CKJ REVIEW

From cardiorenal syndromes to cardionephrology: a reflection by nephrologists on renocardiac syndromes

Borja Quiroga[1],[*], Alberto Ortiz[2],[3],[*], Juan F. Navarro-González[3],[4],
Rafael Santamaría[3],[5],[6], Patricia de Sequera[7] and Javier Díez [8],[9], on behalf of
the CaReSEN working group of the Spanish Society of Nephrology

[1]IIS-La Princesa, Nephrology Department, Hospital Universitario de la Princesa, Madrid, Spain, [2]Division of
Nephrology IIS-Fundacion Jimenez Diaz, Department of Medicine, Universidad Autónoma de Madrid, Madrid,
Spain, [3]RICORS2040, Carlos III Institute of Health, Madrid, Spain, [4]Division of Nephrology and Research Unit,
University Hospital Nuestra Señora de Candelaria, and University Institute of Biomedical Technologies,
University of La Laguna, Santa Cruz de Tenerife, Spain, [5]Division of Nephrology, University Hospital Reina
Sofia, Cordoba, Spain, [6]Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Cordoba, Spain,
[7]Department of Nephrology, University Hospital Infanta Leonor, University Complutense of Madrid, Madrid,
Spain, [8]Center of Applied Medical Research and School of Medicine, University of Navarra, Pamplona, Spain
and [9]Centro de Investigación Biomédica en Red de la Enfermedades Cardiovasculares (CIBERCV), Carlos III
Institute of Health, Madrid, Spain

[*]These authors contributed equally to this work
Correspondence to: Javier Díez; E-mail: jadimar@unav.es

ABSTRACT

Cardiorenal syndromes (CRS) are broadly defined as disorders of the heart and kidneys whereby acute or chronic
dysfunction in one organ may induce acute or chronic dysfunction of the other. CRS are currently classified into five
categories, mostly based on disease-initiating events and their acuity or chronicity. CRS types 3 and 4 (also called
renocardiac syndromes) refer to acute and chronic kidney dysfunction resulting in acute and chronic heart dysfunction,
respectively. The notion of renocardiac syndromes has broadened interest in kidney–heart interactions but uncertainty
remains in the nephrological community's understanding of the clinical diversity, pathophysiological mechanisms and
optimal management approaches of these syndromes. This triple challenge that renocardiac syndromes (and likely
other cardiorenal syndromes) pose to the nephrologist can only be faced through a specific and demanding training plan
to enhance his/her cardiological scientific knowledge and through an appropriate clinical environment to develop
his/her cardiological clinical skills. The first must be the objective of the subspecialty of cardionephrology (or
nephrocardiology) and the second must be the result of collaboration with cardiologists (and other specialists) in
cardiorenal care units. This review will first consider various aspects of the challenges that renocardiac syndromes pose

to nephrologists and, then, will discuss those aspects of cardionephrology and cardiorenal units that can facilitate an effective response to the challenges.

INTRODUCTION

Cardiorenal syndrome (CRS) encompasses a spectrum of disorders involving both the heart and kidneys. The Acute Dialysis Quality Initiative outlined a consensus approach in 2008 that phenotyped CRS into two major groups, cardiorenal and renocardiac syndromes, based on the *primum movens* of the disease process [1]. This was further grouped into five subtypes based on disease acuity and sequential organ involvement. A recent Scientific Statement from the American Heart Association developed the central notion that in CRS, acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ [2].

Although the notion of CRS has stimulated the research of the cross-talk between the heart and the kidney across several clinical scenarios, some aspects deserve to be considered [3]. Mainly due to the influence of aging and increased incidence of common cardiac and renal metabolic and hemodynamic risk factors, the interactions between heart and kidney diseases are of increasing complexity and include important epidemiological, diagnostic, preventive and therapeutic aspects which are not fully addressed in the limited context of simultaneous acute or chronic organ dysfunction. Furthermore, patients with the dual burden of heart and kidney disease continue to experience unacceptably high rates of clinical complications, hospitalization and mortality. On the other hand, the pathophysiological framework underlying the classification of CRS has been challenged by recent mechanistic advances.

Therefore, this review article is based on the consideration that the time has come for the nephrologist to advance the view of heart–kidney interactions proposed in the CRS classification. In this conceptual framework, and by way of example, we will focus on some clinical, mechanistic and therapeutic aspects of types 4 and 3 of CRS (i.e., chronic and acute renocardiac syndromes, respectively) that underlie the complex and broad kidney–heart relationship in these two syndromes. Finally, we will consider how to address the growing clinical and scientific challenge that patients with renocardiac syndromes pose to nephrologists.

DIVERSITY OF CLINICAL MANIFESTATIONS IN RENOCARDIAC SYNDROMES

Both chronic and acute renocardiac syndromes have multiple clinical manifestations, beyond the classically acknowledged and researched conditions.

Chronic renocardiac syndrome

This syndrome is characterized by primary chronic kidney disease (CKD) leading to an increased risk of chronic impairment of cardiac function [1, 2] (Fig. 1). Decreased kidney function worsens chronic heart failure (CHF) prognosis [4]. Adverse left ventricular (LV) remodeling both macroscopic [i.e., progressive development of left ventricular hypertrophy (LVH) with diastolic dysfunction, evolving lately to LV dilatation and systolic dysfunction] and microscopic (e.g., cardiomyocyte hypertrophy and apoptosis, and myocardial interstitial inflammation and fibrosis) is involved in the development and progression of CHF in CKD patients [5].

Increasing interest is being devoted to the role of disturbances of the right ventricle in chronic renocardiac syndrome. In fact, CKD is independently associated with the risk of pulmonary hypertension [6, 7] and right ventricular–pulmonary artery uncoupling [8], which it is recognized as a major mechanism of right ventricular systolic dysfunction [9]. Interestingly, CKD is associated with severe right ventricular systolic dysfunction, which is independently associated with mortality [10].

Recently, a group of experts identified several aspects of CKD that fit criteria of unmet medical needs, among them the prevention and management of cardiac complications beyond CHF [11, 12]. Furthermore, cardiac complications in patients with CKD are more prevalent, with higher complexity and severity compared with the non-CKD population, and are associated with larger economic and societal burden [13–15].

Although classically the cardiac risk of CKD has been related to coronary atherosclerosis [16] and vascular calcification [17], it is now accepted that the risk of other cardiac complications (including coronary microvascular dysfunction, cardiac valve disease, dysrhythmias and sudden cardiac death) is also increased in CKD patients (Fig. 1) [18].

Coronary microvascular dysfunction results from different structural, functional and/or dynamic alterations in the coronary microcirculation associated with CKD that may result in angina even in the absence of atherosclerotic coronary artery disease or coronary calcifications [19]. Coronary microvascular dysfunction is characterized by a reduced coronary flow reserve [20, 21] and is independently associated with adverse cardiovascular events [22, 23].

There is an epidemiological collinearity of the prevalence and incidence of CKD with aortic and mitral valve diseases, which are present in 88–99% of stage 5 CKD patients [24]. Calcification plays an important role in CKD-associated valve disease occurring 10–20 years earlier in CKD patients compared with the general population, with an increase in the incidence and prevalence in parallel to the progression of CKD stage [25]. The presence of aortic and/or mitral valve disease has a strong unfavorable impact on the outcome in patients with CKD, namely in those on dialysis [26]. Compared with the bibliography focusing on left-sided valves and CKD, evidence on tricuspid and pulmonary valve disease is much less. However, tricuspid regurgitation is prevalent in CKD, namely in patients on dialysis (in whom the prevalence is of 63%) and mostly due to pulmonary hypertension [27].

CKD patients have a significant increased burden from atrial fibrillation (AF) compared with subjects without CKD, with a prevalence reaching up to 20% in non-dialysis CKD patients and up to 40% in patients on dialysis [28]. CKD and AF share many risk factors, making it difficult to discern the contributions of individual factors to either condition or associated outcomes (e.g., stroke) [29].

There is an increased risk of sudden cardiac death (SCD) in CKD. While the annual incidence rate of SCD is around 0.1% in the general population, it rises to 1.5%–2.7% in non-dialysis CKD patients, reaching 7% in patients initiating dialysis [28].
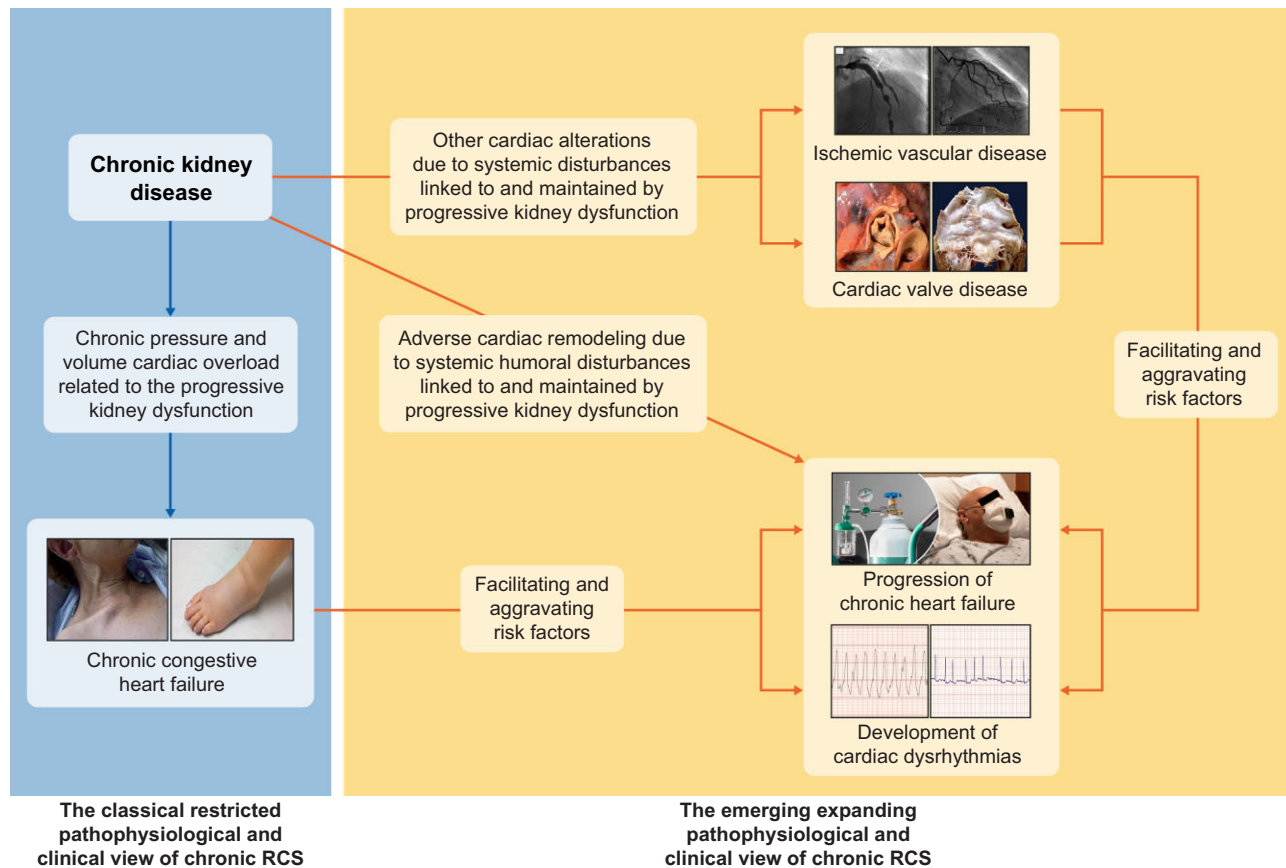
FIGURE 1: Schematic view of the two pathophysiological and clinical relationships participating in views of chronic renocardiac syndrome (RCS) or type 4 cardiorenal syndrome: the classical restricted one (left part of the figure) and the emerging expanding one (right part of the figure). The depicted photographs are the following: ischemic vascular disease: angiographic view of obstructive coronary artery disease (left) and diminished density of coronary microvessels (right). Cardiac valve disease: macroscopic appearance of aortic stenosis (left) and mitral regurgitation (right). Chronic congestive heart failure: clinical aspect of jugular engorgement (left) and peripheral oedema (right). Progression of chronic heart failure: oxygen therapy in a patient suffering from stage D heart failure. Cardiac dysrhythmias: electrocardiographic image of ventricular tachycardia (left) and atrial fibrillation (right).

There is a significant gap of knowledge in the understanding of electrical and hemodynamic mechanisms underlying SCD. In a retrospective study of hemodialysis patients who were prescribed a wearable cardioverter defibrillator, 80% of cardiac arrests were recorded as ventricular tachyarrhythmias (ventricular tachycardia or ventricular fibrillation) compared with 20% bradyarrhythmias, and most events occurred during or immediately after dialysis sessions [30]. In contrast, in a recent prospective study with continuous electrocardiogram monitoring, bradyarrhythmias and asystole, rather than ventricular tachyarrhythmias, were important determinants of SCD during the long interdialytic period [31].

Taken together, the above considerations indicate that nephrologists should be encouraged and educated to discuss cardiac risks and potential cardiac diagnostic and treatment options for CKD patients in a broader manner than is currently the case from the perspective of chronic renocardiac syndrome, which focuses primarily on CHF attributable to LV failure.

Acute renocardiac syndrome

This syndrome occurs when acute kidney injury (AKI) contributes to and/or precipitates the development of acute cardiac injury or dysfunction [1, 2] (Fig. 2). In particular, AKI is associated with increased risk of acute decompensated HF (ADHF). In fact,

in a population-based study involving a large cohort of patients who survived a hospitalization complicated by AKI, 20% of patients were readmitted within 30 days, most often with ADHF [32]. In another study of a large cohort of hospitalized adults, during the first year after discharge the risk of hospitalization for ADHF was increased by 44% [33] in the group with AKI as compared with the group that did not have AKI.

In addition, AKI is also associated with increased risk of other long-term cardiovascular complications (Fig. 2). A 2017 meta-analysis of 25 studies involving a total of 254 408 patients, including 55 150 with AKI, showed that AKI was associated with an 86% increase in the risk of death from cardiovascular causes during a median follow-up of 2.6 years [34]. There was a 58% increase in the risk of CHF during 2.9 years of follow-up, a 40% increase in the risk of acute myocardial infarction during 2.3 years of follow-up, and a 15% increase in the risk of stroke over a period of 2.7 years [34]. Other studies have shown that the increased risks did not differ between AKI patients with and without previous CKD and neither status with respect to recovery of renal function nor severity of AKI [35–37]; there are also no differences between patients with and without previous cardiovascular conditions, including CHF [38, 39], suggesting that the long-term risk of cardiovascular events is associated with AKI itself.

A new category of AKI diagnosed by elevations of tubular damage biomarkers alone [e.g., neutrophil gelatinase-associated lipocalin (NGAL) also known as lipocalin 2], which might evolve
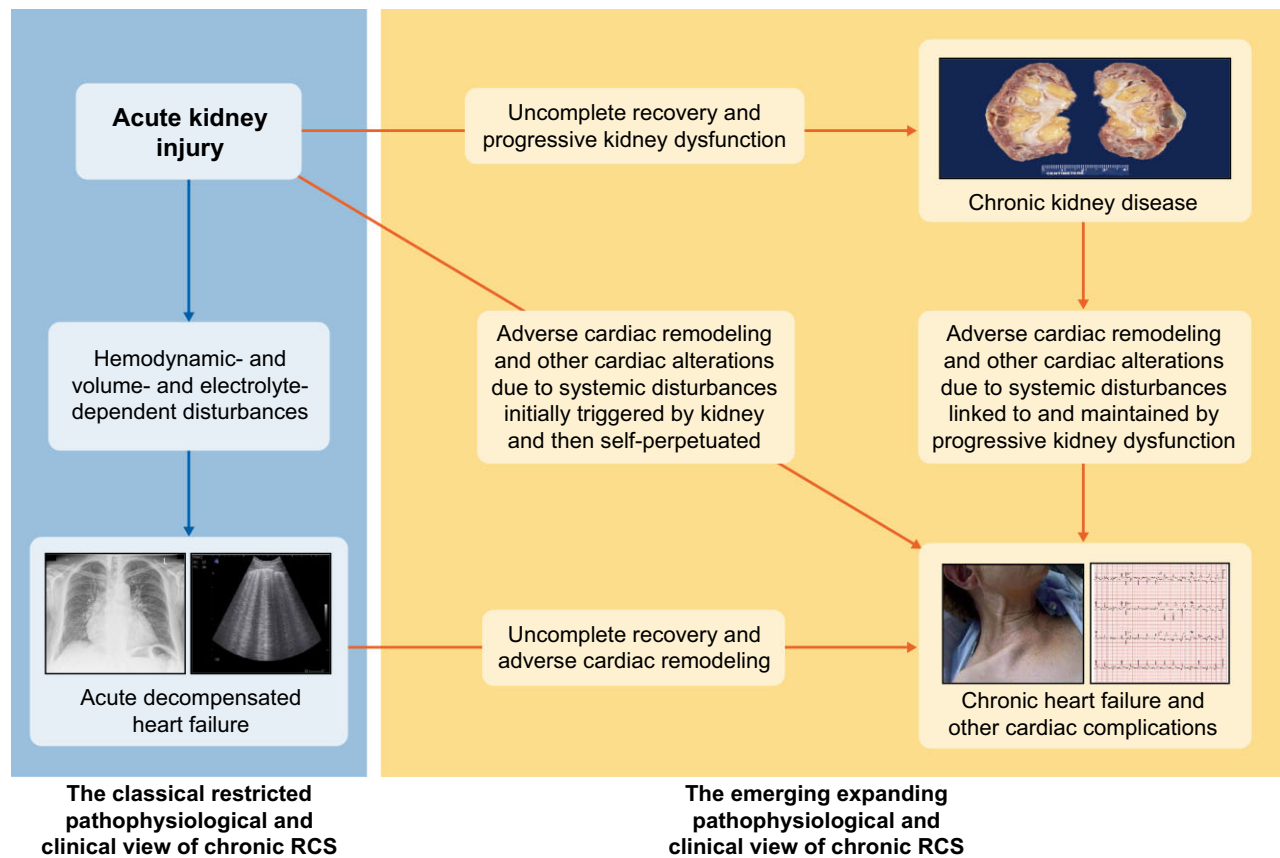
FIGURE 2: Schematic view of the two pathophysiological and clinical views of acute renocardiac syndrome (RCS) or type 3 cardiorenal syndrome: the classical restricted one (left part of the figure) and the emerging expanding one (right part of the figure). The depicted photographs are the following: chronic kidney disease: macroscopic appearance of end-stage kidney disease. Acute decompensated kidney failure: chest X-ray image of pulmonary oedema (left) and lung ultrasound image of B-lines (right). Chronic heart failure and other cardiac complications: clinical aspect of jugular engorgement (left) and electrocardiographic image of acute myocardial infarction (right).

into a clinically manifest syndrome characterized by a rise in serum creatinine levels and a decrease in estimated glomerular filtration rate (eGFR), has been described and termed subclinical AKI [40]. In a pooled data analysis from 2 322 critically ill patients, increased urine or plasma NGAL detects patients with likely subclinical AKI who have an increased risk of adverse outcomes including need for renal replacement therapy (primary endpoint), hospital mortality, their combination and duration of stay in intensive care and in-hospital, in absence of elevated serum creatinine [41]. As increased urinary or blood NGAL levels are an independent risk factor for future CHF and atherosclerotic coronary disease [42], the link between clinically overt AKI and cardiac dysfunction might also extend to subclinical AKI.

Therefore, nephrologists must be aware that AKI is associated not only with increased risk of CKD and ADHF but also with increased risk of future long-term adverse cardiovascular sequelae, especially CHF. These sequelae lead to other complications and poor outcomes, independent of or intertwined with the risks associated with the development of CKD [43].

COMPLEXITY OF MECHANISMS IN RENOCARDIAC SYNDROMES

Recent research has illustrated the growing complexity of the interrelated cellular and molecular mechanisms underlying chronic and acute renocardiac syndromes.

Insights from experimental models

Animal models have been established that induce primary renal damage/dysfunction and allow the assessment of the impact of kidney injury on the initiation and development of cardiac acute and chronic alterations simulating human renocardiac syndromes [44] (Table 1).

The most widely used model of severe CKD is induced by subtotal nephrectomy (STNx) consisting of complete removal of one kidney and upper and lower pole resections of the remnant kidney. STNx-induced CKD was associated with uremic cardiomyopathy, characterized by adverse LV remodeling, and enhanced susceptibility to myocardial ischemia [45, 46]. Of note, an excess of cardiac microRNA-21 has been reported in STNx rats and microRNA-21 inhibition prevented LV remodeling, through changes in the peroxisome proliferator-activated receptor-α signaling pathway [47].

Effects of mild-to-moderate CKD on the heart have been investigated in a unilateral nephrectomy model by which one kidney is removed, whereas the contralateral kidney is left intact. Unilateral nephrectomy caused early LV microscopic remodeling (i.e., apoptosis and fibrosis) with mild LVH and LV diastolic dysfunction, which later progressed to LV dilatation and a reduction in LV ejection fraction [48]. Changes in genes related to transforming growth factor-β1 and apoptosis pathways in the heart were involved in this kidney–heart interaction in

Table 1. Some examples of candidates identified as potential mediators and/or biomarkers of the mechanisms involved in renocardiac syndromes

Type of observation	Type of RCS	Potential mediators	References
Experimental	Chronic	microRNA-21	[47]
		TGF-β1	[48]
		Renal sympathetic nerve activity	[49]
		TWEAK-Fn14	[50, 51]
		α-Klotho	[52]
	Acute	Toll-like receptors 2 and 4	[53]
		Dynamin-related protein-1	[54]
		TWEAK-Fn14	[55, 56]
"Omics"	Chronic	Indoxyl sulfate, p-cresyl sulfate	[57]
		TMAO	[58, 59]
		FGF23	[57]
	Acute	ADMA	[60]
		FGF23	[61]
Clinical	Chronic	CRP, IL-6, IL-1β	[62, 63]
		PICP, CITP:MMP-1	[64]
		α-Klotho	[65, 66]
		Soluble TWEAK	[67, 68]
	Acute	High blood pressure	[69]

Abbreviations: ADMA, asymmetric dimethylarginine; CRP, C reactive protein; FGF23, fibroblast growth factor 23; Fn14, fibroblast growth factor-inducible 14; IL-1β, interleukin-1β; IL-6, interleukin-6; PICP, C-terminal propeptide of procollagen type I; CITP:MMP-1, C-terminal telopeptide of procollagen type I to matrix metalloproteinase-1 ratio; RCS, renocardiac syndrome; TGF-β, transforming growth factor-β; TMAO, trimethylamine-N-oxide; TWEAK, tumor necrosis factor-like weak inducer of apoptosis.

mild-to-moderate CKD [48]. Whether these changes also occur in the remaining kidney from living kidney donors remains to be investigated.

Recent findings obtained in an animal model of CKD due to adenine show that renal dysfunction is associated with left atrial dilation, hyperinnervation, fibrosis and arrhythmogenesis, which are attenuated by renal denervation [49]. While they do not indicate causality, they support the implication of kidney-mediated sympathetic overactivity in left atrial structural and electrical remodeling and in the pathogenesis of AF. Furthermore, these observations add experimental support to the ERADICATE-AF study [70], a single blind randomized clinical trial that demonstrated improved freedom from atrial arrhythmias at 12 months when renal denervation was added to catheter ablation of AF.

Warm ischemia–reperfusion is the most widely used model of hypoxia-induced AKI and is characterized by an abrupt decline in renal function and severe injury in the straight segment of proximal tubules. In this model, kidney injury caused LV macroscopic (i.e., hypertrophy and dilation) and myocardial microscopic (i.e., apoptosis) remodeling accompanied by impairment of LV systolic function [71]. Pathways linked to Toll-like receptors 2 and 4 [53] and maladaptive mitochondrial dynamics mediated by dynamin-related protein-1 [54] may be critically involved in these alterations.

There is also the possibility that some cardiac damaging mechanisms act in conditions of either CKD or AKI, depending on the timing and duration of their actions. In this regard, the potential pathogenic role of the cytokine tumor necrosis factor-like weak inducer of apoptosis (TWEAK) and its receptor, fibroblast growth factor inducible 14 (Fn14) signaling in cardiac and vascular injury accompanying CKD and AKI deserves some attention. The TWEAK–Fn14 axis promotes tissue (either renal, vascular or cardiac) remodeling such as apoptosis, inflammation and fibrosis, while restraining the expression of tissue protective factors such as the antiaging factor α-Klotho and the master regulator of mitochondrial biogenesis peroxisome

proliferator-activated receptor-γ coactivator-1α [72]. Increased tissue expression and activity of Fn14 and, to a lesser extent, TWEAK, have been reported both in experimental CKD [50, 51] and AKI [55, 56] and shown to lead to decreased α-Klotho [52]. Kidney α-Klotho is also lost very early in the course of CKD as, in addition to inflammation, albuminuria itself downregulates α-Klotho before glomerular filtration rate decreases [73].

Insights from systems medicine studies

Limited data exist on genomics, epigenomics, transcriptomics, proteomics and metabolomics in the setting of renocardiac syndromes [74]. However, some examples may illustrate the potential of systems medicine (also termed "omics") studies to gain insight into the heart–kidney interactions in CRS and, more specifically, to identify novel mediators and/or biomarkers of these interactions (Table 1).

Recent findings derived from "multi-omics" approaches have provided a deeper insight into the pathogenesis and diagnosis of CKD-related atherosclerosis beyond traditional and nontraditional risk factors [75]. Combined metabolomics and proteomics approaches added a piece of a puzzle to the knowledge of atherosclerotic endothelial dysfunction in CKD and mainly attributed to inflammation and oxidative stress [57]. The relationship between indoxyl sulfate and p-cresyl sulfate with 181 cardiovascular-related proteins involved in endothelial dysfunction and inflammation was recently analyzed in patients on dialysis [57]. Both metabolites were positively associated with the increased risk of atherosclerotic events and with fibroblasts growth factor 23 (FGF23), a factor produced in bones that participates in the maintenance of mineral homeostasis regulating phosphaturia through the interaction with α-Klotho–FGF receptor complexes expressed in renal tubule cells [76]. However, FGF23 also exerts direct actions on the cardiovascular system. For instance, FGF23 experimentally impairs endothelial function apparently via activation of a FGF receptor-dependent, α-Klotho-independent signaling pathway resulting in oxidative stress [77].

Plasma FGF23 is increased in CKD patients due to a maladaptive compensatory response to acquired α-Klotho deficiency, and is associated with atherosclerotic (e.g., ischemic events) and non-atherosclerotic (e.g., CHF) complications in this patient population [78, 79].

In a proteomics proof-of-concept study, known biomarkers for AKI were integrated to underlying disease conditions in pathway and protein interaction analyses [61]. Both a GeneMania network analysis and a term cluster analysis of AKI-modulated molecules allowed to identify AKI biomarker patterns for molecular pathways potentially involved in extrarenal damage (e.g., cardiac damage). One of these molecular pathways is related to FGF23 that induces LVH and myocardial fibrosis in animals apparently through a FGF receptor-dependent, α-Klotho-independent mechanism resulting in activation of calcineurin-nuclear factor of activated T-cells and upregulation of active β-catenin and transforming growth factor-β1 [80, 81]. Of note, increased serum FGF23 is associated with LVH, LV dysfunction and incident HF in patients with CKD [82–84].

Metabolomics has identified an excess of trimethylamine-N-oxide as a predictor of cardiovascular events [85] and several groups have confirmed the association between trimethylamine-N-oxide and cardiovascular disease among individuals with CKD [58, 59, 86, 87]. Metabolomics also identified novel features of AKI. Increases in acylcarnitines and certain amino acids (methionine, homocysteine, pyroglutamate, asymmetric dimethylarginine and phenylalanine) and a reduction in serum levels of arginine and several lysophosphatidyl cholines were observed in patients with AKI compared with healthy subjects [60]. Of interest, several studies have demonstrated that asymmetric dimethylarginine is an important risk factor for the increase of cardiovascular diseases and CHF in CKD [88].

Insights from clinical observations

Several clinical observations are providing novel insight on the potential primary drivers of pathophysiology in renocardiac syndromes (Table 1).

Systemic inflammation is a key process in the pathophysiology of CKD with relevant involvement in cardiovascular complications [89–91]. In fact, inflammatory biomarkers [e.g., C reactive protein (CRP), interleukins-6 and -1β, and tumor necrosis factor-α] progressively increase as kidney function declines and predict cardiovascular events in CKD patients [62, 63]. In accordance, the CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) focusing on 10 061 stable postmyocardial infarction patients with high high-sensitivity CRP levels demonstrated a benefit of inhibiting interleukin-1β with canakinumab on the incidence of cardiovascular events, which was larger in patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 than in those with eGFR $\geq$60 mL/min/1.73 m^2 [92]. Recently, two studies performed in stages 3–5 CKD patients [93] and patients on hemodialysis [94] demonstrated that blockade of interleukin-6 with ziltivekimab markedly reduced biomarkers of inflammation (e.g., CRP) relevant to atherosclerosis. In addition, ziltivekimab also reduced a biomarker of thrombosis [93] and erythropoiesis-stimulating agent requirements and increased serum albumin [94].

Myocardial fibrosis is a frequent finding in endomyocardial biopsies and necropsy studies in patients with CKD [95, 96]. Interestingly, recent studies have identified causal connections between CKD and myocardial fibrosis [97]. Furthermore, it has been proposed that myocardial fibrosis may play a key role in the development and progression of CHF in CKD patients [98]. Of notice, CKD patients with CHF exhibit a pattern of myocardial fibrosis circulating biomarkers that differs from non-CKD patients with CHF, and characterized by increased C-terminal propeptide of procollagen type I and by a low C-terminal telopeptide of collagen type I to matrix metalloproteinase type 1 ratio [64]. This pattern is thought to reflect extensive deposition of highly stiff collagen type I fibers and is associated with severe adverse macroscopic LV remodeling [64].

It has been proposed that AKI induces structural cardiac damage characterized by myocardial inflammation and cellular apoptosis and necrosis developing within days and myocardial fibrosis developing months or years later [99]. Of note, analyses of claims databases show that patients with AKI are more likely than patients without AKI to develop subsequent hypertension [69]. Chronic pressure overload associated to systemic hypertension is a major inducer of myocardial microscopic adverse remodeling (namely, fibrosis) associated with CHF [100].

Data suggest that FGF23 excess might be future sensitive and specific marker for cardiovascular disease associated with both CKD and AKI. It is not clear, however, that this is the case for its co-receptor α-Klotho. Currently, CKD is considered as a state of α-Klotho deficiency [101] and results from animal experiments showed that α-Klotho deficiency causes vascular calcification, and cardiac hypertrophy and fibrosis [102–104]. Furthermore, intravenous delivery of a transgene encoding soluble α-Klotho ameliorated cardiac hypertrophy in CKD mice with Klotho deficiency [104]. Circulating levels of soluble α-Klotho (which results either from the release of the extracellular domain of membrane α-Klotho after cleavage by the A Disintegrin and metalloproteinases 10 and 17 or by alternative splicing) are directly correlated with eGFR and inversely correlated with circulating FGF23 in CKD patients [105]. Interestingly, a recent clinical study in subjects with established cardiovascular disease and preserved renal function showed that lower soluble α-Klotho levels are associated with a proinflammatory status [65]. Moreover, lower soluble α-Klotho levels are independently associated with subclinical atherosclerosis in patients with moderate-to-severe CKD [66]. However, a cohort study of 444 patients with CKD stages 2–4 showed that plasma-soluble α-Klotho did not predict atherosclerotic events, CHF or cardiovascular death after 2.6 years of follow-up [106]. Further studies are required to elucidate the role of α-Klotho in cardiovascular disease that develops in kidney disease. In this regard, technology to assess α-Klotho levels should be further optimized [107].

Low circulating soluble TWEAK, which results from the proteolytic processing of the full-length protein by furin, is independently associated with both atherosclerosis burden [67] and progression [68] in CKD patients. This is consistent with the development of hypersensitivity to TWEAK related to increased cell membrane Fn14 [108]. Indeed, Fn14 upregulation during tissue stress or injury is the main mechanism driving TWEAK–Fn14 signaling. Thus, decreased soluble TWEAK levels may reflect activation of the TWEAK–Fn14 axis, analogous to low complement levels reflecting complement activation. Alternatively, soluble TWEAK may also bind to the scavenger receptor CD163, which might be a compensatory mechanism to protect from excessive TWEAK–Fn14 signaling [108]. More research is necessary to characterize and clinically validate soluble TWEAK as a biomarker of cardiovascular risk in CKD patients.

ADDRESSING THE CHALLENGE OF RENOCARDIAC SYNDROMES

The aspects developed in the two preceding sections are just some examples supporting the concept that a new

Table 2. Some examples of aspects related to renocardiac syndromes that remain to be investigated and developed in the context of cardionephrology (adapted from Hatamizadeh [114])

Aspects	Examples
Epidemiology	High prevalence of CV-related conditions beyond CHF or ADHF in CKD and AKI patients, respectively
Risk factors	Common classical and emerging risk factors to CKD and chronic CV disease, and to AKI and acute CV disease
Pathophysiology	Emerging pathogenic connections between the kidney and the heart when CKD or AKI are present
Diagnosis	Interference of CKD or AKI on clinical presentation, and indication and interpretation of biomarkers of CV injury and/or dysfunction
Prognosis	Influence of coexisting kidney and CV injury/dysfunction on mutual worsening function and clinical outcomes
Prevention	Modified prophylactic targets of CV disease when CKD or AKI are the initiating conditions
Treatment	Interference of CKD or AKI on the indication of certain modalities of CV therapy
Monitoring	Influence of CKD and AKI on follow-up strategies of associated chronic and acute CV complications
Research	Identify differential phenotypes of renocardiac syndromes using personalized medicine-based approaches

Abbreviations: ADHF, acute decompensated HF; AKI; acute kidney injury; CHF, chronic heart failure; CKD, chronic kidney disease; CV, cardiovascular.

comprehensive approach to renocardiac syndromes in particular, and likely to CRS in general, warrants a subspecialty that combines scientific knowledge and clinical skills from both nephrology and cardiology (i.e., cardionephrology) [109–111] and that is developed in a physical and organizational context of multidisciplinarity (i.e., cardiorenal units) [112, 113].

Aspects related to cardionephrology

There is an extensive relationship between nephrology and cardiology in a variety of aspects, including epidemiology, risk factors, pathophysiology, diagnosis, prognosis, prevention, treatment, monitoring and research, that involve both the kidney and the heart in cardiorenal patients, particularly in those presenting with renocardiac syndromes (Table 2) [114]. The subspecialty of cardionephrology is aimed at the study of the multidirectional interplay of kidney and heart disease from all these standpoints to provide high-quality care in the vulnerable cardiorenal population [114].

As is illustrated by renocardiac syndromes, the interactions between nephrology and cardiology are broad, complex, and include subtleties that are not routinely discussed in either nephrology or cardiology [111]. Any nephrologist or cardiologist should be familiar with those topics, and a cardionephrologist must master them. Cardionephrologists should also lead additional translational research to further discover the extent of those interactions and to establish the optimal clinical approaches to those complexities.

In this regard, it is relevant to emphasize that although the field of oncology has made significant steps toward individualized precision medicine, cardiology and nephrology still often use a "one size fits all" approach. This applies to the intersection of the heart–kidney interaction and the CRS as well [115]. As reviewed here, the pathophysiologic and clinical heterogeneity of renocardiac syndromes is so extensive that more research is needed to bring precision medicine into routine clinical practice for the care of patients with CRS.

Aspects related to cardiorenal units

The clinical rationale of the cardiorenal units is to provide coordinated multidisciplinary care for patients hospitalized with concomitant kidney and heart disease, thereby improving patient outcomes and optimizing utilization of resources. Preliminary data recently published on the impact of a cardiorenal unit on the clinical course and outcomes of patients with AKI and ADHF are encouraging, although they need to be verified in larger series of patients and over a longer period of follow-up [116].

Inpatient cardiorenal units provide support for nephrologists and cardiologists on regular medical floors, telemetry units and intensive care units. Cardiorenal units should allow for a more consistent dialogue between the two specialties, thus providing nephrologists and cardiologists with the clinical and educational environment and activities that allow one to gain substantial experience in solving cardiovascular and renal problems in cardiorenal patients.

In addition, cardiorenal units should contribute to building a foundation to advance research in CRS in general and renocardiac syndromes in particular. Collecting longitudinal electronic medical record data on cardiorenal patients and recruiting directly these patients into clinical research studies are the cornerstones of the scientific component of cardiorenal units. In this regard, it is mandatory to remember that there is an unmet need for evidence-based therapy for patients with chronic renocardiac syndrome, particularly for those with advanced CKD and CHF [117].

CONCLUSIONS

The time has come to move from a taxonomic approach to the concurrence of kidney and heart diseases to a broader approach based on the view of patients primarily diagnosed with either kidney disease or heart disease as cardiorenal patients. This means moving from the limited opportunities for diagnosis and treatment offered by the CRS classification to the growing possibilities for knowledge and clinical development inherent in the subspecialty of cardionephrology.

That said, nephrologists (and cardiologists) should always be grateful to the pioneers who coined and developed the classification of renocardiac syndromes (and other CRS) because thanks to them, today we can realistically consider the new subspecialty of cardionephrology aimed at stimulating us as clinicians and scientists and, above all, to improve the care, prognosis and quality of life of cardiorenal patients.

AUTHORS' CONTRIBUTIONS

CONFLICT OF INTEREST STATEMENT

REFERENCES

1. Ronco C, McCullough P, Anker SD *et al*. Cardio-renal syndromes: report from the Consensus Conference of the Acute Dialysis Quality Initiative. *Eur Heart J* 2010; **31**: 703–711

2. Rangaswami J, Bhalla V, Blair JEA *et al*. Cardiorenal syndrome: Classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation* 2019; **139**: e840–e878

3. Zannad F, Rossignol P. Cardiorenal syndrome revisited. *Circulation* 2018; **138**: 929–944

4. House AA, Wanner C, Sarnak MJ *et al*. Heart failure in chronic kidney disease: conclusions from a kidney disease: improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2019; **95**: 1304–1317

5. Schefold JC, Filippatos G, Hasenfuss G *et al*. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. *Nat Rev Nephrol* 2016; **12**: 610–623

6. O'Leary JM, Assad TR, Xu M *et al*. Pulmonary hypertension in patients with chronic kidney disease: invasive hemodynamic etiology and outcomes. *Pulm Circ* 2017; **7**: 674–683

7. Sise ME, Courtwright AM, Channick RN. Pulmonary hypertension in patients with chronic and end-stage kidney disease. *Kidney Int* 2013; **84**: 682–692

8. Fortuni F, Butcher SC, Dietz MF *et al*. Right ventricular-pulmonary arterial coupling in secondary tricuspid regurgitation. *Am J Cardiol* 2021; **148**: 138–145

9. Sanz J, Damián Sánchez-Quintana D, Bossone E *et al*. Anatomy, function, and dysfunction of the right ventricle. JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019; **73**: 1463–1482

10. Butcher SC, Fortuni F, Dietz MF *et al*. Renal function in patients with significant tricuspid regurgitation: pathophysiological mechanisms and prognostic implications. *J Intern Med* 2021; **290**: 715–727

11. Bello AK, Alrukhaimi M, Ashuntantang GE *et al*. Complications of chronic kidney disease: current state, knowledge gaps, and strategy for action. *Kidney Int Suppl* 2017; **7**: 122–129

12. Levin A, Tonelli M, Bonventre J *et al*. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet* 2017; **390**: 1888–1917

13. Go AS, Chertow GM, Fan D *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**: 1296–1305

14. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020; **395**: 709–733

15. United States Renal Data System. *USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2020

16. Valdivieso JM, Rodriguez-Pujol D, Pascual J *et al*. Atherosclerosis in chronic kidney disease: more, less, or just different? *Arterioscler Thromb Vasc Biol* 2019; **39**: 1938–1966

17. Schlieper G, Schurgers L, Brandenburg V *et al*. Vascular calcification in chronic kidney disease: an update. *Nephrol Dial Trasplant* 2016; **31**: 31–39

18. Herzog CA, Asinger RW, Berger AK *et al*. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2011; **80**: 572–586

19. Konst RE, Guzik TJ, Kaski J-C *et al*. The pathogenic role of coronary microvascular dysfunction in the setting of other cardiac or systemic conditions. *Cardiovasc Res* 2020: **116**: 817–828

20. Chade AR, Brosh D, Higano ST *et al*. Mild renal insufficiency is associated with reduced coronary flow in patients with non-obstructive coronary artery disease. *Kidney Int* 2006; **69**: 266–271

21. Nelson AJ, Dundon BK, Worthley SG *et al*. End-stage renal failure is associated with impaired coronary microvascular function. *Coron Artery Dis* 2019; **30**: 520–527

22. Charytan DM, Skali H, Shah NR *et al*. Coronary flow reserve is predictive of the risk of cardiovascular death regardless of chronic kidney disease stage. *Kidney Int* 2018; **93**: 501–509

23. Shah NR, Charytan DM, Murthy VL *et al*. Prognostic value of coronary flow reserve in patients with dialysis-dependent ESRD. *J Am Soc Nephrol* 2016; **27**: 1823–1829

24. Baumgartner H, Falk V, Bax JJ *et al*. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017; **38**: 2739–2791

25. Urena-Torres P, D'Marco L, Raggi P *et al*. Valvular heart disease and calcification in CKD: more common than appreciated. *Nephrol Dial Transplant* 2019; **1**: 1–8

26. Wang Z, Jiang A, Wei F *et al*. Cardiac valve calcification and risk of cardiovascular or all-cause mortality in dialysis patients: a meta-analysis. *BMC Cardiovasc Disord* 2018; **18**: 12

27. Zhang Y, Ding X-H, Pang F *et al*. The prevalence and independent risk factors of significant tricuspid regurgitation jets in maintenance hemodialysis patients with ESRD. *Front Physiol* 2020; **11**: 568812

28. Turakhia MP, Blankestijn PJ, Carrero J-J *et al*. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Eur Heart J* 2018; **39**: 2314–2325

29. Yew WY, Gupta D, Wong CF *et al*. Pathophysiology of atrial fibrillation and chronic kidney disease. *Cardiovasc Res* 2021; **117**: 1046–1059

30. Wan C, Herzog CA, Zareba W *et al*. Sudden cardiac arrest in hemodialysis patients with wearable cardioverter defibrillator. *Ann Noninvasive Electrocardiol* 2014; **19**: 247–257

31. Wong MC, Kalman JM, Pedagogos E *et al*. Temporal distribution of arrhythmic events in chronic kidney disease: highest incidence in the long interdialytic period. *Heart Rhythm* 2015; **12**: 2047–2055

32. Silver SA, Harel Z, McArthur E *et al*. 30-Day readmissions after an acute kidney injury hospitalization. *Am J Med* 2017; **130**: 163.e4–172.e4

33. Go AS, Hsu C-Y, Yang J *et al*. Acute kidney injury and risk of heart failure and atherosclerotic events. *Clin J Am Soc Nephrol* 2018; **13**: 833–841

34. Odutayo A, Wong CX, Farkouh M *et al*. AKI and long-term risk for cardiovascular events and mortality. *J Am Soc Nephrol* 2017; **28**: 377–387

35. Gallagher M, Cass A, Bellomo R *et al*. Long-term survival and dialysis dependency following acute kidney injury in intensive care: extended follow-up of a randomized controlled trial. *PLoS Med* 2014; **11**: e1001601

36. Linder A, Fjell C, Levin A *et al*. Small acute increases in serum creatinine are associated with decreased long-term survival in the critically ill. *Am J Respir Crit Care Med* 2014; **189**: 1075–1081

37. Hsu C, Chertow GM, McCulloch CE *et al*. Nonrecovery of kidney function and death after acute on chronic renal failure. *Clin J Am Soc Nephrol* 2009; **4**: 891–898

38. Bansal N, Matheny ME, Greevy RA, Jr *et al*. Acute kidney injury and risk of incident heart failure among US veterans. *Am J Kidney Dis* 2018; **71**: 236–245

39. Tecson KM, Hashemi H, Afzal A *et al*. Community acquired acute kidney injury as a risk factor of de novo heart failure hospitalization. *Cardiorenal Med* 2019; **9**: 252–260

40. Haase M, Kellum JA, Ronco C. Subclinical AKI-an emerging syndrome with important consequences. *Nat Rev Nephrol* 2012; **8**: 735–739

41. Haase M, Devarajan P, Haase-Fielitz A *et al*. The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury. *J Am Coll Cardiol* 2011; **57**: 1752–1761

42. Sivalingam Z, Larsen SB, Grove EL *et al*. Neutrophil gelatinase-associated lipocalin as a risk marker in cardiovascular disease. *Clin Chem Lab Med* 2017; **56**: 5–18

43. Bansal N, Zelnick L, Bhat Z *et al*. Burden and outcomes of heart failure hospitalizations in adults with chronic kidney disease. *J Am Coll Cardiol* 2019; **73**: 2691–2700

44. Liu S. Heart-kidney interactions: mechanistic insights from animal models. *Am J Physiol Renal Physiol* 2019; **316**: F974–F985

45. Lekawanvijit S, Kompa AR, Manabe M *et al*. Chronic kidney disease-induced cardiac fibrosis is ameliorated by reducing circulating levels of a nondialysable uremic toxin, indoxyl sulfate. *PLoS One* 2012; **7**: e41281

46. Song Y, Yu Q, Zhang J *et al*. Increased myocardial ischemia-reperfusion injury in renal failure involves cardiac adiponectin signal deficiency. *Am J Physiol Endocrinol Metab* 2014; **306**: E1055–E1064

47. Chuppa S, Liang M, Liu P *et al*. MicroRNA-21 regulates peroxisome proliferator-activated receptor-α, a molecular mechanism of cardiac pathology in cardiorenal syndrome type 4. *Kidney Int* 2018; **93**: 375–389

48. Martin FL, McKie PM, Cataliotti A *et al*. Experimental mild renal insufficiency mediates early cardiac apoptosis, fibrosis, and diastolic dysfunction: a kidney-heart connection. *Am J Physiol Regul Integr Comp Physiol* 2012; **302**: R292–R299

49. Hohl M, Selejan SR, Wintrich J *et al*. Renal denervation prevents atrial arrhythmogenic substrate development in CKD. *Circ Res* 2022; 130: 814–828

50. Muñoz-García B, Moreno JA, López-Franco O *et al*. Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) enhances vascular and renal damage induced by hyperlipidemic diet in ApoE-knockout mice. *Arterioscler Thromb Vasc Biol* 2009; **29**: 2061–2068

51. Ucero AC, Benito-Martin A, Fuentes-Calvo I *et al*. TNF-related weak inducer of apoptosis (TWEAK) promotes kidney fibrosis and Ras-dependent proliferation of cultured renal fibroblast. *Biochim Biophys Acta* 2013; **1832**: 1744–1755

52. Moreno JA, Izquierdo MC, Sanchez-Niño MD *et al*. The inflammatory cytokines TWEAK and TNFα reduce renal klotho expression through NFκB. *J Am Soc Nephrol* 2011; **22**: 1315–1325

53. Trentin-Sonoda M, da Silva RC, Kmit FV *et al*. Knockout of Toll-like receptors 2 and 4 prevents renal ischemia-reperfusion-induced cardiac hypertrophy in mice. *PLoS One* 2015; **10**: e0139350

54. Sumida M, Doi K, Ogasawara E *et al*. Regulation of mitochondrial dynamics by dynamin-related protein-1 in acute cardiorenal syndrome. *J Am Soc Nephrol* 2015; **26**: 2378–2387

55. Sanz AB, Justo P, Sanchez-Niño MD *et al*. The cytokine TWEAK modulates renal tubulointerstitial inflammation. *J Am Soc Nephrol* 2008; **19**: 695–703

56. Hotta K, Sho M, Yamato I *et al*. Direct targeting of fibroblast growth factor-inducible 14 protein protects against renal ischemia reperfusion injury. *Kidney Int* 2011; **79**: 179–188

57. Wu P-H, Lin Y-T, Chiu Y-W *et al*. The relationship of indoxyl sulfate and p-cresyl sulfate with target cardiovascular proteins in hemodialysis patients. *Sci Rep* 2021; **11**: 3786

58. Stubbs JR, House JA, Ocque AJ *et al*. Serum trimethylamine-N-oxide is elevated in CKD and correlates with coronary atherosclerosis burden. *J Am Soc Nephrol* 2016; **27**: 305–313

59. Kim RB, Morse BL, Djurdjev O *et al*. Advanced chronic kidney disease populations have elevated trimethylamine N-oxide levels associated with increased cardiovascular events. *Kidney Int* 2016; **89**: 1144–1152

60. Sun J, Shannon M, Ando Y *et al*. Serum metabolomic profiles from patients with acute kidney injury: A pilot study. *J Chromatogr B Analyt Technol Biomed Life Sci* 2012; **893-894**: 107–113

61. Marx D, Metzger J, Pejchinovski M *et al*. Proteomics and metabolomics for AKI diagnosis. *Semin Nephrol* 2017; **38**: 63–87

62. Kielstein JT, Veldink H, Martens-Lobenhoffer J *et al*. Unilateral nephrectomy causes an abrupt increase in inflammatory mediators and a simultaneous decrease in plasma ADMA: a study in living kidney donors. *Am J Physiol Renal Physiol* 2011; **301**: F1042–F1046

63. Amdur RL, Feldman HI, Dominic EA *et al*. Use of measures of inflammation and kidney function for prediction of atherosclerotic vascular disease events and death in patients with CKD: fiindings from the CRIC Study. *Am J Kidney Dis* 2019; **73**: 344–353

64. Eiros R, Romero-González G, Gavira JJ *et al*. Does chronic kidney disease facilitate malignant myocardial fibrosis in heart failure with preserved ejection fraction of hypertensive origin? *J Clin Med* 2020; **9**: 404

65. Martín-Núñez E, Donate-Correa J, Ferri C *et al.* Association between serum levels of Klotho and inflammatory in cardiovascular disease: a case-control study. *Aging (Albany NY)* 2020; 12: 1952–1964

66. Donate-Correa J, Ferri CM, Martín-Núñez E *et al.* Klotho as a biomarker of subclinical atherosclerosis in patients with moderate to severe chronic kidney disease. *Sci Rep* 2021; 11: 15877

67. Valdivielso JM, Coll B, Martín-Ventura JL *et al.* Soluble TWEAK is associated with atherosclerotic burden in patients with chronic kidney disease. *J Nephrol* 2013; 26: 1105–1113

68. Fernández-Laso V, Menéndez-Barbero N, Valdivielso JM *et al.* Soluble TWEAK and atheromatosis progression in patients with chronic kidney disease. *Atherosclerosis* 2017; 260: 130–137

69. Hsu C, Hsu RK, Yang J *et al.* Elevated BP after AKI. *J Am Soc Nephrol* 2016; 27: 914–923

70. Steinberg JS, Shabanov V, Ponomarev D *et al.* Effect of renal denervation and catheter ablation vs catheter ablation alone on atrial fibrillation recurrence among patients with paroxysmal atrial fibrillation and hypertension: the ERADICATE-AF randomized clinical trial. *JAMA* 2020; 323: 248–255

71. Kelly KJ. Distant effects of experimental renal ischemia/reperfusion injury. *J Am Soc Nephrol* 2003; 14: 1549–1558

72. Blanco-Colio LM. TWEAK/Fn14 axis: A promising target for the treatment of cardiovascular diseases. *Front Immunol* 2014; 5: 3

73. Fernandez-Fernandez B, Izquierdo MC, Valiño-Rivas L *et al.* Albumin downregulates Klotho in tubular cells. *Nephrol Dial Transplant* 2018; 33: 1712–1722

74. Virzì GM, Clementi A, Battaglia GG *et al.* Multi-omics approach: New potential key mechanisms implicated in cardiorenal syndromes. *Cardiorenal Med* 2019; 9: 201–211

75. Tracz J, Luczak M. Applying proteomics and integrative "omics" strategies to decipher the chronic kidney disease-related atherosclerosis. *Int J Mol Sci* 2021; 22: 7492

76. Ho BB, Bergwitz C. FGF23 signalling and physiology. *J Mol Endocrinol* 2021; 66: R23–R32

77. Silswal N, Touchberry CD, Daniel DR *et al.* FGF23 directly impairs endothelium-dependent vasorelaxation by increasing superoxide levels and reducing nitric oxide bioavailability. *Am J Physiol Endocrinol Metab* 2014; 307: E426–E436

78. Seiler S, Reichart B, Roth D *et al.* FGF-23 and future cardiovascular events in patients with chronic kidney disease before initiation of dialysis treatment. *Nephrol Dial Transplant* 2010; 25: 3983–3989

79. Scialla JJ, Xie H, Rahman M *et al.* Fibroblast growth factor-23 and cardiovascular events in CKD. *J Am Soc Nephrol* 2014; 25: 349–360

80. Faul C, Amaral AP, Oskouei B *et al.* FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011; 121: 4393–4408

81. Hao H, Li X, Li Q *et al.* FGF23 promotes myocardial fibrosis in mice through activation of β-catenin. *Oncotarget* 2016; 7: 64649–64664

82. Faul C, Amaral AP, Oskouei B *et al.* FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011; 121: 4393–4408

83. Gruson D, Ferracin B, Ahn SA *et al.* Comparison of fibroblast growth factor 23, soluble ST2 and Galectin-3 for prognostication of cardiovascular death in heart failure patients. *Int J Cardiol* 2015; 189: 185–187

84. Poelzl G, Trenkler C, Kliebhan J *et al.* FGF23 is associated with disease severity and prognosis in chronic heart failure. *Eur J Clin Invest* 2014; 44: 1150–1158

85. Wang Z, Klipfell E, Bennett BJ *et al.* Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature* 2011; 472: 57–63

86. Tang WH, Wang Z, Kennedy DJ *et al.* Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. *Circ Res* 2015; 116: 448–455

87. Missailidis C, Hallqvist J, Qureshi AR *et al.* Serum trimethylamine-N-oxide is strongly related to renal function and predicts outcome in chronic kidney disease. *PLoS One* 2016; 11: e0141738

88. Liu X, Xu X, Shang R *et al.* Asymmetric dimethylarginine (ADMA) as an important risk factor for the increased cardiovascular diseases and heart failure in chronic kidney disease. *Nitric Oxide* 2018; 78: 113–120

89. Tinti F, Lai S, Noce A *et al.* Chronic kidney disease as a systemic inflammatory syndrome: Update on mechanisms involved and potential treatment. *Life (Basel)* 2021; 11: 419

90. Zoccali C, Vanholder R, Massy ZA *et al.* The systemic nature of CKD. *Nat Rev Nephrol* 2017; 13: 344–358

91. Jankowski J, Floege J, Fliser D *et al.* Cardiovascular disease in chronic kidney disease: Pathophysiological insights and therapeutic options. *Circulation* 2021; 143: 1157–1172

92. Ridker PM, MacFadyen JG, Glynn RJ *et al.* Inhibition of interleukin-1β by canakinumab and cardiovascular outcomes in patients with chronic kidney disease. *J Am Coll Cardiol* 2018; 71: 2405–2414

93. Ridker PM, Devalaraja M, Baeres FMM *et al.* IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): A double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet* 2021; 397: 2060–2069

94. Pergola PE, Devalaraja M, Fishbane S *et al.* Ziltivekimab for treatment of anemia of inflammation in patients on hemodialysis: Results from a phase 1/2 multicenter, randomized, double-blind, placebo-controlled trial. *J Am Soc Nephrol* 2021; 32: 211–222

95. Kaesler N, Babler A, Floege J *et al.* Cardiac remodeling in chronic kidney disease. *Toxins (Basel)* 2020; 12: 161

96. Wang X, Shapiro JI. Evolving concepts in the pathogenesis of uraemic cardiomyopathy. *Nat Rev Nephrol* 2019; 15: 159–175

97. Hulshoff MS, Rath S, Xu X *et al.* Causal connections from chronic kidney disease to cardiac fibrosis. *Semin Nephrol* 2018; 38: 629–636

98. Romero-González G, González A, López B *et al.* Heart failure in chronic kidney disease: the emerging role of myocardial fibrosis. *Nephrol Dial Transplant* 2020; 37: 817–824

99. Legrand M, Rossignol P. Cardiovascular consequences of acute kidney injury. *N Engl J Med* 2020; 382: 2238–2247

100. González A, Ravassa S, López B *et al.* Myocardial remodeling in hypertension. *Hypertension* 2018; 72: 549–558

101. Zou D, Wu W, He Y *et al.* The role of klotho in chronic kidney disease. *BMC Nephrol* 2018; 19: 285

102. Hu MC, Shi M, Zhang J *et al.* Klotho deficiency causes vascular calcification in chronic kidney disease. *J Am Soc Nephrol* 2011; 22: 124–136

103. Hu MC, Shi M, Cho HJ *et al.* Klotho and phosphate are modulators of pathologic uremic cardiac remodeling. *J Am Soc Nephrol* 2015; 26: 1290–1302

104. Xie J, Yoon J, An SW *et al*. Soluble Klotho protects against uremic cardiomyopathy independently of fibroblast growth factor 23 and phosphate. *J Am Soc Nephrol* 2015; **26**: 1150–1160

105. Wang Q, Su W, Shen Z *et al*. Correlation between soluble α-Klotho and renal function in patients with chronic kidney disease: a review and meta-analysis. *Biomed Res Int* 2018; **2018**: 9481475

106. Seiler S, Rogacev KS, Roth HJ *et al*. Associations of FGF-23 and sKlotho with cardiovascular outcomes among patients with CKD stages 2-4. *Clin J Am Soc Nephrol* 2014; **9**: 1049–1058

107. Neyra JA, Moe OW, Pastor J *et al*. Performance of soluble Klotho assays in clinical samples of kidney disease. *Clin Kidney J* 2019; **13**: 235–244

108. Poveda J, Vázquez-Sánchez S, Sanz AB *et al*. TWEAK-Fn14 as a common pathway in the heart and the kidneys in cardiorenal syndrome. *J Pathol* 2021; **254**: 5–19

109. Díez J, Ortiz A. The need for a cardionephrology subspecialty. *Clin Kidney J* 2021; **14**: 1491–1494

110. Burlacu A, McCullough PA, Covic A. Cardionephrology from the point of view of the cardiologist: no more agree to disagree-getting to 'yes' for every patient. *Clin Kidney J* 2021; **14**: 1995–1999

111. Hatamizadeh P. Introducing nephrocardiology. *Clin J Am Soc Nephrol* 2022; **17**: 311–313

112. De la Espriella R, González M, Górriz JL *et al*. Setting up a cardiorenal clinic. Consensus document of the cardiorenal working groups of the Spanish Society of Cardiology and the Spanish Society of Nephrology. *CardioClinics* 2021; **56**: 284–295

113. Uppal NN, Jhaveri KD. Cardio-renal service, time for a change. *Clin Kidney J* 2021; **14**: 2278–2279

114. Hatamizadeh P. Introduction to nephrocardiology. *Cardiol Clin* 2021; **39**: 295–306

115. Wettersten N, Maisel AS, Cruz DN. Toward precision medicine in the cardiorenal syndrome. *Adv Chronic Kidney Dis* 2018; **25**: 418–424

116. Bansal N, Arora N, Mariuma D *et al*. Mission and one-year outcomes of a cardio-renal subspecialty consultation service. *Kidney360*, 2022; **3**: 749–751

117. Ortiz A, Navarro-González J, Núñez J *et al*. The unmet need of evidence-based therapy for patients with advanced chronic kidney disease and heart failure: Position paper from the Cardiorenal Working Groups of the Spanish Society of Nephrology and the Spanish Society of Cardiology. *Clin Kidney J* 2021; 15: 865–872