH and/or myocardial fibrosis, with two distinct patterns: subendocardial enhancement reflecting prior infarction and mid-wall or patchy enhancement correlating with increased LV mass and diffuse fibrosis [108].

Native T1 time mapping allows assessment of interstitial fibrosis [109]. In the hemodialysis population, native T1 values are elevated and correlate with impaired myocardial remodeling, linking diffuse fibrosis to early systolic dysfunction [110,111]. T2 mapping confirms these changes occur independently of edema [112]. Clinically, higher native T1 is associated with reduced functional capacity and adverse CV outcomes [113].

Importantly, fibrosis appears to precede overt hypertrophy. In non-dialysis CKD patients, native T1 and fi-

brosis biomarkers rise progressively with disease severity, whereas LV mass increases only in advanced stages. Exercise capacity correlates more closely with fibrosis than LV mass, and kidney function is the strongest determinant of native T1. These findings support a model in which CKD-CM begins at relatively preserved eGFR, with diffuse fibrosis, subtle systolic and diastolic dysfunction, and atrial remodeling, while LVH and reduced ejection fraction are later manifestations [75].

4.2 Circulating Biomarkers

The search for circulating biomarkers that reflect or mediate CKD-CM remains a high priority in CKD research. Released following cleavage of pro b-type natriuretic peptide (proBNP) in response to myocardial pressure and volume overload, N-terminal pro b-type natriuretic peptide (NT-proBNP) reflects ventricular wall stress and has been widely applied for early detection of HF in CKD and dialysis populations [12]. Elevated concentrations are consistently found to be associated with adverse CV outcomes and mortality, including in end-stage renal disease, where very high levels independently predict survival [12,114]. In patients with CKD, elevated BNP concentrations are independently associated with CV events and mortality, even after adjustment for structural cardiac parameters such as left atrial diameter, LVMi, and left ventricular ejection fraction (LVEF) [115,116]. Cardiac troponins, including cardiac troponin T (cTnT), high-sensitivity cardiac troponin T (hs-cTnT), and high-sensitivity cardiac troponin I (hs-cTnI), are frequently elevated in patients with CKD, even in the absence of acute coronary syndromes. Importantly, elevated troponin levels in patients with CKD, including those receiving dialysis, are associated with adverse cardiovascular outcomes [117,118]. In non-dialysis CKD, cTnT associates with LVH and systolic and diastolic dysfunction independent of estimated glomerular filtration rate (eGFR) [117]. High-sensitivity cardiac troponins (hs-cTns) further independently predict all-cause and CV mortality, even in early CKD, supporting their role in CV risk stratification, although their routine clinical application warrants further study [119].

Circulating biomarkers reflecting extracellular matrix remodeling have emerged as promising candidates. Among these are the procollagen type III N-terminal propeptide (P3NP), a marker of type III collagen formation, the carboxy-terminal procollagen I carboxy-terminal propeptide (PICP), which reflects type I collagen synthesis and is less influenced by renal fibrosis and eGFR, and galectin-3 (Gal-3), which links inflammation to aldosterone-mediated fibrosis [7]. In a recent study involving 140 patients with end-stage kidney disease (ESKD), levels of P3NP, Gal-3, and the PICP were linked to reduced LVEF. Additionally, PICP correlates with key echocardiographic parameters, including the E/e' ratio, left atrial volume, and global longitudinal strain, indicating its potential to detect subclinical systolic and diastolic dysfunction in patients with advanced CKD [120]. In another study, elevated levels of PICP and Gal-3 were found to act synergistically, predicting both CV and all-cause mortality in patients on chronic hemodialysis [121].

Dysregulated circulating miRs are key epigenetic regulators in cardiac fibrosis [122]. A relatively recent meta-analysis found consistent downregulation of miR-126 and miR-223, markers of vascular dysfunction, in CKD patients [123]. Clinical evidence for miRs as biomarkers of CKD-CM is limited, though preliminary data link miR-133a to LVH and lower levels of miR-23a-3p, miR-30a-5p, and miR-451a to echocardiographic signs of ventricular dysfunction in dialysis patients [123,124,125].

5. Treatment

CKD-CM is a dynamic process characterized by fibrosis and LVH, which can ultimately progress to a dilated, dysfunctional ventricle. Targeting these pathological mechanisms leading to CKD-CM is therefore a central goal of treatment, aiming to improve patient outcomes and prevent the development of overt clinical disease. Equally important is primary prevention with the optimal management of risk factors, including diabetes, obesity, hypertension, and dietary contributors, which drive both renal and cardiac injury. Interventions that offer nephroprotective and cardioprotective actions are especially promising, as they address the intertwined progression of kidney and heart disease. Despite a mechanistic rationale for such approaches, evidence from clinical studies remains limited, as the routine exclusion of patients with advanced CKD from major CV trials has hindered progress, and robust data demonstrating improvement in hard CV endpoints are still sparse.

5.1 Established Strategies

5.1.1 Inhibition of the Renin–Angiotensin–Aldosterone System and Angiotensin Receptor–Neprilysin Inhibition

In CKD animal models, treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) reduces cardiac remodeling, partly independent of blood pressure [29,126,127,128,129]. In large randomized clinical trials (RCTs), finerenone, a selective non-steroidal MRA, has been shown to reduce CV events and mortality in patients with CKD and type 2 diabetes as well as in those with HFpEF or heart failure with mildly reduced ejection fraction (HFmrEF) [130,131]. Secondary analyses of these trials indicate that baseline LVH may predict a greater benefit of finerenone in reducing hospitalization for HF [132]. However, to date, no study of MRAs has demonstrated a significant reduction in LV mass or fibrosis in CKD patients that is independent of blood pressure. Regarding AF, a recent meta-analysis showed that MRAs, particularly spironolactone, significantly reduced AF events in patients with CKD compared with placebo [133].

Angiotensin receptor–neprilysin inhibitor (ARNI) therapy with sacubitril–valsartan improves outcomes in patients with HFrEF compared with treatment with ACE inhibitors or ARBs [134,135]. In a real-world cohort of patients with HFrEF and advanced CKD (eGFR <30 mL/min/1.73 m^2), ARNI therapy was associated with lower 1-year all-cause mortality and HF rehospitalization, as well as modest improvements in eGFR and LVEF compared with non-ARNI treatment [136].

5.1.2 Inhibition of the Sympathetic Nervous System

The contribution of sympathetic nervous system (SNS) activation to the pathogenesis of CKD-CM has been demonstrated by β-adrenergic receptor blockade, which attenuated cardiac hypertrophy and fibrosis in CKD rats, both in the presence and absence of blood pressure changes [32,137]. In a randomized trial of hemodialysis patients with hypertension and LVH, therapy with atenolol was associated with fewer serious CV events and hospitalizations compared with lisinopril, despite similar reductions in LVMi. However, the blood pressure control was superior with atenolol [138].

In a rat model of CKD, renal denervation attenuated atrial structural and electrophysiological remodeling, reduced AF susceptibility, and improved conduction abnormalities independent of blood pressure or renal function changes, suggesting that modulation of sympathetic overactivity may represent a potential strategy to lower AF risk in CKD-CM [139].

5.1.3 Blood Pressure and Volume Control

In individuals without CKD, LVH regression is linked to fewer CV events, and antihypertensive-induced reductions in LV mass improve outcomes. ACE inhibitors, ARBs, and Ca^{2+} channel blockers are generally more effective than β-blockers, while chlorthalidone, indapamide and potassium-sparing diuretics/hydrochlorothiazide may reduce LV mass more than ACE inhibitors/ARBs or hydrochlorothiazide alone [140]. However, the presence of CKD is associated with persistent LVH and a reduced likelihood of regression with antihypertensive therapy, and the limited number and small size of studies in this population render the evidence less conclusive [140]. Efforts to promote LVH regression in CKD remain important, as a meta-analysis identified that reduction in LV mass is a surrogate marker for improved survival [141]. Moreover, data from the Systolic Blood Pressure Intervention Trial (SPRINT) CKD subgroup indicate that intensive blood pressure control, targeting a systolic blood pressure (BP) of less than 120 mm Hg, improves CV outcomes, and real-world analyses show these benefits largely translate to trial-eligible CKD populations, with only a modest rise in adverse events [142].

Short daily or nocturnal hemodialysis reduces LVMi by 30% and 22%, respectively, with greater benefit in patients with baseline LVH or preserved residual renal function. However, despite LVMi reduction, CV mortality was not improved, highlighting that CKD-CM is only one contributor to the elevated cardiovascular disease (CVD) risk in CKD [7].

5.1.4 Sodium–Glucose Cotransporter 2 Inhibitors

Sodium–glucose cotransporter 2 inhibitors (SGLT2is), beyond glycemic control, provide substantial cardio–renal benefits relevant to CKD-CM [143]. By combining hemodynamic, metabolic, anti-inflammatory, and vascular effects, SGLT2is directly target the pathological mechanisms of CKD-CM, offering a promising strategy to slow or reverse cardiac remodeling and improve prognosis in this high-risk population [144,145,146,147,148,149,150,151,152,153,154]. Indeed, numerous randomized controlled trials have shown that SGLT2is reduce the risk of CV events and mortality in patients with type 2 diabetes, CKD, or HF across the full spectrum of LVEF, independent of diabetic status [155,156,157,158,159]. In these populations, SGLT2is have also been demonstrated to decrease LV mass and improve diastolic function [160].

Regarding patients with AF and CKD, a recent meta-analysis of 10 randomized controlled trials (RCTs) including 28,712 patients showed that SGLT2is modestly reduce atrial arrhythmias. A significant reduction was observed in the composite of AF and atrial flutter, although individual outcomes were not significant overall. Note that AF reduction was seen in larger, longer trials, in CKD patients without diabetes, and with empagliflozin, suggesting a context-specific antiarrhythmic benefit [161].

5.1.5 Glucagon-Like Peptide-1 Receptor Agonists

Preclinical and clinical studies indicate that glucagon-like peptide-1 (GLP-1) receptor activation improves coronary microvascular function by enhancing endothelial performance, increasing nitric oxide availability, and reducing oxidative stress and inflammation. GLP-1 receptor agonists (GLP-1 RAs) have also been associated with improved myocardial blood flow and perfusion reserve, particularly in high-risk individuals [162]. Emerging data further highlight the potential of GLP-1 RAs in managing HFpEF, especially in patients with obesity-related contributions. A recent meta-analysis of six randomized controlled trials including 8788 patients with HFmrEF or HFpEF found that GLP-1 RA therapy significantly reduced the risk of the composite endpoint of CV death or worsening HF [163]. In terms of kidney protection, the FLOW trial of 3533 patients with type 2 diabetes and CKD showed that semaglutide lowered the risk of the primary renal outcome by 24% vs placebo, with favorable effects also observed on eGFR decline, major adverse cardiovascular events (MACEs), CV death, and overall mortality [164]. A sub-analysis of the FLOW trial evaluated the renal effects of semaglutide in pa-

tients with type 2 diabetes and CKD according to baseline SGLT2i use. In participants on SGLT2is, the primary kidney composite outcome occurred in 14.8% of the semaglutide group vs 13.9% with placebo (hazard ratio [HR] 1.07; 95% confidence interval [CI]: 0.69–1.67), while in those not on SGLT2is, events occurred in 19.5% vs 24.9% (HR 0.73; 95% CI: 0.63–0.85), demonstrating that semaglutide provides renal benefits independent of SGLT2i therapy [165].

As for AF, a recent meta-analysis of 24 RCTs including 40,694 participants found that GLP-1 RAs and co-agonists reduced incident AF by 18% compared with placebo (risk ratio [RR] 0.82, 95% CI 0.70–0.96). The effect was consistent across agent type, individual compound, body mass index (BMI) category, diabetes status, trial design, and route of administration, with no modification by the degree of weight loss or concomitant SGLT2i use. This benefit appeared largely independent of weight reduction [166].

5.1.6 Device Therapy

The safety and efficacy of implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) devices have not been well established in patients with advanced CKD, and existing data suggest outcomes may be less favorable than in those without advanced CKD. Several factors may limit device effectiveness in this population. These include a higher prevalence of non-shockable arrhythmias, elevated defibrillation thresholds, loss of capture, myocardial fibrosis, coexisting AF, underuse of guideline-directed HF therapies, and increased rates of nonarrhythmic mortality [167].

In a large noninterventional cohort study of adults with CKD and HF with LVEF ≤40%, ICD placement was not significantly associated with improved survival, but it was linked to a higher risk of subsequent hospitalization for HF and increased all-cause hospitalizations. The excess hospitalizations may have been related to device-associated complications, such as infections and bleeding. Therefore, the potential risks and benefits of ICD therapy should be carefully weighed in patients with coexisting HF and CKD [168]. Furthermore, the ICD2 trial evaluated the efficacy and safety of ICD therapy for primary prevention of sudden cardiac arrest in patients with ESRD receiving dialysis and an LVEF of 35%. Although 13.8% of patients assigned to the ICD group experienced appropriate shocks for ventricular arrhythmias, ICD implantation did not translate into a reduction in all-cause mortality. Consequently, the study was terminated early due to futility [169].

Retrospective studies suggest that CRT may improve outcomes in patients with CKD [167]. In one study of patients with advanced CKD, CRT was associated with reductions in LV volumes and improved LVEF compared with ICD therapy alone, but only 30% met criteria for response, a rate that is lower than in the general HF population. Among responders (≥15% reduction in LV end-systolic volume [LVESV] at 6 months), most showed improvement in kidney function, and response was linked to better long-term outcomes, including survival, fewer HF hospitalizations, and reduced need for defibrillation therapy [170].

5.1.7 Kidney Transplantation

It is reasonable to assume that kidney transplantation, which addresses many of the pathophysiological factors underlying CKD-CM, would help reduce the CV morbidity and mortality associated with CKD. However, a meta-analysis did not support the notion that CKD-CM is fully reversible after renal transplantation. The analysis found no significant changes in LVMi, ejection fraction, or end-diastolic volume following transplantation. Note that the evidence was limited by methodological weaknesses, which should be considered when interpreting these findings [171]. A separate meta-analysis including 4122 kidney transplant recipients reported regression of LVH in studies assessed by echocardiography, whereas no such improvement was observed in studies using CMR. Blood pressure reduction emerged as the factor most strongly associated with LVH regression [172].

5.1.8 Erythropoiesis-Stimulating Agents

Anemia commonly accompanies CKD. Treatment with erythropoiesis-stimulating agents to correct CKD-related anemia has been associated with reductions in LV mass and wall thickness, particularly in patients with severe anemia (hemoglobin <10 g/dL) [173]. Note that hemoglobin levels above 13 g/dL have consistently been associated with higher mortality risk in patients undergoing hemodialysis [174]. Moreover, in patients with CKD or HF, erythropoiesis-stimulating agent resistance is relatively common and is linked to poorer outcomes [21].

5.1.9 Lipid-Lowering Agents

Dyslipidemia contributes to cardiovascular risk in CKD and may also influence myocardial remodeling. Statins have been shown to attenuate LV remodeling, reduce fibrosis, and limit atrial remodeling, although their benefit appears limited in advanced CKD and HFrEF [175,176]. While they remain widely used in earlier stages of CKD, evidence for direct benefit in CKD-CM is modest, particularly in dialysis populations [177,178,179]. Newer lipid-lowering therapies, including bempedoic acid, pemafibrate, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, may offer additional CV benefit. However, data specific to CKD-CM are lacking [176].

5.2 Prospective Treatment Strategies

5.2.1 Antifibrotic Agents

Cardiac and renal fibrosis are key pathological features of CKD-CM, and efforts to develop therapies targeting these processes are of significant clinical impor-

tance. In mouse models of cardiac fibrosis, serelaxin, the recombinant form of the human hormone relaxin, upregulates relaxin family peptide receptor 1 (RXFP1), which mediates inhibition of endothelial-to-mesenchymal transition (EndMT) and cardiac fibrosis. These findings suggest that serelaxin may have potential as an anti-fibrotic therapy in chronic HF [180]. Moreover, in a mouse model of dilated cardiomyopathy, serelaxin demonstrated potential nephroprotective effects by attenuating renal fibrosis and inflammation through reductions in TNF-α and IL-1α levels [181]. In humans, the RELAX-HF trial evaluated patients with acute HF and reported improvements in dyspnea, as well as reductions in all-cause and CV mortality at 180 days [182]. However, a later phase III study did not replicate these findings, showing that serelaxin infusion, compared with placebo, had no significant effect on all-cause or CV mortality, rehospitalization for HF or renal failure, or length of hospital stay [183].

Pirfenidone, approved for pulmonary fibrosis, also exerts cardiac anti-fibrotic effects in rodent and canine HF models [184]. In the PIROUETTE phase II study of patients with HFpEF and myocardial fibrosis detected by CMR, pirfenidone significantly reduced myocardial extracellular volume over 52 weeks [185]. Pirfenidone has also demonstrated renoprotective effects across several experimental models of kidney injury, primarily through modulation of TGF-β signaling [186]. These combined cardiac and renal anti-fibrotic effects suggest potential relevance in CKD-CM. However, data specifically in CKD-CM are lacking. Lastly, inhibition of IL-11 has been shown to reduce the cardiac and renal fibrotic effects of TGF-β in experimental models [57].

5.2.2 Other Prospective Treatment Targets

Neuregulin-1β (NRG-1β) is a stress-induced paracrine growth factor from endothelial cells that plays a key role in embryonic heart development. Abnormal NRG-1β expression is linked to CV diseases, including myocardial infarction and HF. Administration of recombinant human NRG-1β (rhNRG-1β) protects against ischemia/reperfusion injury, reduces cardiac fibrosis, and supports repair [187]. In a CKD rat model, rhNRG-1β slowed renal dysfunction and cardiomyopathy progression while lowering circulating uremic toxins, highlighting its potential as a novel therapeutic strategy for CKD-CM [188].

In patients with CKD, chronic systemic inflammation promotes vascular endothelial dysfunction and heightened arterial stiffness, both of which increase CV risk. Treatment with rilonacept, an IL-1 inhibitor, in patients with kidney failure enhanced brachial artery flow-mediated dilatation and reduced systemic inflammation [189]. However, its role in CKD-CM remains unclear.

Therapies aimed at uremic toxins or their related pathways may offer potential treatment strategies for CKD-CM. A study using an adenine-induced CKD mouse model showed that the oral adsorbent AST-120 can reduce tissue accumulation of uremic toxins, such as indoxyl sulfate and p-cresyl sulfate, and improve CKD-associated organ dysfunction, though clinical evidence in CKD-CM is lacking [190].

In vivo and *in vitro* studies indicate that unsaturated fatty acids may exert anti-inflammatory and antioxidant effects, protect vascular endothelial cells, inhibit thrombosis, modulate autonomic nerve function, improve LV remodeling, and regulate blood lipid levels [191]. A large randomized, double-blind trial in hemodialysis patients showed that daily supplementation with n-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) significantly reduced the rate of serious CV events compared with placebo. Benefits were observed across multiple CV outcomes, including cardiac death, myocardial infarction, stroke, and peripheral vascular disease, without an increase in adverse events [192]. Their direct impact on CKD-CM has not been specifically studied.

Experimental data suggest that blockade of FGF23 signaling may represent a novel strategy to enhance erythropoiesis and potentially improve outcomes in patients with CKD [193].

Finally, emerging evidence suggests that combined cardiorenal therapies may provide benefit in CKD populations, particularly in patients with HFpEF and earlier-stage CKD, where agents such as SGLT2is, MRAs, and GLP-1 RAs improve CV outcomes. However, most data derive from CKD or HF populations rather than CKD-CM specifically [194].

A summary of the major therapeutic strategies investigated for CKD-CM and their reported cardiovascular outcomes is provided in Table 1 (Ref. [7,21,29,32,57,126,127,128,129,130,131,132,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,168,169,170,171,172,173,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194]).

5.3 Practical Clinical Approach to CKD-CM

From a practical perspective, CKD-CM can be difficult to recognize early because structural cardiac changes often precede overt symptoms. Thus, the first step for diagnosis is to have a high index of clinical suspicion for this condition. CKD-CM should be suspected in patients with CKD, particularly those with an eGFR <60 mL/min/1.73 m^2, who present with dyspnea, fatigue, peripheral edema, or signs of volume overload, once alternative causes such as chronic lung disease, anemia, pulmonary embolism, or malnutrition and sarcopenia have been excluded.

Once suspected, echocardiography represents the first-line imaging modality, providing assessment of cardiac structure (LVH, LV geometry, and left atrium [LA] size) and function (LVEF, global longitudinal strain, dias-

Table 1. Pharmacological and interventional therapies in CKD-CM.

Therapeutic category	Intervention/ Compounds	Mechanism relevant to CKD-CM	Cardiac changes relevant to CKD-CM	Cardiovascular outcomes	Evidence source/Level	References
RAAS inhibition	ACE inhibitors/ARBs	↓Ang II-mediated hypertrophy, fibrosis, inflammation	↓LVH, fibrosis (animal models; partly BP-independent)	Established reduction in CV risk in CKD populations	Preclinical studies; RCTs	[29,126,127, 128,129]
	Finerenone (non-steroidal MRA)	Selective MR blockade, antifibrotic, anti-inflammatory	No proven BP-independent LV mass reduction	↓CV events, mortality in CKD + T2D; ↓HF hospitalization (greater with baseline LVH)	Large RCTs; post hoc analyses	[130,131,132]
ARNI therapy	Sacubitril-valsartan	RAAS blockade + neprilysin inhibition	↑LVEF	↓Mortality, HF hospitalization in HFrEF and advanced CKD	RCTs; observational data	[136]
SNS inhibition	β-blockers (atenolol)	↓Sympathetic-driven hypertrophy/fibrosis	↓LVH, fibrosis	↓CV events vs lisinopril (better BP control)	Preclinical studies; RCTs	[32,137,138]
	Renal denervation	↓Sympathetic overactivity	↓Atrial remodeling, AF susceptibility	No clinical data	Preclinical studies	[139]
Blood pressure and volume control	Intensive BP control (SPRINT CKD subgroup)	↓Afterload	Limited LVH regression in CKD	↓CV outcomes, ↑modest adverse events	RCT subgroup analyses; meta-analyses	[140,141,142]
	Nocturnal/ frequent HD	Improved volume control	↓LVMi	No reduction in CV mortality	RCTs	[7]
SGLT2 inhibitors	Empagliflozin, dapagliflozin	Natriuresis, ↓preload, metabolic optimization, anti-inflammatory, antifibrotic	↓LV mass; ↑diastolic function	↓CV events, mortality; ↓AF (modest)	RCTs; meta-analyses	[143,144,145, 146,147,148, 149,150,151,152, 153,154,155, 156,157,158, 159,160,161]
GLP-1 receptor agonists	Semaglutide, others	Metabolic, endothelial, anti-inflammatory	Improved myocardial perfusion; emerging HFpEF benefit	↓CV death/worsening HF; ↓AF; renal benefit	RCTs; meta-analyses	[162,163,164, 165,166]
Device therapy	ICD	Prevention of SCD	No remodeling effect	No survival benefit in CKD; ↑hospitalizations	RCTs; observational studies	[168,169]
	CRT	Resynchronization	↓LVESV; ↑LVEF (~30% responders)	Responders had improved survival and renal outcomes	Observational study	[170]
Kidney transplantation	Renal transplantation	Corrects uremic milieu, volume, anemia	Mixed LVH regression (echo vs CMR discrepancy)	Survival benefit vs dialysis; CKD-CM not fully reversible	Meta-analyses	[171,172]

Table 1. Continued.

Therapeutic category	Intervention/ Compounds	Mechanism relevant to CKD-CM	Cardiac changes relevant to CKD-CM	Cardiovascular outcomes	Evidence source/Level	References
ESA therapy	Erythropoiesis-stimulating agents	Corrects anemia	↓LV mass in severe anemia	No benefit if Hb >12 g/dL; ↑mortality at higher targets	RCTs; meta-analyses	[21,173]
Lipid-lowering drugs	Statins	↓LDL; anti-inflammatory	May improve remodeling (limited in advanced CKD)	No CV benefit in dialysis; benefit in non-dialysis CKD	RCTs	[175,176,177,178,179]
Antifibrotic agents (Investigational)	Serelaxin	Inhibits EndMT; antifibrotic	Preclinical benefit; early human signal	No benefit in phase III trials	Preclinical studies; RCTs	[180,181,182,183]
	Pirfenidone	↓TGF-β signaling	↓myocardial fibrosis (CMR)	Phase II data	Preclinical studies; phase II trial	[184,185,186]
	IL-11 inhibition	↓Fibroblast activation	↓cardiac/renal fibrosis	No clinical data	Preclinical study	[57]
Other emerging targets	rhNRG-1β	Cardiomyocyte repair, antifibrotic	Improved cardiac and renal parameters in CKD rats	Experimental	Preclinical studies	[187,188]
	Rilonacept (IL-1 inhibitor)	↓Inflammation; improved endothelial function	Improved flow-mediated dilation	No hard CV endpoint data	RCT (small)	[189]
	AST-120	↓Uremic toxin accumulation	Improved CKD-related organ dysfunction in mice	No clinical data	Preclinical study	[190]
	n-3 fatty acids (EPA/DHA)	Anti-inflammatory; endothelial protection	Indirect remodeling benefit	↓Serious CV events in HD patients	Preclinical studies; RCTs; meta-analyses	[191,192]
	FGF23 pathway inhibition	Modulates mineral metabolism; enhances erythropoiesis	Experimental	No clinical data	Preclinical study	[193]
Combination therapy	SGLT2i + Finerenone + GLP-1 RA	Multimodal (hemodynamic, metabolic, antifibrotic)	Greater LV mass reduction in HFpEF phenotype	↓MACE, HF hospitalization, CKD progression, mortality vs RAAS alone	Post hoc pooled analyses of RCTs	[194]

RAAS, renin–angiotensin–aldosterone system; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; Ang II, angiotensin II; MRA, mineralocorticoid receptor antagonist; MR, mineralocorticoid receptor; ARNI, angiotensin receptor–neprilysin inhibitor; SNS, sympathetic nervous system; BP, blood pressure; CKD, chronic kidney disease; CKD-CM, chronic kidney disease–associated cardiomyopathy; LVH, left ventricular hypertrophy; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMi, left ventricular mass index; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; AF, atrial fibrillation; CV, cardiovascular; SCD, sudden cardiac death; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; HD, hemodialysis; T2D, type 2 diabetes; SGLT2, sodium–glucose cotransporter 2; SGLT2i, sodium–glucose cotransporter 2 inhibitor; GLP-1, glucagon-like peptide-1; GLP-1 RA, glucagon-like peptide-1 receptor agonist; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; LDL, low-density lipoprotein; EndMT, endothelial-to-mesenchymal transition; TGF-β, transforming growth factor beta; IL-1, interleukin-1; IL-11, interleukin-11; rhNRG-1β, recombinant human neuregulin-1β; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; FGF23, fibroblast growth factor 23; MACE, major adverse cardiovascular event; RCT, randomized controlled trial; SPRINT, Systolic Blood Pressure Intervention Trial; CMR, cardiovascular magnetic resonance.

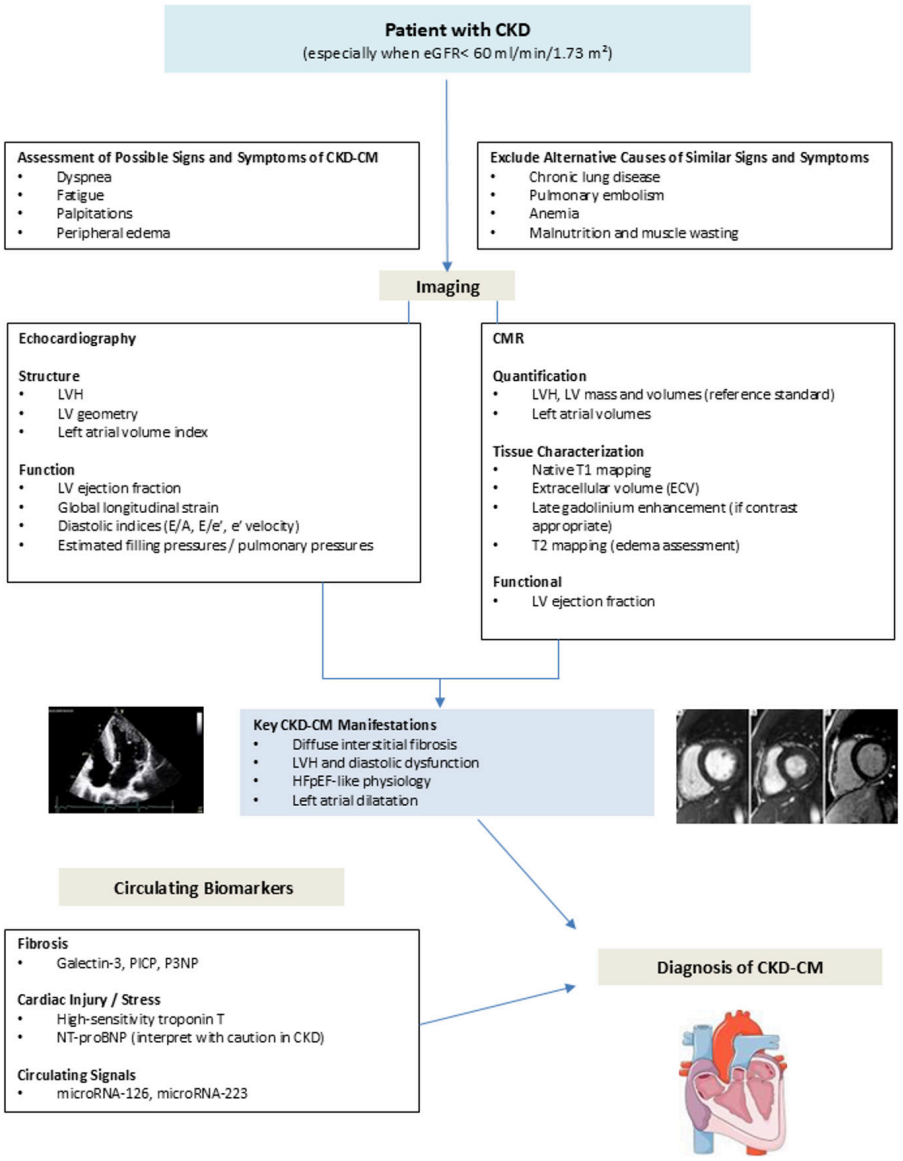

Fig. 2. Diagnostic evaluation of CKD-CM. This figure outlines the evaluation of CKD-CM in patients with CKD. Clinical assessment identifies possible signs and symptoms while excluding other causes. Echocardiography assesses LV structure, function, and filling pressures. CMR provides precise quantification of LV mass, volumes, and tissue characterization using T1 mapping, ECV, LGE, and T2 mapping. Circulating biomarkers of fibrosis, cardiac injury, and micro ribonucleic acid (miRs) support diagnosis. Combining clinical, imaging, and biomarker data helps identify key features of CKD-CM, such as diffuse fibrosis, LV hypertrophy, diastolic dysfunction, HFpEF-like physiology, and left atrial dilation, facilitating accurate diagnosis. eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CKD-CM, CKD-associated cardiomyopathy; LVH, left ventricular hypertrophy; LV, left ventricular; CMR, cardiovascular magnetic resonance; ECV, extracellular volume; HFpEF, heart failure with preserved ejection fraction; PICP, procollagen I carboxyterminal propeptide; P3NP, procollagen type III N-terminal propeptide; NT-proBNP, N-terminal pro b-type natriuretic peptide. Fig. 2 was created using Microsoft PowerPoint 2021 (Microsoft Corporation, Redmond, WA, USA).

tolic indices, and estimated filling pressures). These findings often reveal early concentric remodeling and diastolic dysfunction consistent with CKD-CM.

In selected patients, CMR offers superior tissue characterization and enables quantification of LV mass and volumes, as well as detection of diffuse interstitial fibrosis through T1 mapping and extracellular volume expansion. Late gadolinium enhancement may further identify focal replacement fibrosis, while functional assessment confirms ventricular performance.

Complementary to imaging, circulating biomarkers support disease characterization and risk stratification. Markers of fibrosis (e.g., Gal-3, PICP, P3NP), myocardial injury and stress (hs-cTnT, NT-proBNP), and emerging cir-

culating miRs (e.g., miR-126, miR-223) reflect the multisystem nature of CKD-CM and may enhance early detection.

Collectively, integration of clinical assessment, echocardiography, CMR findings, and circulating biomarkers enables a comprehensive diagnostic framework for CKD-CM, as illustrated in Fig. 2, and provides the basis for subsequent therapeutic stratification.

From a practical standpoint, the management of CKD-CM should prioritize therapies with proven cardio–renal benefit and potential to modify myocardial remodeling. SGLT2is represent the cornerstone of treatment, consistently reducing CV events and HF outcomes across CKD populations, while also improving LV mass and diastolic function [155,156,157,158,159,160]. MRAs, particularly finerenone, provide additional benefit by reducing CV events and mortality in patients with CKD and type 2 diabetes, with emerging evidence suggesting greater efficacy in those with baseline LVH [130,131,132]. GLP-1 RAs further complement this strategy, especially in patients with metabolic comorbidities, improving CV outcomes, reducing progression of kidney disease, and showing benefit in HFpEF phenotypes [163,164,165].

Taken together, these agents form a mechanistically complementary, disease-modifying approach targeting hemodynamic load, metabolic dysfunction, inflammation, and fibrosis. In clinical practice, early initiation and combination of these therapies, on a background of RAAS inhibition and optimal blood pressure control, represent the most effective strategy to attenuate cardiac remodeling and improve outcomes in CKD-CM.

6. Conclusion

CKD-CM begins early in the course of renal dysfunction, progresses in parallel with declining kidney function, and culminates in a high-risk cardiac phenotype marked by diastolic dysfunction, myocardial fibrosis, and arrhythmogenic remodeling. With advancing CKD, hemodynamic stress, neurohormonal activation, inflammation, and metabolic derangements can lead clinically to HFpEF and increased risk of SCD due to arrhythmias.

These findings support the concept of CKD-CM as a potentially modifiable and preventable condition rather than an inevitable complication of advanced CKD, highlighting the importance of early recognition of subclinical cardiac involvement and timely therapeutic intervention targeting key pathophysiological pathways.

Future research should focus on the clinical translation of emerging antifibrotic and cardiorenal-targeted therapies, the development and validation of sensitive biomarkers and advanced imaging techniques for early detection, and the evaluation of long-term outcomes of combination therapeutic strategies addressing multiple pathways. It is important that therapeutic success should extend beyond slowing CKD progression to include prevention of advanced myocardial remodeling, reduction in HF and arrhythmic events, and ultimately improved CV and overall survival.

Key Points

• Chronic kidney disease-associated cardiomyopathy (CKD-CM) is a progressive myocardial disorder that develops across the entire spectrum of CKD and is characterized by structural and functional cardiac alterations.

• The pathogenesis of CKD-CM is multifactorial, involving hemodynamic overload, neurohormonal activation, uremic toxicity, inflammation, and cardiac fibrosis.

• Despite advances in cardiovascular and renal therapeutics, effective disease-modifying treatments for CKD-CM remain limited, particularly in advanced stages of CKD.

• Early detection and timely intervention during the initial phases of CKD represent the most effective strategy to reduce cardiovascular morbidity and mortality.

• Improved understanding of the underlying mechanisms of CKD-CM may facilitate the development of targeted therapies and enable prevention or attenuation of disease progression.

Availability of Data and Materials

Not applicable.

Author Contributions

KG: Conceptualization, Methodology, Investigation, Visualization, Project administration, Writing—original draft. VL: Conceptualization, Methodology, Writing—original draft. AC: Conceptualization, Methodology. PT: Conceptualization, Methodology. PI: Conceptualization, Methodology. AA: Conceptualization, Methodology. NK: Conceptualization, Methodology. EK: Conceptualization, Methodology. APA: Conceptualization, Methodology. NF: Conceptualization, Methodology, Supervision. DP: Conceptualization, Methodology, Supervision. PK: Conceptualization, Methodology, Investigation, Validation, Supervision. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

Given his role as an Editorial Board Member, Dimitrios Patoulias had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Xinghui Li. The other authors declare no conflicts of interest.

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