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CKJ REVIEW

Cardiomyopathy in chronic kidney disease: clinical features, biomarkers and the contribution of murine models in understanding pathophysiology

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ABSTRACT

The cardiorenal syndrome (CRS) is described as a multi-organ disease encompassing bidirectionally heart and kidney. In CRS type 4, chronic kidney disease (CKD) leads to cardiac injury. Different pathological mechanisms have been identified to contribute to the establishment of CKD-induced cardiomyopathy, including a neurohormonal dysregulation, disturbances in the mineral metabolism and an accumulation of uremic toxins, playing an important role in the development of inflammation and oxidative stress. Combined, this leads to cardiac dysfunction and cardiac pathophysiological and morphological changes, like left ventricular hypertrophy, myocardial fibrosis and cardiac electrical changes. Given that around 80% of dialysis patients suffer from uremic cardiomyopathy, the study of cardiac outcomes in CKD is clinically highly relevant. The present review summarizes clinical features and biomarkers of CKD-induced cardiomyopathy and discusses underlying pathophysiological mechanisms recently uncovered in the literature. It discloses how animal models have contributed to the understanding of pathological kidney–heart crosstalk, but also provides insights into the variability in observed effects of CKD on the heart in different CKD mouse models, covering both "single hit" as well as "multifactorial hit" models. Overall, this review aims to support research progress in the field of CKD-induced cardiomyopathy.

Keywords: animal, biomarker, cardiorenal, uremic cardiomyopathy

INTRODUCTION

According to the World Health Organization (WHO), an estimated 17.9 million people globally die from cardiovascular diseases (CVD) every year, particularly from heart attacks and strokes [1]. In Europe, this number is about 1.68 million [2]. Dialysis patients present CVD mortality rates approximately 10–30 times higher than the general population. Overall, ∼50% of patients with advanced chronic kidney disease (CKD) (stage 4–5) face CVD and about 40%–50% of them die as a consequence of this [3].

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This multi-organ disease affecting bidirectionally heart and kidney is called the cardiorenal syndrome (CRS) [4]. CRS is divided into five main types. The first two encompass a primary cardiac injury leading to secondary acute or chronic renal pathology, respectively. The types 3 and 4—also called renocardiac syndrome—involve an acute, respectively, chronic kidney injury that leads to cardiac injury; and in type 5—also referred to as secondary CRS—kidney and heart injury are found concomitant with systemic conditions [5, 6].

CKD patients display an increased prevalence and progression of atherosclerosis, contributing to the increased risk of myocardial infarction and stroke [7]. Furthermore, vascular calcification and vascular stiffness represent crucial factors contributing to elevated cardiovascular morbidity and mortality in the CKD population [8]. Also, cardiac tissue remodeling with development of myocardial interstitial fibrosis and left ventricular hypertrophy (LVH), the hallmarks of uremic cardiomyopathy, together with molecular and electrical alterations in the heart, lead to heart failure and arrhythmias [9].

Systemic molecular alterations contributing to increased cardiovascular risk in CKD include a neurohormonal dysregulation and an accumulation of uremic toxins, playing an important role in the development of tissue and systemic inflammation and oxidative stress [10]. This promotes not only further kidney injury but also heart cellular damage, as well as endothelial and vascular dysfunction [11]. The present review will focus on uremic cardiomyopathy, its clinical features and biomarkers, as well as underlying pathophysiological mechanisms recently uncovered in literature. Also, we will discuss animal models that have been used to study the effect of CKD on the heart, building partly on our recent systematic review with meta-analysis of cardiac phenotyping in mouse models of CKD [12].

UREMIC CARDIOMYOPATHY: CLINICAL FEATURES

Uremic cardiomyopathy is characterized by LVH and cardiac interstitial fibrosis and is associated with cardiac electrical dysregulation. Here we will discuss the clinical features involved in the pathology as well as biomarkers of increased cardiovascular risk in CKD patients.

Cardiac remodeling: left ventricular hypertrophy and fibrosis

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is described as a thickening of the left ventricle wall and an increased LV mass [13]. In patients in early CKD stages [with estimated glomerular filtration rates (eGFRs) above 60 mL/min/1.73 m^2] the prevalence of cardiac hypertrophy is ∼30% [14]. Progressively, LVH incidence increases with loss of renal function [14]. While CKD3–4 patients have a LVH prevalence of up to 40%, this is 70%–90% in patients with end-stage renal disease (ESRD) (Table 1) [14–18].

An increased number of sarcomeres, triggered by mechanical stress, leads to an enlargement of the cardiomyocytes, and forms a compensatory mechanism of the heart to maintain cardiac function [13]. These structural changes are strongly associated with diastolic dysfunction [19], with LVH as a strong independent and early predictor of cardiovascular events and mortality [18, 20–22]. LVH is also associated with an increase in oxidative stress and inflammation [23, 24].

LVH was revealed in CKD patients by echocardiography (Table 1) [14, 15, 17–19, 25]. Furthermore, Izumaru *et al.* reported an increased cardiac cell size in the left ventricular wall as well as an increased myocardial wall thickness in autopsies of CKD patients [26]. LVH is a direct consequence of an increased cardiac preload and afterload in CKD patients [19]. Whereas an increased preload is caused by volume overload, cardiac afterload is a pressure overload as result of arterial stiffness, arterial hypertension or aortic valve stenosis.

Cardiac fibrosis

Myocardial fibrosis after kidney injury is characterized by a production of extracellular matrix, such as collagens [27]. Clinical and autopsy studies revealed that CKD patients present more cardiac interstitial fibrotic tissue than non-CKD patients [26, 28] (Table 1). Aoki *et al.* analyzed left ventricular endomyocardial biopsies of hemodialysis patients, elucidating that 42% of them presented cardiac fibrotic deposits [29]. By contributing to severe left ventricular stiffness, cardiac fibrosis can induce cardiac dysfunction and is an important pathophysiological contributor to ventricular arrhythmias and atrial fibrillation [30].

During CKD, cardiac fibrosis develops together with LVH [31], triggered by hemodynamic alterations (pressure overload) and a disturbed secretion of systemic soluble factors, including catecholamines, angiotensin (Ang) II and aldosterone, cytokines and uremic toxins [32, 33].

Cardiac electrical changes

Around one-third (25%–39%) of mortality in dialysis patients is a result of sudden cardiac death [34–36], which are mainly caused by atrial arrhythmias [37, 38]. One of three dialysis patients present atrial arrythmias [37]. Akoum *et al.* showed that the mean rate of any type of cardiac arrhythmia was 88.8 episodes per person-year in CKD patients, with atrial fibrillation observed at a rate of 37.6 per year [39]. Not only arrhythmias, but also a prolongation of the QT interval is found in CKD patients (Table 1). Approximately 50% of hemodialysis patients had at least one electrical conduction disorder, including a prolongation of the QTc interval (i.e. the QT interval corrected for heart rate), a QTc dispersion or ventricular and atrial premature contractions [40–43].

Arrhythmia was revealed in CKD patients by electrocardiography studies, mainly in patients with LVH [44]. Cardiac fibrosis can contribute to ventricular arrhythmias and atrial fibrillation through left ventricular stiffness [30]. Also, increased inflammatory processes are correlated to the initiation and maintenance of atrial fibrillation [45]. Furthermore, hyperkalemia is frequent in ESRD patients, being observed in 5%–10% of patients undergoing maintenance hemodialysis [46]. It is caused by imbalances between excess potassium intake and insufficient removal as well as alterations in cellular potassium uptake versus secretion, amongst other things [46]. Hyperkalemia triggers cell hyperpolarization and disturbed cardiac conductivity [46]. It is frequently associated with peaked T-waves, a prolonged PR interval and a widened QRS complex, and—in severe hyperkalemia—a total absence of P-waves [47].

Also, the dialysis procedure itself may increase the risk of arrhythmias and atrial fibrillation, as observed during but also directly after the dialysis session [48–50], potentially through electrolyte shifts in the blood and/or volume changes [35, 48]. Hemodialysis increases QTc dispersion and the QTc interval, especially when using a low-calcium dialysate, with the QTc

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Table 1: Clinical features of uremic cardiomyopathy in CKD.

CKD-induced cardiovascular outcome	CKD population studied	Patient number	Observation	Analysis	Ref.
Cardiac remodeling	Patients with eGFR ≥60 (CKD 1 and 2), 45–59 (CKD 3a), 30–44 (CKD 3b) and <30 mL/min/1.73 m² (CKD 4 and 5)	3487	LVH in 32%, 48%, 57% and 75% for CKD1-2, CKD 3a, CKD 3b and CKD 5, respectively	Echocardiography	[14]
	Patients with ESRD (CKD5, for >6 months)	433	Ventricular dilatation in 32% and LVH in 74% of patients	Echocardiography	[15]
	Patients with CrCl between 4 and 163 mL/min (not on dialysis); or under hemodialysis (CKD5HD)	296	LVH in 39%, ∼65% and ∼70% in patients with CrCl of 163 to 75 mL/min; 21 to 4 mL/min and HD, respectively	Echocardiography	[17]
	Patients with eGFR <90 mL/min/1.73 m² (CKD2–5)	225	LVH detected in 38.7% of patients	Echocardiography	[19]
	Patients on hemodialysis (CKD5HD, for >3 months)	153	LVH was present in 90% of patients	Echocardiography	[18]
	Patients with CKD 1–3	90	LV concentric hypertrophy in 22.2% and eccentric in 18.9% of patients	Echocardiography	[25]
	Patients with eGFR <30 mL/min/1.73 m² (CKD3b–5)	334	LVH and cardiac fibrosis in 3.22%, 4.33%, 3.83% and 6.14% for CKD 1-2, CKD 3a, CKD 3b and CKD 4-5	*Post-mortem* histology	[26]
	Patients with eGFR <89 mL/min/1.73 m² (CKD2–5)	160	Intermyocardiocytic fibrosis in 91% of patients	*Post-mortem* histology	[28]
	Patients under hemodialysis (CKD5HD) with dilated cardiomyopathy	40	Severe fibrosis in 42% of patients	Left ventricle endomyocardial biopsies	[29]
Cardiac electrical disturbances	Patients with eGFR 38 ± 13 mL/min/1.73 m² (CKD3a–4)	38	Mean 88.8 episodes of any type of cardiac arrhythmia: 37.6 of atrial fibrillation per year in CKD patients	Electrocardiogram	[39]
	Patients on hemodialysis (CKD5HD)	221	ST-T changes in 60% of patients	Holter electrocardiogram	[40]
	Patients on hemodialysis (CKD5HD)	34	Increased QT and QTc interval and QT and QTc dispersion in all patients	Electrocardiogram	[41]
	Patients on hemodialysis (CKD5HD)	94	Ventricular premature contractions in 85.1%, atrial in 56.4% and supraventricular arrhythmia in 16% of patients	Echocardiography	[42]
	Patients on hemodialysis (CKD5HD)	179	Electrical conduction disorder in 50% of patients (QTc interval prolongation)	Electrocardiogram	[43]

CrCl, creatinine clearance.

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interval changes inversely correlated with calcium changes in the serum [51]. Furthermore, intradialytic hypotension is frequent during hemodialysis, triggering myocardial stunning and increasing the risk of cardiovascular events and mortality [52].

HUMAN BIOMARKERS OF CARDIOVASCULAR RISK IN CKD

Table 2 and Fig. 1 summarize human biomarkers in blood that are associated with increased cardiovascular risk in patients suffering from CKD. Of note, this overview is not restricted to uremic cardiomyopathy but also includes biomarkers of atherosclerosis risk, as specified in Table 2.

Kidney injury parameters

Among markers reflecting the loss of kidney function, urea and cystatin C are associated with increased cardiovascular events in non-dialysis CKD patients [53–55], for urea independently of eGFR [53]. In a Mendelian randomization study, van der Laan *et al.* also identified an association between cystatin C and CVD independent of the eGFR, however without detecting an underlying causal role of cystatin C in CVD risk [56].

Cardiac injury parameters

Among typical cardiac injury biomarkers in the general population, the N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a strong predictor of CRS in CKD patients, and its use has been reported to benefit CKD/dialysis patients for an early identification of heart failure [57–59]. Recently, the prognostic ability of NT-proBNP towards cardiovascular mortality in advanced CKD was questioned, with de la Espriella *et al.* observing that the significant association of NT-proBNP with cardiovascular mortality was progressively lost in patients with an eGFR <45 mL/min/1.73 m^2 [60]. In addition, BNP and cardiac troponin (cTNT) predict adverse cardiovascular outcome in CKD/dialysis patients [61–64], and cTNT in non-dialysis CKD patients associated with LVH, reduced LV ejection fraction and LV diastolic dysfunction, also after adjustment for eGFR [63]. BNP is a member of the natriuretic peptide system with natriuretic, diuretic and vasodilative properties [4]. In response to pressure or volume overload it is increasingly secreted by cardiomyocytes as a compensatory mechanism to reduce pressure and volume overload [65]. Once secreted, proBNP is cleaved into NT-proBNP and the bioactive BNP [66]. cTNT is released from cardiomyocytes into the circulation upon cardiac injury such as ischemia as a consequence of cardiomyocyte necrosis [67].

Another marker, cancer antigen 125 (CA125), emerged in the literature as positively and consistently associated with a higher risk of 1-year all-cause and cardiovascular mortality throughout the whole spectrum of eGFR categories, independent of kidney function [60]. Serum CA125 levels are also associated with LV dysfunction in hemodialysis patients [68].

Galectin-3 (Gal-3), a β-galactoside-binding lectin that is released from injured and inflammatory cells and a biomarker of heart failure and myocardial infarction in the general population [69], is positively associated with both LVH [70] and adverse vascular outcomes in CKD patients, e.g. endothelial dysfunction and increased vascular reactivity [71]. The main pathophysiological role of Gal-3 is described as promoting fibrosis in both cardiac and kidney tissue by inducing fibroblast proliferation but also collagen deposition. Along this line, it has been implicated in the heart in the cardiac remodeling process and the progression to heart failure, while in the kidney Gal-3 is involved in progression of kidney dysfunction [66].

Inflammation parameters

The inflammatory biomarkers interleukin (IL)-6 and C-reactive protein (CRP) can predict overall and cardiovascular mortality, and cardiovascular and vascular events in cohorts of patients at different CKD stages [72–78], independent of eGFR [73, 75]. Stable high levels as well as trimestral variations of IL-6, CRP and tumor necrosis factor alpha (TNF-α) are associated with higher mortality in hemodialysis patients [79, 80]. Increased plasma IL-6 levels, as found in CKD patients, are caused by an increased generation triggered by oxidative stress, chronic inflammation and fluid overload [81], as well as by a minimized clearance of IL-6 in ESRD patients. Increased IL-6 levels further impair kidney function, and stimulate inflammation and atherosclerosis [82]. IL-6 is considered to be a strong biomarker of the severity of inflammation as well as of atherosclerosis in CKD patients [76] and its levels can predict overall and cardiovascular mortality in patients at different stages of CKD [75].

Furthermore, serum levels of osteopontin are negatively correlated to eGFR in CKD patients and can predict cardiovascular events in CKD patients [83]. Also, increased levels of soluble TNF-like weak inducer of apoptosis (sTWEAK) were identified to be associated with all-cause mortality in dialysis patients [84]. On the other hand, Fernández-Laso *et al.* observed sTWEAK to be negatively associated with atherosclerotic plaques and cardiovascular event risk in CKD patients [85]. TWEAK interacts with its specific receptor fibroblast growth factor-inducible molecule 14 (Fn14), which is normally expressed at very low levels, but is highly upregulated in pathological conditions such as atherosclerosis [86]. The TWEAK/Fn14 axis is involved in all steps of atherosclerotic plaque development, such as inducing the expression of adhesion molecules in endothelial cells in the beginning of plaque development, and activation of nuclear factor κB, a transcription factor highly contributing to atherosclerosis [86, 87].

Parameters of mineral bone disorder

In patients with CKD-mineral bone disorder (MBD), plasma fibroblast growth factor 23 (FGF23) concentration is a strong predictor of CRS and increases due to significant changes in phosphate or serum parathyroid hormone (PTH) concentration. High FGF23 levels are associated with mortality, vascular calcification and LVH in CKD/dialysis patients [88–92]. Elevated FGF23 was independently associated with increased LV mass index after adjustment for eGFR and CKD stage [93]. Also, CKD-MBD patients display a deficiency of Klotho and vitamin D. Low levels of Klotho are a robust predictor of CVD in CKD. They are associated with cardiovascular events, mineral-bone disease and subclinical atherosclerosis in CKD/dialysis patients [94–99]. Active vitamin D is important for the absorption of calcium from the intestine into the blood. A decrease in vitamin D in CKD and thereby reduced calcium intestinal uptake, together with a reduction of phosphate urine excretion, triggers a compensatory increase in PTH and FGF23, which can lead to secondary hyperparathyroidism [100, 101]. Furthermore, vitamin D deficiency is associated with cardiovascular outcomes, sudden cardiac death and inflammation in CKD/dialysis [102–104].

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Table 2: Human biomarkers of increased cardiovascular risk in blood of CKD patients.

	Biomarker	Description
Kidney injury	Urea	Predictor of CVD in patients with CKD, independently of eGFR [53]
	Cystatin C	Predictor of CVD and mortality in patients with CKD [55]
Cardiac injury	NT-proBNP	Predictor of CVD in patients with CKD [57–59]. Early biomarker of HF for patients in initial stages of CKD (eGFR >45 mL/min/1.73 m^2) [60]
	BNP	Predicts adverse cardiovascular outcome and death in CKD/dialysis patients [61, 62]
	cTnT	Predicts cardiovascular events in patients with CKD [64]. It is correlated to LVH, LV systolic and diastolic dysfunction, independently of eGFR [63]
	CA125	Associated with all-cause and cardiovascular mortality in patients with CKD in all eGFR categories and independently of kidney function [60]. Associated with cardiac dysfunction [68]
	Gal-3	Associated with LVH [70] and adverse vascular outcomes in patients with CKD [71]
Inflammation	CRP	Predicts future myocardial infarction and mortality in patients with CKD [72]
	IL-6	Associated with history of CVD and predicts mortality in patients with CKD [73–76, 78, 79], independently of eGFR [73, 75]
	TNF-α	Stable high levels are related to mortality in hemodialysis patients [79]
	Osteopontin	Predicts cardiovascular events in CKD [83]
	sTWEAK	Increased levels are associated to all-cause mortality in dialysis patients [84], although others identified sTWEAK to negatively associate to atherosclerotic plaques and cardiovascular event risk in CKD [85]
Mineral-bone disorder	FGF23	Strong predictor of CVD in CKD. Associated with CVD and mortality in patients with CKD [88–92]. Associated with increased LV mass independently of eGFR and CKD stage [93]
	α-Klotho	Strong predictor of CVD in CKD. Low levels are associated with CVD, mineral-bone disease and subclinical atherosclerosis in patients with CKD [94–99]
	Vitamin D	Low levels are associated with CVD, sudden cardiac death, inflammation and hypocalcemia in patients with CKD [104]. Supplementation promotes improvement of vascular function [186]
Uremic toxins	IS	Strong predictor of CVD in CKD. Associated with vascular calcification, ventricular septal thickness, mitral regurgitation and mortality in CKD [106, 109, 111], independently of kidney function [109]
	PCS	Strong predictor of CVD in CKD. Predicts CVD risk in patients with CKD [108, 110, 112], independently of GFR [108]

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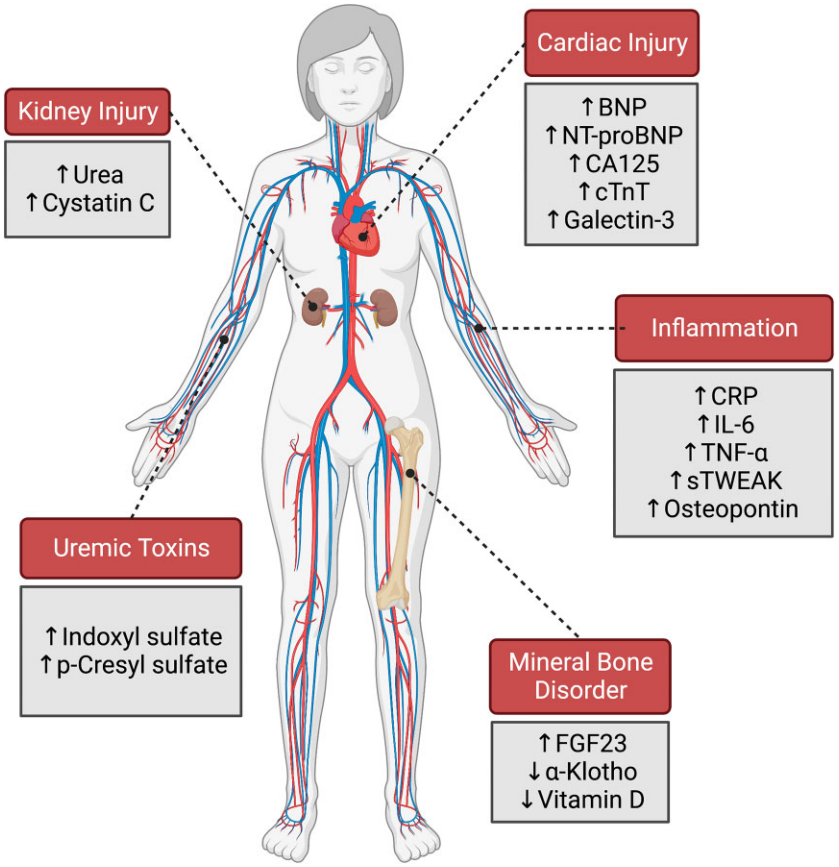


Figure 1: Human biomarkers of increased cardiovascular risk in patients with CKD. Parameters of kidney injury, cardiac injury, inflammation and mineral bone disorder, as well as uremic toxins have been associated with increased cardiovascular risk in patients with CKD. For more information, see text.

Uremic toxins

The accumulation of uremic toxins can predict cardiac outcomes in CKD patients. Both indoxyl sulfate (IS) and p-cresyl sulfate (PCS) are associated with CKD progression and are effective in the detection and prediction of mortality risk and CVD in CKD/dialysis patients [105–108], with mortality prediction (by IS) and predictability of cardiovascular events (by PCS) also after adjustment for kidney function markers [109, 110]. In addition, IS and PCS are associated with vascular calcification, ventricular septal thickness, mitral regurgitation and mortality in CKD [111, 112].

UREMIC CARDIOMYOPATHY: PATHOPHYSIOLOGICAL MECHANISMS

Pathophysiological mechanisms that are involved in the establishment of CKD-induced cardiomyopathy include hemodynamic alterations, inflammatory processes, oxidative stress, disturbances in the mineral metabolism as well as the accumulation of uremic toxins [113]. The understanding of not only the signals that initiate these mechanisms in response to kidney damage, but also of their consequences in distant organs, is of paramount importance. Yet, rather few studies clarified effects of CKD on cardiac remodeling on mechanistic level. Table 3 and Fig. 2 summarize the main mediators that have been studied in animal models and their role in cardiac outcomes in CKD.

RAAS, SNS and mineralocorticoid receptor signaling: hemodynamic regulation and beyond

During CRS 4, a permanent status of fluid overload is frequent [114] and 60%–90% of patients display hypertension, dependent on CKD stage [115]. This is caused by a chronic activation of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system (SNS) [116] as well as of mineralocorticoid receptor (MR) overactivation [117]. In addition to hemodynamic and blood pressure effects, their activation also contributes to vascular stiffness and processes of inflammation, oxidative stress and fibrosis [116, 117].

The importance of the RAAS in the pathogenesis of CKD is widely appreciated, with Ang II as a central mediator of kidney injury due to its ability to produce glomerular capillary hypertension damaging glomerular epithelial, endothelial and mesangial cells [118, 119]. Furthermore, the inhibition of RAAS by angiotensin-converting enzyme (ACE) inhibition or angiotensin receptor blockers (ARB) appears to be beneficial to the heart in uremic cardiomyopathy. At least in part, these effects seem to be independent of blood pressure reduction. Kovács *et al.* studied the role of Ang II by inhibiting its effect through Ang II type 1 receptor (AT1) using the ARB losartan in a model of 5/6 nephrectomy (SNX)-induced CKD for 13 weeks. They observed that uremic cardiomyopathy, including CKD-induced diastolic dysfunction, LVH, cardiac fibrosis and cardiac inflammation, can be prevented or strongly slowed by losartan when the administration starts in early CKD stage before the manifestation

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Table 3: Mediators studied in animal models for their role in cardiac outcomes in CKD.

Pathological process	Mediator studied	CKD model	Species	Treatment or genetic deficiency	Cardiac outcome (compared with CKD group)	Ref.
RAAS, SNS and MR signaling: hemodynamic regulation and beyond	Ang II	SNX-induced CKD for 13 weeks	Wistar rats	Losartan treatment (AT1 inhibitor)	Prevention of diastolic dysfunction, LVH, cardiac fibrosis and cardiac inflammation. Blood pressure–independent effect	[120]
		SNX-induced CKD for 12 weeks	C57BL/6 mice	Valsartan treatment (AT1 inhibitor); AT1 knockout mice	Reduced cardiomyocyte hypertrophy and interstitial fibrosis. Blood pressure–independent effect	[121]
		SNX-induced CKD for 8 weeks	Sprague Dawley rats	LCZ696 treatment (Ang receptor + neprilysin inhibitor)	Reduced cardiac fibrosis. Attenuation of cardiac hypertrophy, inflammation and oxidative stress markers	[122]
	ACE	Unilateral urinary obstruction for 3 weeks	C57BL/6 mice	Enalapril treatment (ACE inhibitor)	Attenuation of cardiac fibrosis. Blood pressure–independent effect	[123]
	β1-AR	SNX-induced CKD for 10 weeks	Wistar rats	Atenolol and carvedilol (selective and non-selective blockers of β1-AR, respectively)	Reduced blood pressure, cardiac hypertrophy, fibrosis and cardiac apoptotic signaling	[126]
	MR	Subtotal Nx-induced CKD for 10 weeks	B6D2 mice	Finerenone treatment	Prevention of LVH and cardiac fibrosis; attenuated decrease of LV fractional shortening and ejection fraction; improvement in diastolic dysfunction	[132]
Inflammation	IL-6	SNX-induced CKD for 4 weeks	129S1/SvImJ mice	MR16-1	Reduced cardiac fibrosis and inflammation	[134]
	TLR4	Aldosterone administration for 12 weeks	Wistar rats	TAK-242 (TLR4 inhibitor)	Reduced cardiac fibrosis and inflammation	[135]
	NOD1	SNX-induced CKD for 6 weeks	C57BL/6 mice	NOD1 knockout	Prevention of intracellular Ca^{2+} mishandling	[136]
Regulators of mineral metabolism	FGF23	SNX-induced CKD for 4 weeks	Sprague Dawley rats	FGFR4 monoclonal antibody	Prevention of LVH	[137]
	FGF23	High phosphate diet	C57BL/6 mice	FGFR4 knockout	Prevention of LVH	[137]
	Klotho	SNX-induced CKD for 5 weeks	129S1/SvImJ mice	Klotho heterozygous knockout; treatment with recombinant soluble Klotho	Aggravated cardiac hypertrophy compared with wild-type CKD mice. Klotho treatment ameliorated cardiac hypertrophy in Klotho-deficient CKD mice	[142]
Uremic toxins	IS	Klotho +/–; IS induced-CKD	C57BL/6 and Balb/c mice	Long IS administration (8 weeks)	In WT, IS induced LVH; Klotho-deficient mice, aggravated IS-induced LVH	[145]
	IS	SNX-induced CKD for 12 weeks	Sprague Dawley rats	AST-120 (uremic toxins-reducing agent)	Attenuation of cardiac fibrosis	[146]
	PCS	SNX-induced CKD for 8 weeks	C57BL/6 mice	Long PCS administration (8 weeks)	Impairment of LV diastolic function, cardiac apoptosis and cardiac fibrosis	[147]
Other	mTOR	UNX-induced CKD for 8 weeks	129S1/SvImJ mice	Rapamycin (mTOR inhibitor)	Inhibition of cardiac hypertrophy and fibrosis. Blood pressure–independent effect	[149]

β1-AR, beta-1 adrenergic receptor; LCZ696, combination of sacubitril and valsartan; Nx, nephrectomy; TAK-242, TLR4 inhibitor; UNX, unilateral nephrectomy.

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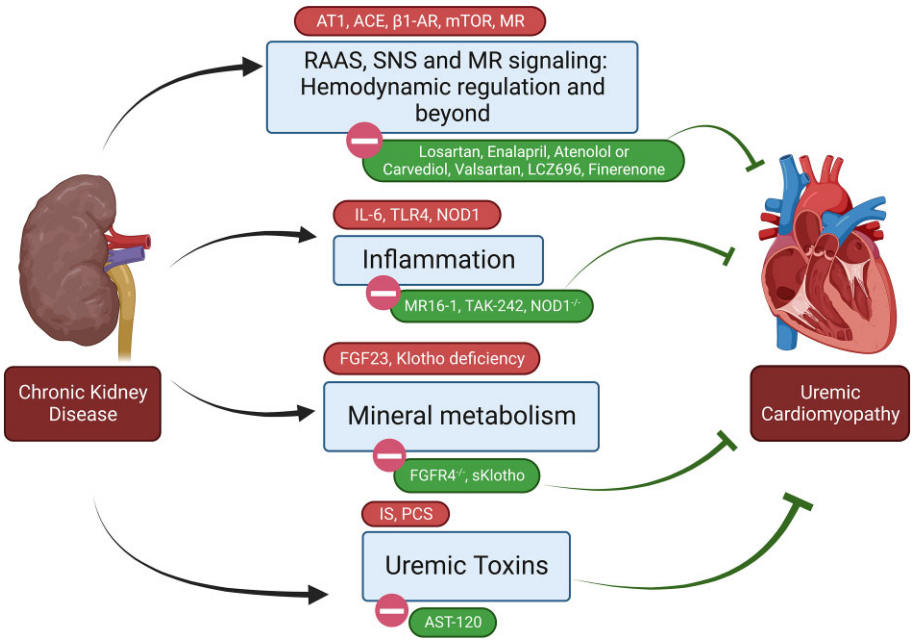


Figure 2: Pathophysiological mechanisms studied in animal models of CKD-induced cardiomyopathy. CKD triggers pathophysiological effects like hemodynamic alterations through the RAAS, the SNS and MR signaling, inflammation and oxidative stress, disturbances in mineral metabolism and the accumulation of uremic toxins. In red, molecular mediators are indicated that have been identified to contribute to uremic cardiomyopathy. In green, treatments or conditions that were effective in reducing or attenuating uremic cardiomyopathy, are highlighted. For more information, see text. β1-AR, beta-1 adrenergic receptor; LCZ696, combination of sacubitril and valsartan; TAK-242, TLR4 inhibitor.

of LVH, and these observations were independent of significant blood pressure effects [120]. Similar effects were found when treating either with another ARB, valsartan, or knocking out the AT1 receptor genetically in mice [121]. Also, the combination of valsartan and the neprilysin-inhibitor sacubitril (in the form of the combination drug LCZ696) exerted cardioprotective effects after SNX-induced CKD [122]. When the ACE blocker enalapril was administrated to mice with CKD after unilateral urinary obstruction for 3 weeks, it significantly attenuated blood pressure, cardiac hypertrophy, cardiac fibrosis and pro-fibrotic transforming growth factor beta (TGF-β) signaling [123]. Since treatment with the anti-hypertensive hydralazine did lower blood pressure without impacting on cardiac structural remodeling, a blood pressure–independent effect of enalapril on cardioprotection in CKD was suggested [123]. Compared with ACE blocking by enalapril, omapatrilat—which blocks both ACE and neutral endopeptidases, the latter downregulating natriuretic peptide levels—had a similar systemic antihypertensive effect in rats subjected to SNX-induced CKD for 12 weeks; however, omapatrilat was more effective in reducing glomerular capillary hydraulic pressure and showed an improved renoprotection on long-term compared with enalapril [124]. The influence of omapatrilat on CKD-induced cardiac effects has not yet been examined.

The SNS is fundamental to blood pressure control, whether continuously (long-term) or moment-to-moment, being responsible for hemodynamic stability [114]. CKD-induced activation of the β-adrenergic receptors (β-ARs) by catecholamine neurotransmitters results in abnormalities in the β-AR signaling system that may ultimately lead to the cardiac outcomes observed in CKD [125]. In line with this, its inhibition was shown to be beneficial to the cardiovascular system in CKD: treating nephrectomized rats with atenolol (a selective blocker of ARβ1) or carvedilol (a non-selective ARβ blocker) reduced blood pressure, cardiac hypertrophy, cardiac fibrotic deposition as well as cardiac apoptotic signaling pathways [126]. In contrast, ARβ3 exerts cardioprotective functions [127] and the β-AR3 agonist mirabegron reduced diastolic dysfunction, cardiac fibrosis and cardiac inflammation, but not LVH, in rats subjected to SNX. This was observed in the absence of significant blood pressure effects and independent of β-AR3/endothelial nitric oxide synthase (eNOS) signaling, but potentially mediated through a downregulation of the AT1 receptor [120].

The MR is an important regulator of electrolyte and fluid homeostasis. However, MR overactivation negatively impacts on the kidney and the heart by increasing sodium retention and hypertension, and by contributing to inflammation and kidney fibrosis, as well as cardiac hypertrophy and fibrosis [128, 129]. The steroidal MR antagonist spironolactone has shown beneficial effects on the cardiovascular system in CKD: it reduced systemic and vascular inflammation as well as vascular calcification independently of blood pressure level in rats with adenine-induced CKD [130], with vascular calcification contributing to increased cardiovascular mortality in CKD patients [8, 131]. Also, treatment of mice with subtotal nephrectomy-induced CKD with the non-steroidal MR antagonist finerenone for 6 weeks mostly restored CKD-induced diastolic dysfunction, prevented LVH and cardiac fibrosis, and attenuated the CKD-induced decrease of LV fractional shortening and ejection fraction without effects on kidney dysfunction or systolic blood pressure [132].

Inflammation

Immune system activation and inflammatory processes are among the most studied candidates for pathological kidney–heart crosstalk. Inflammatory markers upregulated by kidney injury include cytokines, chemokines, acute-phase proteins and adhesion molecules, by which cells and receptors of the innate immune response system are involved [133].

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For example, the inhibition of important inflammatory mediators such as IL-6 and toll-like receptor 4 (TLR4) have a beneficial effect on the heart in CKD animal models. Blockage of IL-6 signaling using a monoclonal antibody for the IL-6 receptor (MR16-1) reduced cardiac fibrosis after SNX-induced CKD [134]. In addition, pro-inflammatory gene expression (including monocyte chemoattractant protein-1, TNF-α, IL-1β and IL-6) and macrophage infiltration were significantly reduced in the hearts of CKD mice treated with MR16-1 [134]. In the same line, inhibition of TLR4 protected from cardiac inflammation and fibrosis in rats with aldosterone-salt-induced CKD [135].

Furthermore, a role for nucleotide-binding oligomerization domain–containing protein 1 (NOD1) in CKD-induced cardiac Ca^{2+} mishandling was revealed, with NOD1 known to trigger inflammatory nuclear factor κB signaling upon cell injury. In a mouse model of SNX-induced CKD, genetic deficiency of NOD1 improved CKD-induced cardiac Ca^{2+} mishandling, the latter observed as an impairment in the properties and kinetics of intracellular Ca^{2+} transients in cardiomyocytes isolated from CKD mice [136].

Regulators of mineral metabolism

The phosphaturic hormone FGF23 is increased and independently associated with LVH in CKD patients [93]. FGF23 is able to induce cardiomyocyte hypertrophy *in vitro* as well as LVH when administered to mice, and blocking the FGF receptor in rats subjected to SNX reduced CKD-induced LVH [93]. In line with this, antibody-mediated blockade of fibroblast growth factor receptor 4 (FGFR4), one of the FGF23 receptors, in rats with SNX-induced CKD inhibited hypertrophy of isolated cardiac myocytes and attenuated LVH *in vivo* [137]. Also, knockout mice for FGFR4 did not develop LVH in response to a high-phosphate diet, as observed in wild-type mice [137]. Furthermore, FGF23 has been reported to contribute to cardiac calcium mishandling. Cardiomyocytes isolated from either mice with SNX-induced CKD or mice treated with FGF23 displayed a slower increase in cytosolic calcium during systole and a slower decay in cytosolic calcium during diastole compared with controls [138]. Also, FGF23 reduced cardiomyocyte contractility and triggered spontaneous pro-arrhythmic events through intracellular Ca^{2+} mishandling, which could be blocked by soluble Klotho (sKlotho) [139]. Although the precise mechanisms of these protective effects by sKlotho remain unclear, it has been suggested that sKlotho might trigger protective signaling that counteracts FGF23 effects. Alternatively, sKlotho might operate as an FGF23 co-receptor altering or impeding downstream FGF23 signaling, or sKlotho might couple to circulating FGF23 as a decoy receptor [139].

Klotho deficiency is also well studied for potential cardiac effects in CKD. Hu *et al.* suggested that Klotho deficiency represents a condition of CKD, and Klotho deficiency not only worsens renal disease but also exacerbates extra-renal complications like vascular calcification and secondary hyperparathyroidism [140]. Furthermore, heterozygous Klotho-deficiency was associated with spontaneous cardiac hypertrophy and dysfunction, linked with an increase in p-SMAD2/3 and p-ERK [141]. When inducing SNX-triggered CKD for 5 weeks, heterozygous Klotho-deficient mice displayed aggravated cardiac hypertrophy and fibrosis as well as increased cardiac dysfunction compared with wild-type CKD mice. After delivery of soluble Klotho to Klotho-deficient CKD mice, these signatures of adverse cardiac remodeling were ameliorated without significant impact on kidney clearance function [142].

Uremic toxins

Uremic toxins have been strongly implicated in the manifestation and progression of the inflammatory state associated with CKD, by modulating a series of mediators such as CRP, cytokines and transcription factors [143]. The most studied protein-bound uremic toxins in CRS are IS and PCS, which are both also highly associated with pro-inflammatory properties [144]. IS treatment induced cardiac hypertrophy in mice and even to a greater extent in mice heterozygous for Klotho [145], with a role shown for the p38/ERK pathway in IS-induced cardiomyocyte hypertrophy *in vitro*. Treatment with AST-120—an orally administered adsorbent of low molecular weight substances from the intestinal lumen, including the IS precursor indole—attenuated CKD-induced cardiac fibrosis in nephrectomized rats [146]. Also, PCS was demonstrated to be cardiotoxic, inducing NADPH oxidase expression and the production of reactive oxygen species in cardiomyocytes *in vitro*, and mediating cardiac apoptosis, cardiac fibrosis and diastolic dysfunction in a mouse model of SNX-induced CKD for 8 weeks [147].

Other

Activation of the mammalian target of rapamycin (mTOR) complex during CKD has been related to the development of cardiac hypertrophy and fibrosis [148]. When treating mice with the mTOR inhibitor rapamycin in a normotensive model of unilateral nephrectomy–induced CKD, the development of cardiac hypertrophy and fibrosis was reduced when compared with vehicle-treated CKD animals [149].

ANIMAL MODELS TO STUDY UREMIC CARDIOMYOPATHY: OVERVIEW AND CONSIDERATIONS

Mouse models

Unraveling the contribution of pathophysiological mechanisms to uremic cardiomyopathy requires the availability of appropriate animal models, with mouse models offering the advantage of genetically modified strains enabling the study of selected molecular mediators. However, despite the studies discussed in the previous chapter, development of uremic cardiomyopathy in mice has shown to be very variable. To support future studies, Table4 summarizes the main cardiac outcomes of CKD models using C57BL/6 and 129/Sv strains. The table is based on our previous systematic review and meta-analysis by Soppert *et al.* [12], in which we provided a detailed description and comparison of cardiac pathological changes in different mouse models of uremic cardiomyopathy. Compared with Soppert *et al.* [12], Table 4 is updated with novel literature published until September 2022 and identified according to the same search strategy and eligibility criteria applied before; resulting in the inclusion of nine further studies [150–158].

"Single hit" approaches

For surgical CKD models, the inclusion of these recent studies hardly affects the incidence and conclusion of cardiac outcomes as previously summarized [12]. SNX induced cardiac hypertrophy, cardiac fibrosis and diastolic dysfunction in C57BL/6 (41 studies included) and 129/Sv mice (14 studies included) in ≥70% of the studies that assessed those parameters, while 129/Sv mice seemed to be more prone to these effects (≥90% of studies vs 70%–82%). Effects on systolic function were more

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Table 4: Summary of cardiac effects reported in different mouse models of CKD.

Single hit	SNX or similar surgical procedures[a]		Other surgery-induced, bilateral kidney damage[b]		Diet or treatment[c]		Alport syndrome	
	C57BL/6	129/Sv	C57BL/6	129/Sv	C57BL/6	129/Sv	C57BL/6	129/Sv
No. of studies included	41	14	3	1	9	3	5	4
Blood pressure	10(23)	11 (12)			3 (5)	1 (1)	2 (3)	2 (2)
Hypertrophy	21 (30)	11 (11)	2(2)	1(1)	3 (6)	0 (2)	4 (5)	0 (2)
Fibrosis	19 (23)	9 (10)	2(2)	1(1)	4 (7)	1 (2)	1 (2)	1 (2)
Inflammation/Ox Stress	12 (14)	1 (2)			3 (5)	2 (2)		
Systolic function[d]	16 (28)	3 (8)	0 (2)	1 (1)	2 (6)	0 (1)	2 (3)	4 (4)
Diastolic function[e]	14 (20)	8 (8)	0(1)		1 (2)			1 (1)

Multifactorial hit	CKD + hypertension[f]		CKD + mineral bone disorder[g]		CKD + hyperlipidemia[h]	
	C57BL/6	129/Sv	C57BL/6	129/Sv	C57BL/6	129/Sv
No. of studies included	17	5	3	3	9	
Blood pressure	13 (13)	5 (5)	0 (2)	1 (1)	0 (7)	
Hypertrophy	9 (13)	3 (3)	1 (1)	3 (3)	4 (8)	
Fibrosis	12 (15)	1 (1)		3 (3)	2 (5)	
Inflammation/Ox Stress	5 (6)	2 (2)			3 (4)	
Systolic function[d]	6 (11)		1 (1)		3 (6)	
Diastolic function[e]	3 (4)				3 (6)	

Effect of CKD—without or with additional cardiovascular risk factors in CKD—on blood pressure, pathophysiological cardiac changes and LV function in C57BL/6 versus 129/Sv strains, summarized from the systematic review by Soppert *et al.* (2022) [12] and updated with additional literature until September 2022 using an identical search strategy. Studies from all time points of CKD analysis are summarized; parameters are expressed as numbers of studies with significant effects vs number of total studies that addressed this parameter (in brackets). Color code represents the percentage of studies with significant effects (white = 0 to <30%, light grey = 30 to <70%, dark grey = 70%–100%, dashed = parameter not assessed). Different studies from one paper using identical methods but different time points were summarized and counted as "1," while studies from one paper using different methods were counted separately.

[a]SNX or UNX + pole ligation of remnant kidney.

[b]Bilateral IRI or UNX + IRI of remnant kidney.

[c]Adenine/oxalate/cisplatin.

[d]Other than LV volume; parameters considered: ejection fraction; fractional shortening; cardiac output; stroke volume; maximal rate of LV pressure change (dP/dt max).

[e]Other than LV volume; parameters considered: Tei or myocardial performance index; isovolumetric relaxation time; isovolumic relaxation time constant (Tau, τ); E/A ratio; E/e′ ratio.

[f]CKD via UNX/SNX/Adenine in combination with DOCA/salt/Ang II/aldosterone/high protein/renal artery clipping.

[g]CKD (various) in combination with high phosphate.

[h]CKD via UNX/SNX/adenine in combination with *ApoE*$^{-/-}$/high fat diet.

As described in detail by Soppert *et al.* [12], in case of studies reporting multiple readouts for blood pressure or pathophysiological cardiac changes, outcomes were summarized according to mean effects (averaging all readouts with $P > .05 = 0$, $P < .05 = 1$, $P < .01 = 2$, $P < .001 = 3$) with means ≥0.5 being considered as a statistically significant change. Increased fibrosis and oxidative stress identified through immunohistochemical staining always resulted in "increase" in the heat maps, independent of the outcome of potential gene expression/western blot analyses. Also, increased oxidative stress readouts always resulted in "increase" in the "inflammation/oxidative stress" outcome in the heat maps, independent of the outcome of potential other inflammatory readouts.

IRI, ischemia/reperfusion injury; Nx, nephrectomy; Ox stress, oxidative stress; UNX, unilateral nephrectomy.

variable and only detected in roughly 60% of studies examining these strains, while hypertension was again more stably induced in studies performing SNX in 129/Sv mice (92% of studies vs 43% in C57BL/6). Studies inducing bilateral kidney damage via other surgical procedures (four studies included in total) similarly caused cardiac hypertrophy and fibrosis in both strains.

When CKD was induced via adenine diet or oxalate treatment in C57BL/6 mice (nine studies in total), cardiac pathophysiological effects were more variable than after SNX, showing significant changes only in 30%–70% of the studies for the cardiac parameters summarized in this review. Although our previous systematic review reported a consistent increase of cardiac effects among diet- and treatment-induced CKD models in C57BL/6 mice [12], these variable results following inclusion of recent literature are mainly caused by our latest findings with primarily neutral effects of different adenine diet–induced CKD models on cardiac morphology and function [158]. Variable observations of the effect of adenine diet on the heart might, amongst other factors, be due to high protocol variability, including, e.g. adenine concentration, duration of feeding and substrain differences. 129/Sv were only rarely analysed for cardiac effects upon CKD induction via adenine diet or cisplatin treatment (three studies in total). Blood pressure and cardiac inflammation/oxidative stress were increased in the studies that assessed this parameter. In contrast, no effects on hypertrophy or cardiac function were detected, and only one out of two studies documented cardiac fibrotic changes.

Alport syndrome induced cardiac pathophysiological effects again more consistently in 129/Sv mice in terms of hypertension, systolic or diastolic dysfunction (in >70% of the studies, four studies included) compared with C57BL/6 (30%–70%, five studies included), while cardiac fibrosis was observed in one of two studies for each strain and only cardiac hypertrophy was more apparent in C57BL/6, with four out of five studies reporting significant effects.

Clearer cardiac pathophysiological effects of CKD in studies using 129/Sv mice could be attributed to their higher susceptibility for proteinuria/kidney inflammation in response to albumin overload [159] and stronger efficacy of SNX in terms of histological damage of the remnant kidney [160], although no statistical differences were detected in serum or plasma creatinine/urea among these strains upon SNX [12]. Furthermore, 129/Sv mice

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express two instead of one renin genes [161], which through altered RAAS signaling could favor renal and cardiac pathophysiological effects. A detailed discussion can be found in Soppert *et al.* [12]. In summary, the highest number of studies applying "single hit" approaches to study the effect of CKD on the heart used surgical procedures (~75%/68% of all single hit approaches in C57BL/6 and 129/Sv mice, respectively), with a relatively high reliability to detect effects on cardiac morphology and function.

"Multifactorial hit" approaches

Combining CKD with hypertensive strategies led to the induction of cardiac fibrosis, cardiac inflammation/oxidative stress and diastolic dysfunction in C57BL/6 mice in >70% of the studies that assessed these parameters (17 studies included). Changes in heart size and systolic function were more variable (30%–70% of studies). 129/Sv mice seemed again to be superior to C57BL/6 mice, showing 100% efficacy in detecting cardiac hypertrophy, fibrosis and inflammation/oxidative stress (though with only five studies reported). CKD in combination with hyperlipidemia led to more variable cardiac effects in C57BL/6 mice (nine studies included), detecting significant changes in only 30%–70% of studies with cardiac inflammation/oxidative stress being the only parameter increased in >70% of studies (129/Sv not available).

Since Table 4 was greatly simplified compared with the detailed reporting in our systematic review previously [12] and neither accounts for CKD duration or for effect sizes, it is not suitable for the comparison of uremic cardiomyopathy models applying single vs multifactorial hit approaches. Hence, we refer to our meta-analysis in Soppert *et al.* [12]. for such detailed comparison. There, we reported that multifactorial hit models, especially the combination of CKD and hypertension-inducing strategies, more consistently induced cardiac hypertrophy in C57BL/6 mice at intermittent time points compared with single hit surgical approaches [12]. Taken together, compared with single hit approaches in C57BL/6, genetics and additional cardiovascular risk factors can increase the susceptibility to organ damage and favor the development of clinically relevant pathophysiological effects of CKD on the heart.

Summary and considerations

In summary, dependent on the study aim, the particular mouse strain, CKD induction method, duration as well as additional cardiovascular risk factors should be carefully chosen. As update of the meta-analysis by Soppert *et al.* [12], we here reported that surgical induction of CKD in C57BL/6 mice induced cardiac fibrosis in many studies but did have more variable effects in terms of systolic dysfunction. Also, our recent meta-analysis showed that especially at intermittent study durations (5–13 weeks of CKD), surgical interventions triggered only mild and inconsistent hypertrophic responses in the heart [12]. For these timeframes, additional application of hypertensive-inducing strategies in C57BL/6 mice could make it a more suitable model to study all pathophysiological features of uremic cardiomyopathy, displaying more reproducible signs of cardiac hypertrophy and fibrosis [12]. In comparison, 129/Sv mice were more prone to develop SNX-induced cardiac hypertrophy, cardiac fibrosis and hypertension than C57BL/6 even in single hit approaches (Table 4). Furthermore, 129/Sv mice consistently developed diastolic dysfunction with primarily preserved systolic function (Table 4) [12]. Thus, surgical CKD induction (alone) in 129/Sv mice could be a suitable model to study CKD-induced cardiac fibrosis and hypertrophy, already at early time points (up to 4 weeks, see detailed overview per timeframe in Soppert *et al.* [12]).

Overall, it is important to consider that cardiac outcomes in CKD mouse models can be highly variable and experimental designs need to be carefully considered. This includes a specific emphasis on strain and substrain genetic differences (129/Sv vs C57BL/6, C57BL/6 N vs C57BL/6 J) that may play an important role in the cardiac pathophysiological outcome during CKD, as well as on the CKD model and the presence of potential additional cardiovascular risk factors. (Sub)strain differences in cardiac outcomes could, amongst others, be due to an altered susceptibility to fibrosis, inflammation or oxidative stress responses. This is for example observed when comparing C57BL/6 N vs C57BL/6 J mice: the latter strain presents with the absence of a functional mitochondrial nicotinamide nucleotide transhydrogenase (NNT), which has been associated with protection from reactive oxygen stress upon pressure overload [162]. Other factors that may contribute to the observed study variability of CKD effects on the heart include CKD methodology, housing, mouse gender and age, as well as the choice of outcome parameters/readouts to detect cardiac impairment. Also, a risk of publication bias with reduced reporting of "no impact" observations cannot be excluded.

Rat models

Using the exact same search strategy as we recently applied for cardiorenal mouse studies [12], a PubMed-based literature search for studies examining cardiac effects of CKD in rats was performed, revealing (total, non-selected) 911 hits (thus exceeding the 642 hits retrieved by Soppert *et al.* for mice). This number highlights the high interest of researchers in the rat model to study CKD-induced cardiac effects. Although a systematic discussion of these studies is out of scope for this review, we here provide a brief summary of the main models of CKD-induced effects on the heart in rats.

"Single hit" approaches

Similar to mouse models, SNX is the most common surgical method of CKD induction in rats [163]. In 2015, Hewitson *et al.* [163] reviewed that cardiac hypertrophy was reported to be a consistent cardiac outcome parameter upon SNX in rats, accompanied by early occurring diastolic dysfunction and cardiac fibrosis. These findings were further supported in several studies published more recently (e.g. [120, 146, 164–166]). In addition, increased myocardial artery wall thickness and capillary density were observed in nephrectomized rats [146, 167].

Diwan *et al.* [168] summarized in 2018 experimental models using rats with adenine diet–induced CKD and reported cardiac hypertrophy and fibrosis, as well as left ventricular stiffness and aortic medial calcification, in adenine-fed rats, again supported by several more recent publications [169–172].

Further, Chang *et al.* recently performed unilateral ureteral obstruction in rats by single ureter ligation and reported cardiac fibrosis and hypertrophy with persistent cardiac dysfunction 6 months after performing the surgery [173]. Bilateral kidney ischemia reperfusion, initially being a model for acute kidney injury, was characterized in rats at several months following ischemia-reperfusion to resemble CKD by Amador-Martínez *et al.* in 2019 [174]. After 4 months, they reported cardiovascular injury shown by cardiac hypertrophy and fibrosis.

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"Multifactorial hit" approaches

As models of hypertensive CKD, spontaneously hypertensive rats are used. In the age of 5–6 weeks these rats develop hypertension, resulting in mainly cardiac hypertrophy and fibrosis after several weeks, as supported by multiple studies [175–178]. Similar models reflect the use of Dahl salt-sensitive rats fed a high salt diet as well as the administration of the aldosterone precursor deoxycorticosterone acetate (DOCA) combined with unilateral nephrectomy and a high salt diet. Several studies reported cardiac remodeling in form of hypertrophy and fibrosis along with hypertension in both models [179–183].

Summary and considerations

One of the advantages of rat models is the size of the rat compared with the mouse. Surgical procedures such as ureteral obstruction or SNX are performed more easily in larger animals such as rats. Additionally, rats provide more material for *ex vivo* experiments and analyses of tissue or blood. As a disadvantage, the availability of genetic modifications and knockouts is much more restricted in rats compared with mice, thus offering fewer opportunities in analyzing underlying molecular mechanisms of diseases. Also, whereas most of the common mouse strains are inbred mouse strains, the rats mostly used are outbred strains (e.g. Wistar or Sprague Dawley), imposing a higher genetic variability and in general a potential reduction in reproducibility of experimental outcomes [184, 185].

Nonetheless, based on current literature, effects of CKD on the heart seem to be more reproducible in rats compared with current mouse models (although a systematic analysis of studies examining CKD-induced cardiac effects in rats was out of scope for this review). The underlying causes remain currently unclear and remain topic of further investigation in future studies.

CONCLUSIONS, CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

With CKD patients at increased cardiovascular risk, this review aimed to summarize the clinical features, biomarkers and pathophysiological mechanisms of uremic cardiomyopathy. Also, it discussed animal experimental models that have been studied, with a comparison according to mouse strains and CKD model, as well as summarizing rat models of CKD-induced cardiac remodeling. In this way, this review aims to support future research in the field of CKD-induced cardiomyopathy.

On the clinical level, deeper insights into increased cardiovascular risk in CKD patients could promote a higher degree of clinical suspicion and diagnosis and an increased focus on the importance of a multidisciplinary, cardiorenal approach in following up and treating CKD patients. Identification and clinical translation of biomarkers for an early identification of CKD, CKD-associated CVD and underlying pathophysiological processes (as potential targets of therapy) are highly important on this level and could support improved targeted therapeutic strategies in earlier stage.

An inherent difficulty concerning the CRS is the fact that kidney and cardiac diseases share pathophysiological pathways as well as other comorbidities, which complicates the identification of the true main drivers of pathophysiological "crosstalk of the kidney to the heart." Thus, additional research is also required to provide further insights into the pathophysiological processes underlying CKD-induced CVD to support the development of improved diagnostic and therapeutic strategies in relation to CVD in CKD patients.

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DATA AVAILABILITY STATEMENT

There were no datasets generated or analyzed in this review article.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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