

CONTEMPORARY REVIEW

Cardiorenal Nexus: A Review With Focus on Combined Chronic Heart and Kidney Failure, and Insights From Recent Clinical Trials

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ABSTRACT: The cardiorenal nexus encompasses a bidirectional relationship between the heart and the kidneys. Chronic abnormalities in cardiac function can lead to progressive kidney disease, and chronic kidney disease can lead to progressively decreasing cardiac function and increasing risk of cardiovascular disease, including heart failure. About 15% of US adults have chronic kidney disease, 2% have heart failure, and 9% have cardiovascular disease. Prevalence rates of chronic kidney disease, cardiovascular disease, and associated morbidities such as type 2 diabetes are expected to increase with an aging population. Observational studies provide evidence for the cardiorenal nexus. Follow-up data from placebo arms of clinical trials in chronic kidney disease or cardiovascular disease show higher rates of renal and cardiovascular outcome events in patient subgroups with type 2 diabetes than in those without type 2 diabetes. The cardiorenal syndromes develop along an interlinked pathophysiological trajectory that requires a holistic, collaborative approach involving a multidisciplinary team. There is now a compendium of treatment options. Greater understanding of the underlying pathophysiology of the cardiorenal nexus will support optimization of the management of these interlinked disease states.

Key Words: cardiorenal nexus ■ cardiorenal syndromes ■ cardiovascular disease ■ chronic kidney disease ■ heart failure ■ type 2 diabetes

The cardiorenal nexus encompasses a bidirectional relationship between the heart and the kidneys whereby acute or chronic dysfunction of one can lead to acute or chronic dysfunction of the other.^{1,2} The term “cardiorenal syndrome” has become established to capture the nexus of heart and kidney dysfunction.^{1–4}

The cardiorenal syndrome can be subdivided into 5 types to allow characterization by initiating organ and acuity or chronicity.^{1–4} Types 1 and 3 describe the acute onset setting, and types 2 and 4 describe the chronic setting. Type 5 cardiorenal syndrome is characterized by the simultaneous injury or dysfunction of the heart and kidney due to acute or chronic systemic disorders such as sepsis or amyloidosis. Although this subdivision helps facilitate diagnosis and therapy, the

syndrome types can co-occur, and an acute condition can progress to chronicity if not identified and managed early.

There are a renewed focus and optimism around the cardiorenal nexus and its management, brought about by the beneficial potential of recent treatment advances. However, broader understanding and recognition of the cardiorenal nexus and its underlying chronic syndromes are needed to support early recognition and a holistic, comprehensive management approach. We present a narrative review that focuses on chronic cardiorenal syndromes type 2 and type 4, providing an overview of their epidemiology, outcomes, pathophysiology, and the most recent advances in patient care. This narrative review was developed with the help of nonsystematic, targeted literature searches

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Nonstandard Abbreviations and Acronyms

RAAS	renin–angiotensin–aldosterone system
SGLT-2	sodium–glucose cotransporter-2
UACR	urinary albumin-to-creatinine ratio

in PubMed, and its reporting is aligned with the Scale for the Assessment of Narrative Review Articles principles.⁵

EPIDEMIOLOGY

Cardiovascular disease (CVD) and chronic kidney disease (CKD) represent a substantial disease burden, with type 2 diabetes being a major underlying risk factor (discussed further under “Pathophysiology”).⁶ About 9% of adults in the United States have CVD, which broadly includes atherosclerotic heart disease, myocardial disease, valvular abnormalities, and arrhythmias; and, among those with CVD, about 20% have heart failure (HF).⁷ Prevalence rates of HF with preserved and reduced ejection fractions are approximately equal.⁷ CVD and HF burden rises with age, with a corresponding increase in the number of associated comorbidities.^{7,8} Older age is associated with an increase in CVD-related hospitalizations, including those for HF, in individuals with CKD.⁹

The general population prevalence of CKD in the United States is about 15%.⁷ Relative to the general population, CKD prevalence is increased among adults with hypertension or diabetes.⁷ Prevalence of CKD rises with age.^{7,10}

The prevalence of CKD in the population with HF is about 45% to 63%,¹¹ suggesting a cardiorenal syndrome type 2 population prevalence of about 1%. The prevalence of CVD in people with CKD is about 65%,⁷ suggesting a cardiorenal syndrome type 4 population prevalence of about 10%.

Type 2 diabetes, which is a major risk factor for CVD and CKD, occurs in about 12% of adults in the United States.⁷ For hypertension, the prevalence is about 46%.⁷ With age, there is an increase in prevalence rates for diabetes (ages 18–44 years: 4%; 45–64 years: 18%; ≥65 years: 27%) and hypertension (ages 20–44 years: 26%; 45–64 years: 59%; ≥65 years: 78%).^{7,12} Older adults are also more likely than younger adults to be obese.^{7,13} Approximately 38% of US adults are obese.^{4,7} High prevalence of obesity—a risk factor for CKD and CVD—supports high prevalence of CKD and CVD in hypertension and type 2 diabetes.^{4,7}

It can be anticipated that, with an aging population, the numbers of patients with multimorbid CVD, CKD, and associated diseases will increase, making clinical

management more complex and increasing the burden on health care systems.

OUTCOMES

Real World Data

Real world observational studies provide evidence of the cardiorenal nexus and of the evolution of CVD to CKD and vice versa (Table 1). Among US veterans with or without HF (n=156 743 and 3 414 122, respectively) who had normal kidney function at baseline, risks of incident CKD and rapid decline in estimated glomerular filtration rate (eGFR; slope steeper than -5 mL/min/1.73 m²/year) were about twice as high in individuals with HF than in those without HF (adjusted hazard ratio [aHR], 2.12; 95% CI, 2.10–2.14; and aHR, 2.13; 95% CI, 2.10–2.17, respectively; median follow-up: 7.6 years).¹⁴ The associations were significant irrespective of whether comorbid diabetes was present.¹⁴

An ARIC (Atherosclerosis Risk in Communities) study analysis showed that, compared with individuals with healthy blood pressure at baseline (systolic/diastolic <120/80 mm Hg; n=6200), there was a decline in eGFR over 30-year follow-up of 0.12, 0.14, and 0.39 mL/min/1.73 m² per year in individuals with elevated blood pressure (n=1554), stage 1 hypertension (n=2058), and untreated stage 2 hypertension (n=1374), respectively (adjusted for baseline covariates).¹⁵ The predicted probability of developing CKD over 30 years increased with worsening hypertension.¹⁵ Reduced kidney function at baseline in the ARIC study was an independent risk factor for CVD: the adjusted relative hazard of incident HF was 1.94 (95% CI, 1.49–2.53) in individuals with baseline eGFR <60 mL/min/1.73 m² (n=403) compared with the reference category of ≥90 mL/min/1.73 m² (n=7143; mean follow-up: 13.2 years).¹⁶ In study participants free of CVD history at baseline, low eGFR, high urinary albumin-to-creatinine ratio (UACR) and anemia were each independently associated with risk of incident CVD: the aHR for CVD was 1.62 (95% CI, 1.29–2.03) in individuals with eGFR <60 mL/min/1.73 m² (versus ≥90 mL/min/1.73 m²) and 2.06 (95% CI, 1.69–2.52) in individuals with UACR ≥30 mg/g (versus <10 mg/g) (median follow-up: 15.6 years).¹⁷ The association of low eGFR with incident CVD was increased among participants with anemia compared with normal or high hemoglobin.¹⁷

In individuals with CKD in the CRIC (Chronic Renal Insufficiency Cohort) study (n=3791), HF hospitalizations were associated with increased risks for CKD progression and all-cause death, and rates of 30-day rehospitalization for subsequent HF were high (20.6%).¹⁸ In the GARFIELD-AF (Global Anticoagulant Registry in the Field-Atrial Fibrillation) registry, which enrolls patients with new atrial fibrillation and at least 1 stroke risk

Table 1. Real World Observational Studies

Study	Population	No.	Follow-up	Key findings
US veterans study ¹⁴	US veterans with or without HF, with normal kidney function at baseline	3 570 865	Median: 7.6 y	<ul style="list-style-type: none"> Individuals with HF had higher risks of incident CKD and rapid decline in eGFR than individuals without HF
Atherosclerosis Risk in Communities study ^{15–17}	Middle-aged US community members	15 792 enrolled	30 y	<ul style="list-style-type: none"> Individuals with hypertension had a decline in eGFR compared with individuals with healthy blood pressure (follow-up) Reduced eGFR was an independent risk factor for CVD Low eGFR, high urinary albumin-to-creatinine ratio, and anemia were each independently associated with risk of incident CVD
Chronic Renal Insufficiency Cohort study ¹⁸	US patients with mild to severe CKD	3939 enrolled	Median: 7.8 y	<ul style="list-style-type: none"> HF hospitalizations were associated with increased risks for CKD progression and all-cause death
Global Anticoagulant Registry in the Field-Atrial Fibrillation registry ¹⁹	International patients with AF at risk of stroke	34 854 enrolled	1 y	<ul style="list-style-type: none"> Patients with moderate-to-severe CKD had a higher risk of death, new onset of acute coronary syndrome, and HF than patients with no CKD
Multistudy analysis ^{20*}	Participants without CVD from 3 US community-based studies	14 462	Maximum: 6–10 y	<ul style="list-style-type: none"> Presence of CKD was an independent risk factor for incident HF and incident CHD
UK primary care database study ²¹	Patients with incident CKD selected from a population with prevalent type 2 diabetes	30 222	Median: 4.3 y	<ul style="list-style-type: none"> Patients with fast CKD deterioration were at increased risk of HF and myocardial infarction relative to patients with no CKD progression

AF indicates atrial fibrillation; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; and HF, heart failure.

*Jackson Heart Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis.

factor, patients with moderate-to-severe CKD ($n=3613$) were at significantly increased risk of cardiovascular death, noncardiovascular death, new onset of acute coronary syndrome, and HF within the first year of follow-up (aHR, 2.65; 95% CI, 2.12–3.31; aHR, 1.61; 95% CI, 1.29–2.01; aHR, 1.75; 95% CI, 1.24–2.47; and aHR, 1.52; 95% CI, 1.19–1.94, respectively), compared with patients with no CKD ($n=23\ 816$).¹⁹ Differences in mortality were also statistically significant for comparisons of mild CKD ($n=5595$) compared with no CKD.¹⁹ HF was the most common cause of death.¹⁹

In people without prevalent heart disease ($n=14\ 462$), the presence of CKD (eGFR <60 mL/min/1.73 m²) was an independent risk factor for incident HF and incident coronary heart disease (adjusted risk difference per 1000 person-years, 2.3; 95% CI, 1.2–3.3; and 2.3; 95% CI, 1.2–3.4, respectively), relative to participants without CKD (eGFR ≥ 60 mL/min/1.73 m²), in an analysis of 3 population-based studies (Jackson Heart Study, Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis).²⁰ Mean time to first HF event was 8.2 years and to first coronary heart disease event 7.5 years.²⁰ In a UK primary care database study of patients with prevalent type 2 diabetes and newly diagnosed CKD ($n=30\ 222$), relative to patients with no CKD progression, those with fast deterioration (eGFR slope decline >3 mL/min/1.73 m²) were at significantly increased risk of HF and myocardial infarction (aHR,

1.50; 95% CI, 1.27–1.76; and aHR, 1.39; 95% CI, 1.01–1.91, respectively; median follow-up: 4.3 years).²¹

Clinical Trial Placebo Arm Data

Placebo arms of recent pivotal, randomized trials provide a window to the natural history of HF and CKD in terms of adverse outcomes according to baseline morbidities (Table 2).^{22–30}

The DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) trials both enrolled patients with chronic HF with reduced left ventricular ejection fraction.^{22,24,25,27} The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trial enrolled patients with chronic HF with preserved left ventricular ejection fraction.³⁰ In the DAPA-HF placebo arm ($n=2371$), event rates for worsening HF, worsening renal function, CVD death, and all-cause death were 10.1, 1.2, 7.9, and 9.5 per 100 patient-years, respectively.²⁴ All event rates were higher in the subgroup with diabetes than in the subgroup without diabetes.²⁷ The incidence of the primary end point of first episode of worsening HF or cardiovascular death in the placebo arm was about 50% higher in patients with diabetes than in those without

diabetes (19.4 versus 12.7 per 100 patient-years [*P* not reported]).²⁷ In the EMPEROR-Reduced placebo arm (*n*=1867), event rates for worsening HF, worsening renal function, CVD death, and all-cause death were 15.5, 3.1, 8.1, and 10.7 per 100 patient-years, respectively,²⁵ and rates were higher in patients with than without diabetes.²² The incidence of the primary outcome of cardiovascular death or hospitalization for HF was about 40% higher in patients with diabetes than in those without diabetes (24.6 versus 17.6 per 100 patient-years, *P*<0.001).²² The rate of renal function decline was almost twice as high in patients with diabetes than in those without diabetes (−2.9 versus −1.7 mL/min/1.73 m² per year, *P*=0.02).²² In the EMPEROR-Preserved placebo arm (*n*=2991), 49% of patients had diabetes and 50% had CKD; event rates for worsening HF, worsening renal function, CVD death, and all-cause death were 6.0, 2.2, 3.8, and 6.7 per 100 patient-years, respectively.³⁰

DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) enrolled patients with CKD, and CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation), FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease), and FIGARO-DKD (Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease) enrolled patients with CKD plus type 2 diabetes.^{23,26,28,29} In DAPA-CKD the primary outcome was a composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. In the placebo arm (*n*=2152), event rates for the primary outcome, worsening renal function, CVD death, and all-cause death were 7.5, 5.8, 1.7, and 3.1 per 100-patient-years, respectively.²³ All event rates were higher in patients with type 2 diabetes than in those without type 2 diabetes.³¹ Patients with diabetes were, on average, 9 years older than those without diabetes.³¹ In CREDENCE, the primary outcome was a composite of end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death.²⁶ In FIDELIO-DKD, the primary outcome was a composite of end-stage kidney disease, sustained decrease in eGFR of ≥40% or to <15 mL/min/1.73 m², or renal death.²⁸ In FIGARO-DKD, the primary outcome was a composite of CVD death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF.²⁹ The incidence of the primary outcome increased with increasing baseline CKD severity (as per eGFR and UACR parameters) in CREDENCE, FIDELIO-DKD, and FIGARO-DKD.^{26,28,29} The primary outcome event rate in CREDENCE was higher in the subgroup with HF than in the subgroup without HF (6.6 versus 6.1 per 100 person-years).³²

Insights on the natural history of CKD or HF by baseline morbidities also come from older studies such as RALES (Randomized Aldactone Evaluation Study) and EPHEsus (Eplerenone Post-AMI Heart Failure Efficacy and Survival Study), which assessed aldosterone antagonist therapy.^{33,34} In RALES, which included 1663 patients with HF, baseline eGFR <60 mL/min/1.73 m² (versus ≥60 mL/min/1.73 m²) was associated with a higher incidence of all-cause death in the placebo group.³⁴ In EPHEsus, which enrolled 6632 patients with acute myocardial infarction and HF, early eGFR decline was independently associated with all-cause death, CVD death, and HF progression.³³

PATHOPHYSIOLOGY

The cardiorenal syndromes develop along an interlinked pathophysiological trajectory (Figure).^{1–3} In the type 2 syndrome, the presence of long-term cardiac dysfunction and the associated chronic adaptations to reduced cardiac output and flow rate and raised venous pressure lead to chronic renal hypoperfusion. In response, there is a chronic compensatory activation of both the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system. Angiotensin promotes vasoconstriction and an increase in blood volume resulting from aldosterone-triggered sodium and water retention. Excess aldosterone can stimulate maladaptive interstitial fibrosis and contribute to the development and progression of CVD and CKD.³⁵ Differences in rebound after acute decompensation in patients with chronic HF are likely due to the status of the renal parenchyma and the overall function of remnant intact or hyperfiltering nephrons—there is a discrepancy between current GFR measurement or estimation and the effective GFR achievable (also called renal functional reserve), which is not routinely measured in patients.³⁶ Chronic cardiorenal syndromes in individuals with HF with preserved ejection fraction involve the sequelae of systemic inflammation, elevated central venous pressure, and endothelial, diastolic, and right ventricular dysfunction.³⁷

Reduction in renal blood flow, if sufficiently severe, will result in a decreasing GFR. Renal function decline leads to cardiac function decreases driven by progressive cardiac sodium and water overload, calcium and potassium abnormalities, and CKD-related anemia. Development of chronicity can occur in the setting in which acute kidney injury, induced by acute HF, accelerates cardiovascular pathophysiology via inflammatory pathway activation. In a renal ultrasonography study in patients with chronic HF (*n*=68), individuals with a renal Doppler pulsatile index above median had a worsening of CKD stage after 6 months as compared with those with lower pulsatile index.³⁸ Pulsatile index—an indicator of downstream renal

Table 2. Baseline Morbidities and Outcomes in Placebo Arms of Recent Pivotal Clinical Trials

Study	Placebo group, n (mean age)	Placebo group baseline morbidities			Placebo group outcomes, events/100 patient-years			
		HF	T2D	CKD*	Worsening HF†	Worsening renal function‡	Cardiovascular death	All-cause death
Patients with HF with reduced ejection fraction								
DAPA-HF ^{24,27} (dapagliflozin [§] vs placebo; N=4744)								
Overall ²⁴	2371 (67 y)	100%	45%	41%	10.1	1.2	7.9	9.5
With diabetes ²⁷	1064 (67 y)	100%	100% [¶]	47%	12.6	1.6	9.7	11.7
Without diabetes ²⁷	1298 (66 y)	100%	0% [¶]	36%	8.2	0.8	6.5	7.8
EMPEROR-Reduced ^{22,25} (empagliflozin [§] vs placebo; N=3730)								
Overall ²⁵	1867 (66 y)	100%	50%	49%	15.5	3.1	8.1	10.7
With diabetes ²²	929 (67 y)	100%	100% [¶]	52%	18.6	4.2	9.1	NR
Without diabetes ²²	938 (66 y)	100%	0% [¶]	45%	12.6	2.0	7.2	NR
Patients with HF with preserved ejection fraction								
EMPEROR-Preserved ³⁰ (empagliflozin [§] vs placebo; N=5988)								
Overall	2991 (72 y)	100%	49%	50%	6.0	2.2	3.8	6.7
Patients with CKD								
DAPA-CKD ^{23,31} (dapagliflozin [§] vs placebo; N=4304)								
Overall ²³	2152 (62 y)	11%	67%	100%	NR	5.8	1.7	3.1
With diabetes ³¹	1451 (65 y)	13%	100% [¶]	100%	NR	6.0	2.1	3.5
Without diabetes ³¹	701 (56 y)	7%	0% [¶]	100%	NR	5.3	1.0	2.3
CRENDENCE ^{26,32} (albuminuric CKD and T2D [canagliflozin [§] vs placebo; N=4401])								
Overall ²⁶	2199 (63 y)	15%	100%	100%	2.5	4.0	2.4	3.5
With HF ³²	323 (66)	100% [¶]	100%	100%	4.9	3.3	NR	5.4
Without HF ³²	1876 (63)	0% [¶]	100%	100%	2.2	4.2	NR	3.2
FIDELIO-DKD ²⁸ (CKD and T2D [finerenone [#] vs placebo; N=5734])								
Overall	2481 (66 y)	9%	100%	100%	2.2	9.1	2.0	3.2
FIGARO-DKD ²⁹ (CKD and T2D [finerenone [#] vs placebo; N=7437])								
Overall	3666 (64 y)	8%	100%	100%	1.4	3.6	1.7	3.0

CKD indicates chronic kidney disease; CRENDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; eGFR, estimated glomerular filtration rate; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; FIGARO-DKD, Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; NR, not reported; T2D, type 2 diabetes; and UACR, urinary albumin-to-creatinine ratio.

*DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved: eGFR <60 mL/min/1.73 m²; DAPA-CKD: eGFR 25–75 mL/min/1.73 m² and UACR 200–5000 mg/g; CRENDENCE: eGFR 30–90 mL/min/1.73 m² and UACR 300–5000 mg/g.

†DAPA-HF: hospitalization or urgent visit resulting in intravenous therapy for HF; EMPEROR-Reduced: hospitalization for worsening HF; EMPEROR-Preserved, CRENDENCE, FIDELIO-DKD, and FIGARO-DKD: hospitalization for HF.

‡DAPA-HF and DAPA-CKD: ≥50% reduction in eGFR sustained for ≥28 days, end-stage renal disease or death from renal causes; EMPEROR-Reduced and EMPEROR-Preserved: chronic dialysis, renal transplantation, sustained ≥40% reduction in eGFR, sustained eGFR <15 mL/min/1.73 m² (if baseline eGFR ≥30 mL/min/1.73 m²) or sustained eGFR <10 mL/min/1.73 m² (if baseline eGFR <30 mL/min/1.73 m²); CRENDENCE: end-stage kidney disease, doubling of serum creatinine level or renal death; FIDELIO-DKD: end-stage kidney disease, sustained decrease in eGFR to <15 mL/min/1.73 m², sustained ≥40% reduction in eGFR or renal death; FIGARO-DKD: kidney failure, sustained ≥40% decrease in eGFR from baseline over ≥4 weeks or renal death.

§Sodium–glucose cotransporter-2 inhibitor.

||Inclusion criterion.

¶Subgroup definition.

#Mineralocorticoid receptor antagonist.

artery resistance and stiffness—was an independent predictor of change in eGFR.³⁸ The results suggest that renal pulse pressure rises in chronic HF because of increased arterial stiffness, resulting in an increase in

renal vascular resistance and a decrease in renal blood flow and GFR.³⁸

In the type 4 syndrome, CKD-related anemia, electrolyte imbalances, increases in uremic toxins, chronic

inflammation, and oxidative stress lead to cardiac and vascular dysfunction.¹⁻³ With progressively declining kidney function, phosphate retention increases, and phosphate homeostasis is disrupted despite elevated levels of FGF23 (fibroblast growth factor 23) and parathyroid hormone.³⁹ The increase in FGF23 levels and hyperphosphatemia trigger pathways that promote hypertension, left ventricular hypertrophy, and vascular calcification, contributing to CVD progression.³⁹ Progression of CKD is often due to underlying diabetes and/or hypertension. Chronic renal dysfunction is linked with disruption of erythropoietin signaling and red blood cell turnover, leading to anemia, which is an important comorbidity of CKD and HF.⁴⁰ Cachexia is common in individuals with chronic cardiorenal syndromes and may augment the pathophysiological interaction between the heart and kidneys via immune, neuroendocrine, and proinflammatory pathways.⁴¹

Right HF and hemodynamic dysfunction from pulmonary hypertension may also lead to the development of chronic cardiorenal syndromes as well as contribute to the progression of CKD.^{42,43} In patients with end-stage CKD on hemodialysis, the arteriovenous fistula required for access can cause excessive pulmonary blood flow, leading to preload increase on the right heart and pulmonary hypertension.^{43,44}

Type 2 diabetes is a common underlying causal factor in HF and CKD. In addition to its link with endothelial

dysfunction and atherosclerotic vascular disease, type 2 diabetes is also associated with glomerular hyperfiltration and volume expansion, and tubuloglomerular feedback disruptions.⁴⁵ The vascular theory of type 2 diabetes describes dysregulation of vasoactive factors and inactivation of tubuloglomerular feedback in type 2 diabetes, which lead to dilation of the renal afferent arteriole and constriction of the efferent arterioles, thereby resulting in glomerular hypertension and hyperfiltration.⁴⁶

PATIENT CARE

The interlinked pathophysiology between the heart and the kidneys in the cardiorenal syndromes requires a holistic, comprehensive approach to management. There is a need for both primary and secondary prevention of adverse outcomes in patients with CVD, CKD, type 2 diabetes, and HF. CKD and chronic HF deteriorate progressively and need to be managed proactively. In addition, the risk of evolution of an acute condition to chronicity requires prompt identification of at-risk patients and implementation of preventative measures. It is crucial that leading risk factors such as hypertension and diabetes, and important comorbidities such as anemia, are managed. Patient–physician communication is an important part of care. Care planning includes management decisions around the often

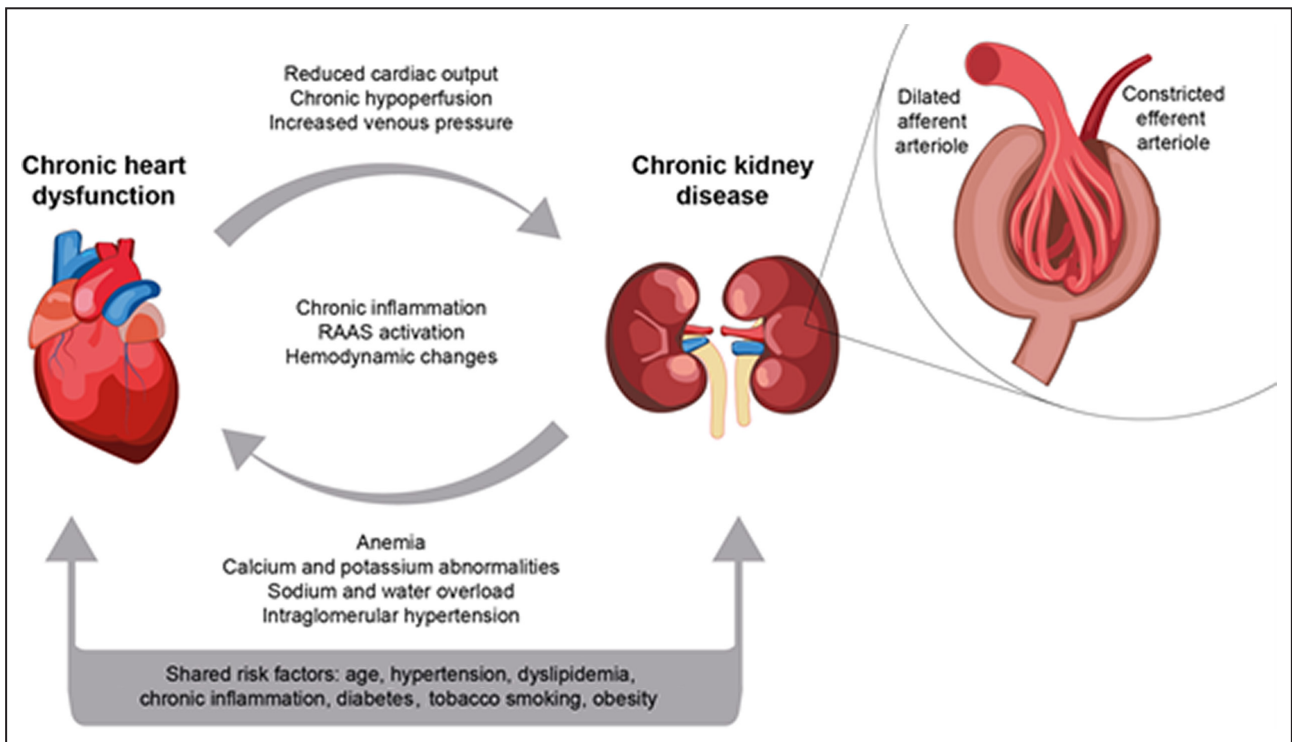


Figure 1. Flow diagram showing interplay of cardiovascular and renal systems in chronic kidney disease and cardiovascular disease.

RAAS indicates renin–angiotensin–aldosterone system.

high symptom burden, which includes fatigue, chronic pain, and depression.³

Optimal management first requires screening and early disease recognition. Patients with HF, as well as those with earlier forms of CKD who have proteinuria but preserved GFR, need to be identified in routine clinical care. However, the rate of screening of at-risk populations by routine testing (eg, by annual UACR assessment) is low (35%–57%) in primary care,^{42,47} highlighting the need for increased awareness of the cardiorenal nexus in the primary care setting. The UACR is now positioned as an important trigger for lower systolic blood pressure targets of 120 mm Hg or below according to the 2021 Kidney Disease Improving Global Outcomes guideline.⁴⁸ Once identified, the complexity of the chronic cardiorenal syndromes requires a collaborative approach to management, involving a multidisciplinary team that includes a primary care physician, cardiologist, nephrologist, and endocrinologist. Guidance from a dietitian can aid patients with following a heart- and kidney-healthy diet. Continuity of care between hospital and out-of-hospital follow-up needs to be ensured. Transitions of care and adherence to medications are significant strategies in disease prevention and mitigation of progression of disease.

Historically, therapy to relieve HF symptoms in particular was limited by fear of detrimental impact on declining kidney function. Fear of adverse events such as hyperkalemia can be a barrier to therapy with aldosterone antagonists, because many patients with advanced CKD—particularly those receiving angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy—are already at increased risk of hyperkalemia.⁴⁹

There is now a compendium of treatment options, from RAAS inhibitors to, more recently, sodium–glucose cotransporter-2 (SGLT2) inhibitors—both of which have positive outcome data in dedicated HF and CKD trials—and glucagon-like peptide-1 receptor antagonists, which have positive data in type 2 diabetes.^{6,50} Early, hypothesis-generating results from cardiovascular outcome trials with glucagon-like peptide-1 receptor antagonists noted some degree of renal protection with these agents, in addition to their ability to reduce CVD outcomes in patients with type 2 diabetes.⁵¹ Evaluation of the effect of a glucagon-like peptide-1 receptor antagonist on renal outcomes in patients with type 2 diabetes is ongoing (NCT03819153). Recent results with aldosterone antagonism, from FIDELIO-DKD and FIGARO-DKD, show decreased CKD and CVD events in patients with CKD and type 2 diabetes.^{28,29} The SGLT2 inhibitor class offers a new option that can have meaningful effects on the cardiorenal nexus: SGLT2 inhibition decreased CKD progression and CVD events in patients with CKD in DAPA-CKD²³

and reduced adverse CVD-related outcomes including worsening HF in DAPA-HF,²⁴ EMPEROR-Reduced,²⁵ and EMPEROR-Preserved,³⁰ regardless of the presence or absence of type 2 diabetes.

SGLT2 inhibitors have a multifactorial role in ameliorating the insults of the cardiorenal syndromes. In addition to improving glycemic control, SGLT2 inhibitors can increase red blood cell mass and hematocrit via renal erythropoietin production and potentially have a role in reducing oxidative stress and inflammation by inhibiting proinflammatory pathways, inducing autophagy, and activating nonclassic RAAS pathways.^{52,53} SGLT2 inhibition with canagliflozin reduced the risk of hyperkalemia in patients treated with RAAS inhibitors (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) in CREDENCE, which may contribute to cardiorenal benefits.⁵⁴ However, a secondary analysis of DAPA-CKD showed no statistically significant difference in hyperkalemia between the dapagliflozin and placebo arms (regardless of mineralocorticoid receptor antagonist use).⁵⁵ The risk of hyperkalemia is lower with nonsteroidal than steroidal mineralocorticoid receptor antagonists.⁵⁶ There are different mechanisms that can be hypothesized for how SGLT2 inhibitors might affect RAAS,⁵⁷ including hemodynamic modification of glomerular blood flow and level of hyperfiltration in intact nephrons. Hyperfiltration induces activation of profibrotic pathways and thus modulation of hyperfiltration, and tubular activity may have an impact on long-term nephron function.

FUTURE DIRECTIONS

With the beneficial potential of new medications comes a renewed focus on the cardiorenal nexus. The underlying pathophysiology of the cardiorenal nexus remains to be further elucidated. Capturing the underlying pathophysiology will enable physicians to choose the appropriate treatment earlier. Broader recognition of the cardiorenal nexus will emphasize the need to evaluate and manage CKD in patients who are primarily being treated for CVD issues and vice versa. Paying attention to underlying cardiorenal syndromes will enable primary care physicians and endocrinologists to take a comprehensive approach to the care of their patients with hypertension, type 2 diabetes, and obesity. Development of a combined heatmap system that visually presents cardiorenal syndrome risk in the electronic medical record based on CVD and CKD severity, and how this risk is affected by type 2 diabetes, would aid earlier identification and treatment of high-risk patients. Further research into the mechanisms of action of potentially disease-modifying medications, and the role that these medications may have when used in combination, will improve treatment

algorithms. Further research on health economics and outcomes will drive improvements in long-term continuity of care.

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