Circulation

Cardiorenal Syndrome Revisited

ABSTRACT: Cardiorenal syndromes have been categorized into 5 clinical subtypes based on which organ is perceived to be the primary precipitant of the vicious and interrelated cycle of declining function in both organs. This clinical classification has broadened interest in cardiorenal interactions, but it is merely descriptive, does not rely on or inform predominant pathophysiology, and has produced little change in either practice or the research agenda. In contrast, recent scientific work identifies common pathophysiological pathways for several categories of cardiorenal syndromes, suggesting a unifying pathogenesis. Fibrosis is a common consequence of inflammation- and oxidative stress–related endothelial dysfunction in aging, hypertension, diabetes mellitus, obesity, ischemia, and organ injury. It is a common feature in heart failure and chronic kidney disease. Therefore, we suggest that fibrosis may be not only a marker but also the primary driver of pathophysiology in several cardiorenal syndromes. Interstitial fibrosis in the heart, large arteries, and kidneys may play a key role in the pathophysiology of the cardiorenal syndrome continuum. Focusing on fibrosis as a disease mediator might enable the identification of fibrosis-related biotargets that could potentially be modulated with renin-angiotensin-aldosterone system inhibitors, mineralocorticoid receptor antagonists, or other novel antifibrotic agents in development. This conceptual approach may be an effective new strategy for the prevention and treatment of fibrosis within the cardiorenal syndrome continuum.

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Cardiorenal syndromes 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."[1] Consensus groups have provided guidance for physicians on the classification and clinical management of patients affected by these syndromes,[1] but uncertainty remains in the medical community's understanding of pathophysiological mechanisms, the interactions that contribute to cardiorenal syndromes, and the optimal management approaches for these patients (Table 1).[2,3]

In this article, we aim to raise awareness about the importance of harmonizing evaluation metrics and clinical event definitions across the cardiovascular and renal communities; highlight gaps in evidence in the pathophysiology, prevention, and management of cardiorenal syndromes and the need to prioritize research in this area; and propose new concepts for pathophysiology-based disease-specific management strategies.

THE CLASSIC DEFINITION

The Acute Dialysis Quality Initiative produced a definition and clinical classification structure for cardiorenal

syndromes in 2010. Cardiorenal syndromes were categorized into 5 types based on the organ presumed to be the primary precipitant and the time course of progression (ie, acute or chronic).[1] These definitions provided a clinically relevant construct to raise awareness of cardiorenal syndromes and prompt consideration of management approaches. Precise epidemiological data are difficult to obtain, but it is estimated that 25% to 63% of patients with heart failure have some form of cardiorenal syndrome as defined by the Acute Dialysis Quality Initiative (ie, acute kidney injury in the setting of acute heart failure or chronic kidney disease [CKD] in the setting of chronic heart failure).[4] In a retrospective cohort study of 30681 patients with transthoracic echocardiography and up to 110 months of follow-up, 8% of patients developed at least 1 cardiorenal syndrome subtype. Of those patients who developed a chronic type of cardiorenal syndrome, 19% subsequently developed an acute syndrome.[5]

Potential pathophysiological mechanisms for the various types of cardiorenal syndromes have been previously described,[1,6] but a categorization starting from clinical descriptions limits the ability to distinguish the predominant pathophysiology in an individual patient.

Table 1. Research Needs to Address Knowledge Gaps

Gaps in Knowledge	Research Needs
Utility of novel biomarkers (eg, NGAL, KIM-1) to detect kidney injury	Validation studies
Better differentiation between rises in serum creatinine and other kidney biomarkers that signal worsening renal function vs decongestion in patients with heart failure and relationship of these to prognosis	Prognostic modeling using prospective registries with prespecified definitions, followed by prospective validation studies
Association between fibrosis biomarkers and reversibility of worsening renal function	Prospective biomarker studies
Predictors of improved renal function after mechanical circulatory support or transplantation	Prognostic modeling using prospective registries
Efficacy of matching therapy to biomarker phenotypes (eg, MRAs in patients with elevated inflammatory or fibrosis markers)	Prospective randomized trials, antifibrotic agent (eg, MRA, ACE inhibitor, ARB, novel small molecules) vs no antifibrotic agent in biomarker-positive and biomarker-negative patients; usefulness of registry-embedded platform trials, with master protocols to study multiple therapies
Time course of fibrosis, when is it reversible, when is it nonreversible, implications for preventive therapies	Prospective studies

ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; KIM-1, kidney injury molecule-1; MRA, mineralocorticoid receptor antagonist; and NGAL, neutrophil gelatinase-associated lipocalin.

DISEASE-SPECIFIC MANAGEMENT IN THE CARDIORENAL SYNDROME: CURRENT KNOWLEDGE AND EVIDENCE GAPS

Heart Failure and the Cardiorenal Syndrome

The interplay between heart failure and kidney disease in patients with a chronic cardiorenal syndrome can lead to highly complex and challenging clinical scenarios. First, the diagnosis of worsening heart failure may be uncertain in a patient with cardiorenal syndrome. Natriuretic peptides can be elevated in the setting of CKD, which may confound their interpretation in the setting of worsening heart failure. It may not be possible to distinguish volume overload resulting from worsening heart failure from that caused by progressively declining kidney function. Volume overload in patients with heart failure also becomes more difficult to manage as CKD progresses.

Increasing serum creatinine that occurs in the setting of decongestion or titration of neurohormonal antagonists is commonly encountered. Small increases in serum creatinine are expected after the initiation or titration of these agents, primarily as a result of their effects on renal hemodynamics. Interesting recent data showed that when heart failure medications (ie, angiotensin-converting enzyme inhibitor, mineralocorticoid receptor [MR] antagonist [MRA], β-blocker, di-

uretics) were held for 48 hours, serum creatinine decreased but natriuretic peptides and cardiac volumes increased.[7] These data support the concept that serum creatinine increases should not be evaluated in isolation but rather considered in the context of the entire clinical picture. Not all increases in serum creatinine adversely affect prognosis.

Differentiation between true and pseudoworsening renal function is an important determinant of treatment decisions, although in many cases it may be difficult or impossible[2] because the methods of measuring renal function in clinical settings are imprecise. Acute kidney injury has typically been categorized into prerenal azotemia (ie, renal hypoperfusion that leads to a decreased glomerular filtration rate [GFR] without injury to the renal parenchyma), intrinsic acute kidney injury (ie, involving damage to the tubules, glomeruli, interstitium, or intrarenal vasculature), or postrenal acute kidney injury (ie, resulting from acute obstruction of urinary flow). These designations are somewhat theoretical in nature because methods other than biopsy are lacking to distinguish between prerenal azotemia and intrinsic damage.[8] In addition, prerenal azotemia and intrinsic acute tubular necrosis can coexist.[9] In the acute setting, equations for estimated GFR (eGFR) assume steady state, which is absent in such situations. Serum creatinine to estimate GFR continues to be the predominant measure of kidney function in clinical settings, but serum creatinine has several limitations, including its inability to differentiate between prerenal azotemia and intrinsic kidney injury.[10] Several biomarkers of renal injury are being evaluated for their utility to detect kidney injury and to differentiate it from functional decline without injury. Novel "tubular dysfunction markers" (eg, neutrophil gelatinase–associated lipocalin [NGAL], kidney injury molecule-1 [KIM-1]) are promising, but further validation is needed before adoption in clinical practice.[2,11]

In a post hoc analysis of the DOSE study (Diuretic Optimization Strategies Evaluation) in patients with heart failure, worsening renal function was not associated with a higher risk of the composite end point, but improved renal function was associated with a higher risk of death, hospitalization, or emergency room visit.[12] These patients may simply have been more severely ill or suboptimally decongested; only 7.7% of patients were considered congestion free by the treating physician. More patients (19%) with worsening renal function were considered congestion free at 72 hours by the treating physician, but the occurrence of worsening renal function was associated with a significantly shorter duration of study drug (diuretic) treatment, which could also have implications for readmission resulting from incomplete decongestion.[12]

Worsening renal function defined by rising serum creatinine is not uncommon after initiation of renin-angiotensin-aldosterone system (RAAS) inhibitors, which most likely reflect changes in renal hemodynamics rather than intrinsic kidney injury. An analysis of the SOLVD trial (Studies of Left Ventricular Dysfunction) showed that early worsening renal function after angiotensin-converting enzyme inhibitor initiation was not associated with an increased mortality risk, and among those patients who continued therapy despite the change in renal function, the associated mortality benefit persisted.[13] A recently published meta-analysis showed that worsening renal function in patients with heart failure with reduced ejection fraction (HFrEF) randomized to RAAS inhibitor therapy was associated with a greater mortality risk compared with patients without worsening renal function (relative risk, 1.19, 95% confidence interval [CI], 1.08–1.31; $P<0.001$), but this risk was less than the mortality risk associated with worsening renal function in patients randomized to placebo (relative risk, 1.48; 95% CI, 1.35–1.62; $P<0.001$; P for interaction with patients randomized to RAAS inhibitors=0.005).[14] In contrast, worsening renal function in patients with heart failure with preserved ejection fraction (HFpEF) randomized to RAAS inhibitor therapy was associated with a greater mortality risk, whereas worsening renal function in patients with HFpEF randomized to placebo was not significantly associated with mortality.[14] It should be emphasized that RAAS inhibitors have convincing evidence of benefit on prolonging survival and reducing morbidity in patients with HFrEF, and both US and European guidelines give a Class I, Level of Evidence A recommendation for their use.[15,16] In contrast, randomized trials to date have not demonstrated the efficacy of RAAS inhibitors in HFpEF, except perhaps for MRAs.[17]

New definitions for worsening renal function in heart failure have been proposed.[3] In addition to typical threshold changes in serum creatinine or eGFR, these definitions require a deterioration in heart failure status not leading to hospitalization (chronic heart failure) or deterioration in heart failure status, failure to improve, or a need for inotropes, ultrafiltration, or renal replacement therapy (acute heart failure). These definitions may enable better detection of true worsening renal function, but the subjective assessment of deterioration or no clinical improvement may be a limitation of the definition because many factors unrelated to renal function can contribute to in-hospital worsening or a lack of clinical improvement.

One study categorized 132 patients with acute heart failure according to whether they had true worsening renal function (serum creatinine rise ≥0.3 mg/dL or >25% decrease in eGFR and deterioration or no clinical improvement during hospitalization), pseudoworsening renal function (serum creatinine rise ≥0.3 mg/dL or >25% decrease in eGFR and uneventful clinical course), or no worsening renal function.[18] Urinary lev-

els of NGAL, KIM-1, and cystatin C were measured at baseline, day 2, and day 3. After adjustment for other prognostic factors, urinary NGAL at all time points and KIM-1 at day 2 were significant predictors of true worsening renal function.[18] An analysis from the Renal Optimization Strategies Evaluation in Acute Heart Failure study (ROSE-AHF) showed no correlation between worsening renal function (≥20% reduction in eGFR from baseline to 72 hours) and the tubular injury biomarkers N-acetyl-b-ᴅ-glucosaminidase, NGAL, or KIM-1 in patients with acute heart failure undergoing aggressive diuresis.[19] Worsening renal function was not associated with worse 6-month survival. Paradoxically, increases in NGAL, N-acetyl-b-ᴅ-glucosaminidase, and KIM-1 were associated with improved survival.[19]

Altogether, acknowledging the limitations of serum creatinine to accurately depict acute glomerular function changes, these data suggest that further studies are warranted to unravel the complexity of observed acute changes in kidney function and their interplay with clinical outcomes. At this stage, one might hypothesize that acute kidney injury biomarkers may be helpful to differentiate between true kidney injury and pseudoworsening renal function in the setting of heart failure. If validated, this biomarker-based approach would provide complementary, objective biomarker criteria to the proposed definition requiring deterioration of heart failure status.[3] Furthermore, whether the reversibility of worsening renal function and its interplay with future cardiac and renal outcomes may be critically influenced by the underlying cardiorenal fibrotic disease, as assessed by circulating fibrosis biomarkers, deserves dedicated studies.

A cardiorenal syndrome can be a barrier to the use of advanced heart failure therapies such as destination mechanical circulatory support or cardiac transplantation. Baseline renal function is an independent predictor of postimplantation mortality, but some patients will experience an improvement in renal function after implantation caused by resolution of venous congestion and improved cardiac output.[20] Patients whose renal function does not improve may have renal injury from causes other than heart failure (eg, diabetes mellitus, hypertension). Destination mechanical cardiac support is contraindicated in patients with end-stage kidney disease on permanent dialysis.[21] Renal impairment is associated with worse graft survival after cardiac transplantation, and an eGFR <30 mL·min⁻¹·1.73 m⁻² is a relative contraindication for transplantation (Class IIa, Level of Evidence C).[22] At present, identifying before implantation (or transplantation) which patients are likely to experience improved renal function is difficult, but some data suggest that markers of venous congestion may identify patients with reversible renal impairment, and renal injury markers may distinguish patients with irreversible renal impairment.[20]

Hypertension and the Cardiorenal Syndrome

Hypertension is prevalent in ≈30% of patients with CKD.[23] Hypertension is a risk factor for the development of CKD and can result from or be worsened in the setting of renal impairment caused by sodium and water retention, RAAS or sympathetic nervous system activation, or endothelial dysfunction. SPRINT (Systolic Blood Pressure Intervention Trial) contributed importantly to knowledge about blood pressure targets for the CKD population because it enrolled the largest proportion of patients with CKD (28%) of any blood pressure target trial[24–32] (Table 2). SPRINT randomized 9361 patients at increased cardiovascular risk with a systolic blood pressure ≥130 mm Hg to a blood pressure target of <120 mm Hg (intensive treatment) or <140 mm Hg (standard treatment). Patients with diabetes mellitus were excluded, as were patients with eGFR <20 mL·min⁻¹·1.73 m⁻², end-stage renal disease, polycystic kidney disease, or glomerulonephritis. The primary end point was a composite of myocardial infarction (MI), other acute coronary syndrome, stroke, heart failure, or cardiovascular death. In the overall study population, intensive treatment reduced the primary composite end point compared with standard treatment (hazard ratio [HR], 0.75; 95% CI, 0.64–0.89). This treatment effect was similar across several different prespecified subgroups, including CKD.[25] CKD at baseline was present in 1330 patients randomized to the intensive treatment group and in 1316 patients randomized to the standard treatment group. A primary composite outcome occurred in 112 patients in the intensive group and 131 patients in the standard group (HR, 0.81; 95% CI, 0.63–1.05). The rate of all-cause death was lower in the intensive treatment group (HR, 0.72; 95% CI, 0.53–0.99). There was no evidence of a differential treatment effect on cardiovascular outcomes between patients with or without CKD (P for interaction ≥0.3), and there was no difference in the composite of ≥50% decrease in baseline eGFR or end-stage kidney disease between the intensive and standard treatment groups (HR, 0.90; 95% CI, 0.44–1.83).[25] Nevertheless, the number of renal events by this definition was very small; thus, this end point was markedly underpowered. In parallel, intensive blood pressure lowering was associated with increased serious events of acute kidney injury and acute renal failure (4.1% versus 2.5%; HR, 1.66; P<0.001).[24] Altogether, these data suggest that cardiovascular outcomes in patients with CKD and hypertension without diabetes mellitus may be improved by achieving systolic blood pressure of ≈120 mm Hg (mean systolic blood pressure, 121.5 mm Hg in the intensive treatment group at 3.26 years of follow-up).

The prevalence of resistant hypertension is increased in patients with CKD, whereas CKD is asso-

Table 2. Major Clinical Trials in Cardiorenal Syndrome

Trial	Intervention	n	Primary End Point	Primary Results
Hypertension and cardiorenal syndrome				
SPRINT[25]	Intensive (<120 mm Hg) vs standard (<140 mm Hg) blood pressure control	Subgroup with CKD at baseline (n=1330 intensive, n=1316 standard)	Composite of MI, other ACS, stroke, heart failure, or cardiovascular death	Primary outcome (intensive vs standard): HR, 0.81, 95% CI, 0.63–1.05 All-cause death: HR, 0.72; 95% CI, 0.53–0.99
PATHWAY-2[26]	Spironolactone 25–50 mg/d vs doxazosin 4–8 mg/d vs bisoprolol 5–10 mg/d vs placebo	335 Patients with hypertension (clinic SBP ≥140 mm Hg, home SBP ≥130 mm Hg) despite maximally tolerated doses of 3 drugs eGFR <45 mL·min^{-1}·1.73 m^{-2} were excluded Mean baseline eGFR, 91.1 mL/min	Hierarchical primary end points: Difference in averaged home SBP between spironolactone and placebo, followed by difference in averaged home SBP between spironolactone and average of other 2 active drugs, followed by difference in averaged home SBP between spironolactone and each of the other 2 drugs	Spironolactone vs placebo: −8.7 mm Hg; 95% CI, −9.72 to −7.69, P<0.0001 Spironolactone vs mean of other drugs: −4.26 mm Hg, 95% CI, −5.13 to −3.38; P<0.0001 Spironolactone vs doxazosin: −4.03 mm Hg; 95% CI, −5.04 to −3.02; P<0.0001 Spironolactone vs bisoprolol: −4.48 mm Hg; 95% CI, −5.50 to −3.46; P<0.0001
AMBER (NCT03071263)	Spironolactone plus patiromer vs spironolactone plus placebo	290 Patients with eGFR 25–≤45 mL·min^{-1}·1.73 m^{-2}	Proportion of patients remaining on spironolactone at week 12	Ongoing
Diabetes mellitus, kidney disease, and cardiorenal syndrome				
ARTS-DN[27]	Finerenone 1.25 to 20 mg/d vs placebo plus RAS blocker standard of care	823 Type 2 diabetes mellitus, albuminuria, eGFR >30 mL·min^{-1}·1.73 m^{-2}	Ratio of UACR at day 90 vs baseline	Placebo-corrected mean ratio of UACR was reduced in all finerenone dosing groups.
FIDELIO-DKD (NCT02540993)	Finerenone 10–20 mg/d vs placebo	4800 Patients with type 2 diabetes mellitus, diabetic kidney disease with persistent high albuminuria, on ACE inhibitor or ARB at maximally tolerated doses, serum K$^+$ ≤4.8 mmol/L	Time to first occurrence of composite of onset of kidney failure, sustained decrease of eGFR ≥40% from baseline over at least 4 wk, and renal death	Ongoing
FIGARO-DKD (NCT02545049)	Finerenone 10–20 mg/d vs placebo	6400	Time to first occurrence of composite end point of cardiovascular death and nonfatal cardiovascular events (MI, stroke, or hospitalization for HF)	Ongoing
EMPA-REG OUTCOME[28]	Empagliflozin vs placebo	1,212 empagliflozin and 607 placebo post hoc subgroup of patients with eGFR ≤49 mL·min^{-1}·1.73 m^{-2}	Prespecified renal outcomes: incident or worsening nephropathy, incident albuminuria Post hoc composite of doubling of SCr level, initiation of RRT, or death resulting from renal disease	Incident or worsening nephropathy (empagliflozin vs placebo): HR, 0.61; 95% CI, 0.53–0.70; P<0.001 Progression to macroalbuminuria: HR, 0.62; 95% CI, 0.54–0.72; P<0.001 Doubling SCr: HR, 0.56; 95% CI, 0.39–0.79; P<0.001 RRT initiation: HR, 0.45; 95% CI, 0.21–0.97; P=0.04
CANVAS[29]	Canagliflozin vs placebo	5795 canagliflozin, 4347 placebo patients with type 2 diabetes mellitus and eGFR >30 mL·min^{-1}·1.73 m^{-2} (mean, 76.5±20.5 mL·min^{-1}·1.73 m^{-2} at baseline)	Secondary end point progression of albuminuria	Progression of albuminuria (canagliflozin vs placebo): HR, 0.73; 95% CI, 0.67–0.79

(*Continued*)

Table 2. Continued

Trial	Intervention	n	Primary End Point	Primary Results
HF				
RECONNECT	Systematic assessment of circulating renal drivers of HFpEF onset, progression, and prognosis using well-characterized HFpEF cohorts. Studies to determine underlying mechanisms and causal relationships. Identify prognostic markers and unique targets for therapeutic intervention. Specific mechanistic pathways will be examined with ex vivo bioassays to assess patient material and in vivo small and large animals. The most promising therapeutic targets will be tested in newly developed animal models of CKD-induced HFpEF.[31]		Consortium to test hypothesis that renal impairment and systemic consequences adversely affect pathophysiology, course, and prognosis of HFpEF	Ongoing
Bioprofiling and targeted therapy				
HOMAGE (NCT02556450)	Spironolactone vs usual care	Patients at risk of HF	Extracellular matrix remodeling assessed by changes in PIIINP; evaluate differences in treatment effect based on Gal-3	Ongoing
PRIORITY (NCT02040441)[30]	Spironolactone vs placebo	Patients identified as high risk by urinary proteome test	Progression to microalbuminuria	Ongoing
FIBROTARGETS[32]	Novel cardiorenal therapies tailored to fibrotic mechanistic bioprofiles			Ongoing

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; AMBER, Spironolactone With Patiromer in the Treatment of Resistant Hypertension in Chronic Kidney Disease; ARB, angiotensin receptor blocker; ARTS-DN, Mineralocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy; CANVAS, Canagliflozin Cardiovascular Assessment Study; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; FIBROTARGETS, targeting cardiac fibrosis for heart failure treatment; FIDELIO-DKO, Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and 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; Gal-3, galectin-3; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HOMAGE, Bioprofiling Response to MRAs for the Prevention of Heart Failure Within the Heart Omics in Aging; HR, hazard ratio; MI, myocardial infarction; PATHWAY-2, Prevention and Treatment of Hypertension With Algorithm-Based Therapy-2; PIIINP, procollagen-III-N-terminal peptide; PRIORITY, Proteomic Prediction and Renin Angiotensin Aldosterone System Inhibition Prevention of Early Diabetic Nephropathy in Type 2 Diabetic Patients With Normoalbuminuria; RAS, renin angiotensin system; RECONNECT, Renal Connection to Microvascular Disease and Heart Failure With Preserved Ejection Fraction; RRT, renal replacement therapy; SBP, systolic blood pressure; SCr, serum creatinine; SPRINT, Systolic Blood Pressure Intervention Trial; and UACR, urinary albumin-creatinine ratio.

ciated with an impaired cardiovascular prognosis in patients with resistant hypertension.[33] Current guidelines suggest that after optimization of the ongoing treatment, the next step is to consider the addition of other antihypertensive drugs, with the current suggested fourth-line therapy being a MRA.[26,33] However, it is unknown whether this may be applicable to a cardiorenal syndrome population, because the landmark PATHWAY-2 trial (Prevention and Treatment of Hypertension With Algorithm-Based Therapy-2) excluded patients with an eGFR <45 mL·min^{-1}·1.73 m^{-2} (ie, patients more prone to experience hyperkalemia and discontinue an MRA). The ongoing AMBER (Spironolactone With Patiromer in the Treatment of Resistant Hypertension in Chronic Kidney Disease; ClinicalTrials.gov identifier NCT03071263) randomized, double-blind, placebo-controlled study of pati-

romer and spironolactone use for blood pressure control in patients with resistant hypertension and CKD (eGFR, 25–≤45 mL·min^{-1}·1.73 m^{-2}) aims to determine whether patiromer, the potassium-binding polymer that uses calcium as the counterexchange ion (recently approved in both the United States and European Union), used concomitantly with spironolactone will prevent or manage hyperkalemia, allow more persistent use of the MRA for the management of blood pressure, and ultimately enable better blood pressure control.

Diabetes Mellitus, Kidney Disease, and the Cardiorenal Syndromes

Finerenone is a nonsteroidal, selective MRA.[34] In the ARTS-DN study (Mineralocorticoid Receptor Antago-

nist Tolerability Study-Diabetic Nephropathy), finerenone improved the urinary albumin-creatinine ratio compared with placebo in patients with diabetic nephropathy.[27] Placebo-corrected systolic blood pressure was reduced by 3 to 5 mm Hg (depending on dosing group). The mean baseline eGFR in this trial was 66 to 72 mL·min^{-1}·1.73 m^{-2} across the treatment groups, and 60% of patients had an eGFR >60 mL·min^{-1}·1.73 m^{-2}. Serum potassium values of >5.6 mmol/L occurred in 1.5% of finerenone-treated patients, prompting study drug discontinuation[27]; serum potassium results might be different at lower levels of eGFR. Although MRAs are not routinely recommended on top of RAAS inhibitors, they have been proposed for patients with CKD and resistant hypertension.[33] Two ongoing studies will clarify the role of finerenone in patients with CKD. The FIDELIO-DKD study (Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease; ClinicalTrials.gov identifier NCT02540993) is a randomized, double-blind trial of finerenone versus placebo in patients with type 2 diabetes mellitus and diabetic kidney disease with albuminuria treated with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker at maximally tolerated labeled doses. The study will enroll 4800 patients and evaluate the composite end point of time to onset of kidney failure, a sustained decrease in eGFR ≥40% from baseline over ≥4 weeks, and renal death. A similar study, FIGARO-DKD (Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease; ClinicalTrials.gov identifier NCT02545049), will enroll a similar population of 6400 patients and compare finerenone and placebo on the primary composite end point of cardiovascular death and nonfatal cardiovascular events (MI, stroke, or heart failure hospitalization).

Other agents used for the treatment of diabetes mellitus have demonstrated a cardiorenal protective effect. The EMPA-REG OUTCOME trial [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients] evaluated the cardiovascular safety of empagliflozin compared with placebo in 7020 patients with type 2 diabetes mellitus, established cardiovascular disease, eGFR ≥30 mL·min^{-1}·1.73 m^{-2}, and glycosylated hemoglobin between 7% and 9% (or 10% if on stable glucose-lowering therapy before randomization).[35] The primary end point was a composite of cardiovascular death, nonfatal MI, or nonfatal stroke, assessed with a hierarchical strategy testing first noninferiority in the primary and key secondary outcome and then superiority for the primary and key secondary outcome. Empagliflozin reduced the risk of the primary composite outcome compared with placebo (HR, 0.86; 95% CI, 0.74–0.99; P=0.04 for superiority), as well as all-cause (HR, 0.68; 95% CI, 0.57–0.82; P<0.001) and cardiovascular (HR, 0.62;

95% CI, 0.49–0.77; P<0.001) mortality.[35] The secondary outcome of hospitalization for heart failure was also reduced (HR, 0.65; 95% CI, 0.50–0.85; P=0.002). Neither serum potassium or serum creatinine changed appreciably from baseline, and more patients in the placebo than the empagliflozin group experienced acute renal failure (6.6% versus 5.2%; P<0.01) or acute kidney injury (1.0% versus 1.6%; P<0.05).[35] A major achievement was that prespecified renal outcomes were consistently simultaneously improved by empagliflozin.[28]

Similarly, the CANVAS program (Canagliflozin Cardiovascular Assessment Study) program randomized 10 142 patients with type 2 diabetes mellitus (glycohemoglobin ≥7%, ≤10.5%), a history of symptomatic atherosclerotic cardiovascular disease or ≥2 cardiovascular risk factors, and eGFR >30 mL·min^{-1}·1.73 m^{-2} to canagliflozin or placebo.[29] A composite of cardiovascular death, nonfatal MI, or nonfatal stroke was assessed as the primary outcome, tested first for noninferiority and then for superiority if noninferiority was met. Canagliflozin reduced the risk of the primary composite outcome compared with placebo (HR, 0.86; 95% CI, 0.75–0.97), as well as the risk of hospitalization for heart failure (HR, 0.67; 95% CI, 0.52–0.87). Canagliflozin also reduced the risk of renal outcomes.[29]

Both empagliflozin and canagliflozin are sodium-glucose cotransporter 2 inhibitors that decrease renal glucose reabsorption and increase urinary glucose and sodium excretion.[36] Thus, sodium-glucose cotransporter 2 inhibitors exert a diuretic effect, which has been suggested as a possible mechanism of the cardiorenal benefit observed in EMPA-REG OUTCOME and CANVAS.[36] Ongoing trials will further explore the efficacy of empaglifozin on cardiorenal outcomes in patients with and without diabetes mellitus and HFrEF or HFpEF (EMPEROR-Reduced [Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduction Ejection Fraction], NCT3057977; EMPEROR-Preserved [Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction], NCT03057951), and a trial in patients with CKD has been announced.

NEW CONCEPT IN CARDIORENAL SYNDROME

Overview

Careful reflection on these clinical descriptions of patients with cardiorenal syndrome reveals the commonality in the pathophysiological pathways that are present across the various subtypes. It may be time to move away from the current segmentation toward a model reflecting that the cardiovascular system and kidneys

are affected by the same risk factors (eg, dyslipidemia, atherosclerosis, hypertension, tobacco use, diabetes mellitus, obesity, amyloidosis, vasculitis, scleroderma) but to varying degrees and time frames. Patients with these diseases or risk factors fall along a cardiorenal syndrome continuum, and we propose consideration of a single cardiorenal syndrome umbrella. Cardiorenal syndrome could then encompass concomitant cardiovascular and renal disorders that result from systemic diseases and their related neurohormonal, inflammatory, immunologic, and fibrotic consequences. These common pathophysiological pathways have varying various of clinical expression in the heart (eg, diastolic dysfunction, HFpEF, HFrEF, left ventricular hypertrophy) and in the kidney (acute injury[37] or CKD) (Figure 1).

Rather than categorizing patients on the basis of subjective differences in clinical presentation, we propose that a better strategy for the future may be to differentiate patients according to the predominant pathophysiological mechanism, which may be identified with biomarker phenotyping. We acknowledge that research validation of such an approach is essential and has not yet been accomplished. Addressing the widespread clinical availability of biomarker technology is also a critical factor. As a working hypothesis, biomarker-based phenotypes may point physicians toward biotargets amenable to therapeutic intervention. For example, patients whose biomarker profile revealed a primary inflammatory/fibrotic pathway may benefit from optimization of anti-inflammatory/antifibrosis therapies (eg, MRAs).[38,39] Such an approach requires testing in randomized controlled outcome trials, but it is a concept worth investigating.

We acknowledge that some clinical entities would not be considered cardiorenal syndromes under our proposed paradigm. For example, not all abnormalities of kidney structure or function influence cardiovascular health. CKD is classified on the basis of cause, eGFR, albuminuria category, altered phenotypes, and kinetics, and it should not be construed as synonymous with cardiorenal syndrome in the absence of cardiovascular involvement, as assessed with in-depth phenotyping. In addition, multiorgan failure (eg, brain, lung, liver, gut, and bone marrow, simultaneously or in succession, potentially along with heart and kidney) triggered by exogenous insults (eg, acute drug toxicity or infection) occurring in otherwise healthy people is a different pathophysiological entity. These acute syndromes may involve a variety of mechanisms and are not limited to cardiorenal interactions. Including these patients under the cardiorenal syndrome umbrella is not necessarily helpful for applying or designing therapeutic strategies.

Fibrosis as a Unifying Pathophysiology of the Cardiorenal Syndrome Continuum

Disease-related injury in any organ triggers a complex cascade of cellular and molecular responses that culminate in tissue fibrosis. Although this fibrogenic response may have adaptive features in the short term, parenchymal scarring and ultimately cellular dysfunction and organ failure ensue when it progresses over a prolonged period of time.[40] Whether in the heart or in the kidney, fibrosis is the common consequence of inflammation- and oxidative stress–related endothelial dysfunction in aging, hypertension, diabetes mellitus, and obesity,[41] ultimately leading to cardiovascular disease, heart failure, and CKD (Figure 2).

Myocardial remodeling occurs after cardiac injury and involves the secretion of extracellular matrix pro-
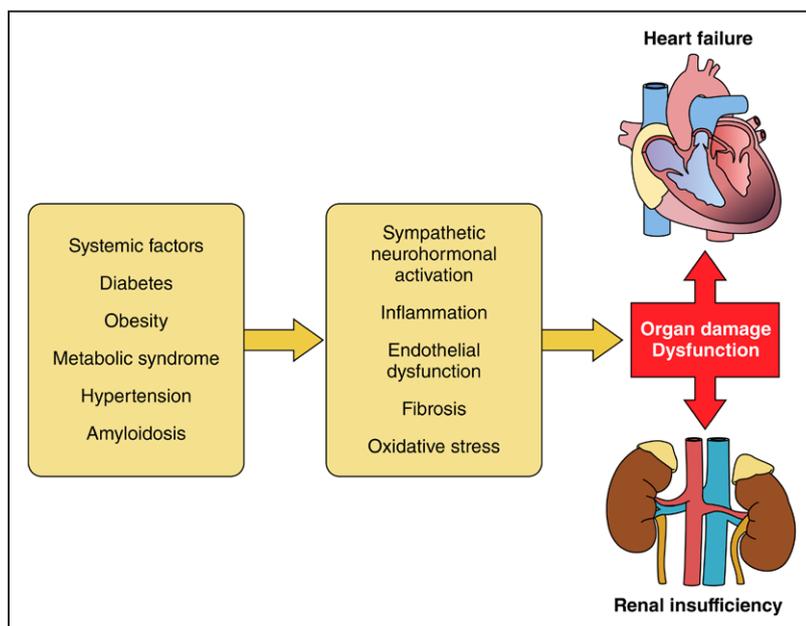
Figure 1. Conceptual framework for cardiorenal syndrome.
Cardiorenal syndrome represents concomitant cardiovascular and renal disorders that result from systemic diseases with common pathophysiological pathways. These distinct processes converge and over time promote organ damage and dysfunction in both the heart (eg, diastolic dysfunction, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, left ventricular hypertrophy) and kidney (acute injury, chronic kidney disease).
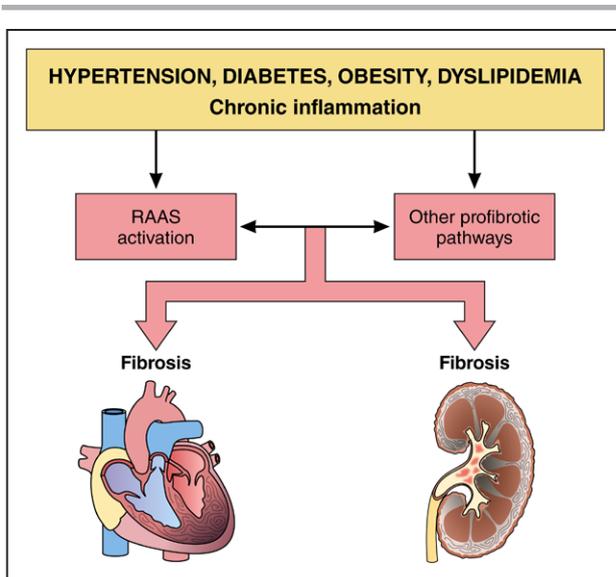
Figure 2. Signaling and cross-talk leading to kidney fibrosis.
RAAS indicates renin-angiotensin-aldosterone system.

teins by myofibroblasts to promote cardiac fibrosis and preserve myocardial structure and function, but this fibrotic state leads to chamber dilatation, cardiomyocyte hypertrophy, apoptosis, and heart failure.[41] At the kidney level, tubulointerstitial fibrosis and dysfunction may be generated by the differentiation of tubular epithelial cells to myofibroblasts toward an epithelial-mesenchymal transition phenotype, leading to the loss of polygonal shape and epithelial markers (eg, E-cadherin) and the acquisition of a fibroblastic phenotype with enhanced synthesis of extracellular matrix (eg, collagen I, III, fibronectin). Aldosterone may trigger a cascade of mechanisms that typically lead to fibrosis in the heart, vessels, and kidneys and may reciprocally evolve into a cardiorenal syndrome. Aldosterone-salt–treated rats present an MR-dependent epithelial-mesenchymal transition and increased interstitial, glomerular, and vascular fibrosis manifested by kidney hypertrophy, glomerular hypertrophy, hyperfiltration, albuminuria, and increased sodium and NGAL urine excretion.[38] In a rat model of acute kidney injury induced by bilateral renal ischemia/reperfusion, treatment with the MRA spironolactone prevented subsequent CKD by avoiding the activation of fibrotic (including the epithelial-mesenchymal cell transition) and inflammatory pathways.[42] These results were recently confirmed with the new nonsteroidal MRA finerenone.[43]

In a rat model of mild kidney function impairment induced by uninephrectomy, cardiac fibrosis with mild diastolic impairment was observed early (after 4 weeks) and accompanied by contralateral kidney hypertrophy and fibrosis, independently of significant increases in blood pressure or sodium and water retention. These changes were amplified after 16 weeks, with still no significant blood pressure changes or alterations in

sodium and water excretion. At this time point, compared with sham controls, an increase was observed in plasma B-type natriuretic peptide and aldosterone in uninephrectomized rats. Heart microarray studies showed changes in apoptosis and transforming growth factor-β (profibrotic) pathways (ie, compared with week 4, overexpression of transforming growth factor-β2 and connective tissue growth factor, both genes involved in increased collagen deposition and alteration of cardiac contraction).[44]

These experimental data provide an example of a typical cardiorenal syndrome model, but the extent to which they translate to humans requires further study. These animal data match the recent finding that, compared with healthy controls, living kidney donors develop a significant decrease in the measured GFR after 12 months, accompanied by a significant increase in the left ventricular mass as assessed by magnetic resonance imaging, without changes in ambulatory blood pressure. Change in GFR was independently associated with change in left ventricular mass. Compared with control subjects, healthy donors had significant increases in fibroblast growth factor-23 and high-sensitivity C-reactive protein, although the clinical significance of these findings is uncertain given that living kidney donors generally have good long-term outcomes. Of note, although observational studies of kidney donors have been reassuring with adverse event rates lower than those of the general population,[45,46] studies using highly selected healthy control groups suggest that there may be a small increase in the risk of cardiovascular events and in the risk of developing end-stage CKD, particularly in nonwhite ethnic groups.[47–49] Detectable highly sensitive cardiac troponin T and microalbuminuria became significantly more common in donors than in controls.[49] In 100 renal transplant recipients, the regression of left ventricular hypertrophy was associated with better composite outcomes (ie, death and any cardiovascular and any renal event).[50] Furthermore, the cross-sectional clinical observation in 2548 subjects from a general population (the Dallas Heart Study) showed that an elevated serum cystatin C, reflecting reduced renal function, was associated with blood pressure–independent increased left ventricular mass[51] as assessed by cardiac magnetic resonance imaging. At the experimental level, a 5/6 nephrectomy of rats after an MI was followed by increased interstitial cardiac fibrosis and collagen type I expression in the noninfarct zone of the myocardium and increased tubulointerstitial necrosis.[52]

Lipocalin 2, also known in humans as NGAL, was previously identified as a novel MR target in the cardiovascular system.[53] In a recent study from our group, we demonstrated that NGAL plays a key role in blood pressure and cardiovascular extracellular matrix remodeling after MR activation. Genetic NGAL inactivation in mice blunted hypertension and vascular fibrosis induced by

aldosterone-salt challenge.[53] Furthermore, we recently demonstrated the beneficial effects of NGAL deletion in mice subjected to left artery coronary ligation by limiting cardiac fibrosis, inflammation, and left ventricular dysfunction associated with MI. We also demonstrated the detrimental effect of increased cardiac NGAL levels within days of MI and showed a correlation between circulating NGAL levels and reduced recovery of systolic function in patients during the first 6 months after an MI.[54]

Other conditions related to cardiac and renal disease are also associated with fibrosis. Obesity is considered as heart failure stage A, and it is frequently associated with hypertension, diabetes mellitus, and CKD. Obesity is also associated with increased aldosterone concentrations in humans.[55] Abdominal obesity is associated with adverse cardiac and vascular remodeling,[56] and it may directly impair kidney function through hyperfiltration, increased glomerular capillary wall tension, and podocyte stress.[57] In a cohort of normotensive, asymptomatic obese subjects and age- and sex-matched healthy volunteers, abdominal obesity was associated with early cardiac structural remodeling, increased aldosterone concentrations, and serum collagen type I aminoterminal peptide, a biomarker of collagen synthesis.[56] Higher blood pressure, procollagen-III-N-terminal peptide, a biomarker of collagen synthesis, and abdominal obesity were independently associated with early cardiac structural and functional (ie, diastolic dysfunction) changes.[53,56] We also reported that MR expression is increased in visceral adipose tissue in a preclinical mouse model of metabolic syndrome and in obese patients.[58] We recently showed that obesity upregulated galectin-3 (Gal-3) production in the cardiovascular system in a normotensive rat model of diet-induced obesity, whereas Gal-3 inhibition with modified citrus pectin reduced cardiovascular and renal levels of Gal-3, fibrosis, and inflammation in obese animals without inducing changes in body weight or blood pressure.[59] A key mechanism that drives the development and progression of kidney disease in obesity is endothelial dysfunction and associated tubulointerstitial fibrosis,[60] which likely occur concomitantly with the development of aortic and myocardial fibrosis, although their joint occurrence has not been thoroughly studied.

The different mechanistic pathways leading to myocardial interstitial fibrosis are being investigated in a large European Union consortium.[61] In addition, the RECONNECT consortium (Renal Connection to Microvascular Disease and Heart Failure With Preserved Ejection Fraction) aims to study the common mechanisms underlying renal dysfunction, coronary microvascular dysfunction, and HFpEF, with specific exploration of systemic fibrosis and endothelial dysfunction.[31]

Several extracellular and intracellular targets such as Gal-3,[38,39] NGAL,[53] ST-2,[62] and cardiotrophin-1[63] are involved in interstitial fibrosis in the heart, artery, and kidney. In addition, the MR pathway plays a key role in pathophysiology along the cardiorenal syndrome continuum. Through several mechanisms (eg, inflammation, rise in serum potassium,[64] directly induced proarrhythmic effects[65]), the MR pathway induces fibrosis in the heart, arteries, and kidneys.

Implications of Pathophysiology for Future Treatment Strategies

We hypothesize that mitigating fibrosis-related targets[66] (eg, fibroblast differentiation to myofibroblasts, collagen synthesis over degradation, or collagen maturation) may be an effective new strategy for the prevention and treatment of fibrosis in the myocardium, heart valves,[67] large arteries, and kidney. This may be accomplished with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, MRAs, or other antifibrotic agents such as novel small molecules to interrupt the fibrogenic axis, with MRAs specifically able to block the actions of aldosterone. Exercising, losing weight, reducing inflammation and oxidative stress, targeting MR signaling, and inhibiting the sodium channel could also improve tubulointerstitial fibrosis and mitigate the progression of kidney disease in individuals with obesity and diabetes. Future studies should evaluate the effectiveness of these interventions to prevent the progression of fibrosis and its pathophysiological consequences.

Galectin-3, NGAL, ST-2, and cardiotrophin-1 are mediators of aldosterone-induced fibrosis in animal models. One hypothesis is that these may be potential biomarkers in humans[68] to enable a precision medicine approach. Potentially used as companion diagnostic tools, these biomarkers may identify patients with activated profibrotic pathways. If confirmed in prospective randomized trials, such patients could be targeted for treatment with an MRA or other specific inhibitors of fibrosis. These agents could be avoided in patients without a profibrotic profile because the potential for benefit is likely to be less and exposure to the risk of side effects is unnecessary in the setting of uncertain benefit. Off-target adverse effects of new antifibrotic compounds need to be thoroughly ruled out by preclinical and early clinical development to avoid a negative clinical benefit-risk ratio such as observed with bardoxolone[69] (which induced hypertension) or the endothelin antagonist avosentan (which induced fluid retention and heart failure).[70]

Two proof-of-concept trials are ongoing that will test this approach in the cardiorenal syndrome, both funded by the EU FP7 programs. The HOMAGE program (Bioprofiling Response to MRAs for the Prevention of Heart Failure Within the Heart Omics in Aging; ClinicalTrials. gov identifier NCT02556450) is investigating whether

spironolactone treatment (versus usual care) favorably alters extracellular matrix remodeling (assessed by changes in procollagen-III-N-terminal) after 9 months of treatment in patients at increased risk of developing heart failure. The study will evaluate whether the treatment effect is greater in patients with increased plasma concentrations of Gal-3. Worsening renal function is a secondary end point. This trial may provide the foundation for a biomarker-guided heart failure prevention outcome trial. The PRIORITY trial[30] (Proteomic Prediction and Renin Angiotensin Aldosterone System Inhibition Prevention of Early Diabetic Nephropathy in Type 2 Diabetic Patients With Normoalbuminuria; ClinicalTrials.gov identifier NCT02040441) is a prospective multicenter study of the urinary proteome test for identifying patients at high risk of incident microalbuminuria. In the second phase of research, patients identified as high risk by the urinary proteome test are randomized to double-blind treatment with spironolactone or placebo on top of standard care to determine whether progression to microalbuminuria is reduced. More generally, clustering cardiorenal patients on the basis of fibrosis mechanistic bioprofiles is appealing. The FIBROTARGETS biomarker program aims to explore fibrotic pathways allowing the bioprofiling of patients into specific "fibrotic" bioprofiles and identifying novel therapeutic targets that will potentially allow the development of novel cardiorenal therapies tailored to patients' fibrotic mechanistic bioprofiles.[32] Obviously, further improving the specificity of blood fibrotic biomarkers is necessary because other processes beyond cardiorenal interactions may be reflected by these markers. For example, the interplay between kidney and bones on collagen metabolism may be a confounder.[71]

OPTIMIZING THE MANAGEMENT OF PATIENTS WITH CARDIORENAL SYNDROME: CAN WE MIND BOTH THE HEART AND THE KIDNEY?

Renal impairment that occurs in the setting of cardiorenal syndrome can create challenging scenarios for the clinical management of patients because the pharmacodynamics and pharmacokinetics of many drugs (not limited to cardiovascular drugs) are altered in the face of changing renal function. It is outside the scope of this article to review all possible affected agents, but nephrologists and cardiologists must be aware of the potential impacts and adjust dosing regimens or avoid nephrotoxic agents (eg, intravenous contrast, aminoglycosides) as clinically indicated.

RAAS inhibitors are useful across the many aspects of cardiorenal syndrome, including patients with hypertension, heart failure, and CKD with albuminuria or proteinuria. Their use is highly recommended by evidence-based cardiology[15] and nephrology guidelines.[72] Physicians who are reluctant to optimize RAAS inhibitor therapy in patients with cardiorenal syndrome are concerned primarily about safety, although the perception of risk is often out of proportion to actual risks. In patients with HFrEF, observational studies have repeatedly shown that RAAS inhibitors are underused, suboptimally dosed,[73] and inadequately monitored.[74] These practices are associated with worse outcomes.[75] Fears of inducing hyperkalemia or worsening renal function are the primary reasons cited for underuse or underdosing.[76] New potassium binders may enable RAAS inhibitor optimization, as shown with patiromer (OPAL-HK [A Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia][77] and PEARL-HF [Plasma Extracellular RNAs and Biomarkers of Heart Failure During Decongestion][78]), but whether this strategy translates into improved outcomes needs be tested prospectively.[79]

Guidelines recommend close monitoring of serum potassium and renal function during periods of RAAS inhibitor titration. Monitoring should continue until the patient is stable and at regular intervals thereafter. This dynamic management of RAAS inhibitor dosing was implemented in landmark MRA randomized trials such as RALES (Randomized Aldactone Evaluation Study),[80] EPHESUS (Eplerenone Post- Acute Myocardial Infarction Heart Failure Efficacy and Survival Study),[81] and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure).[82] Although hyperkalemia and worsening renal function were reported in these trials that demonstrated reductions in total mortality with MRA therapy, no deaths were attributed to these conditions.[83] It is unclear why some physicians inadequately monitor potassium and kidney function after discharge, but the reason might be related to the lack of validated therapeutic algorithms for managing RAAS inhibitor and diuretic therapies. Patients also may be reluctant to comply with repeated physician and laboratory visits and multiple venipunctures. The hesitation on the part of both physicians and patients to use RAAS inhibitors, especially MRAs, is especially important to overcome, and new strategies are needed to combat the misperceptions contributing to the underuse of this life-prolonging therapy.

OPTIMIZING KNOWLEDGE WITH DEDICATED CARDIORENAL SYNDROME TRIALS: CALL FOR ACTION

It has been well documented that patients with kidney disease are frequently excluded from cardiovascular clinical trials (Figure 3).[84a,84b,85] Undeniably, conducting randomized clinical outcome trials in patients with cardiorenal syndromes has unique challenges. Decisions about patient selection (ie, inclusion of early versus late-stage
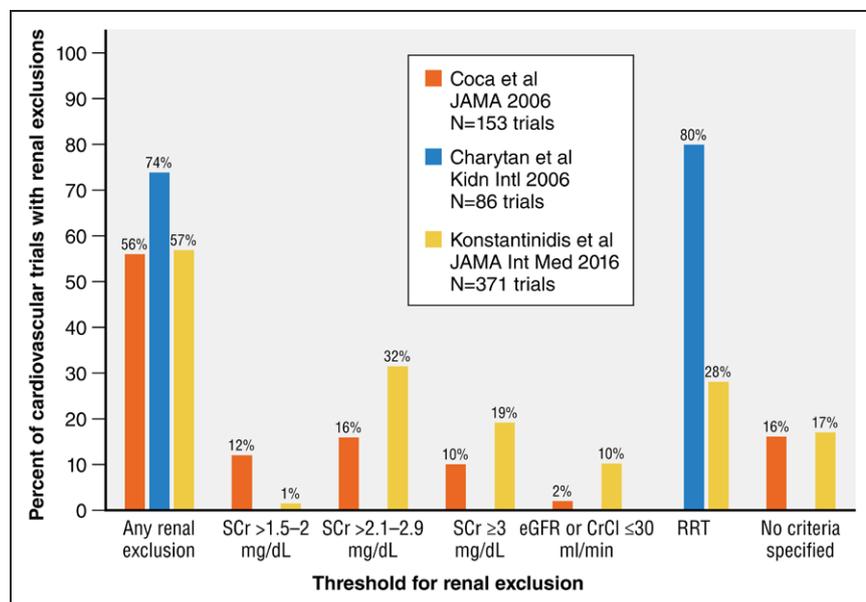
Figure 3. Summary of data from published systematic reviews reporting the percent of cardiovascular trials that excluded patients with kidney impairment and the thresholds applied for the exclusion.
CrCl indicates creatinine clearance; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; and SCr, serum creatinine. Reprinted from Zannad and Rossignol[84] with permission of the publisher. Copyright ©2017, American Heart Association.

kidney disease, identification of patients with pathophysiology likely to respond to treatment under study) or the choice of study end points and how to define them (ie, differentiating worsening heart failure from worsening renal function, interpreting biomarkers affected by impaired kidney function [natriuretic peptides, high-sensitivity cardiac troponin], statistical handling of competing risks) are critical decisions that, if incorrect, can prevent a trial from answering its intended question. A limited body of evidence is available to researchers on which to base assumptions used in clinical trial design, but we have previously suggested research priorities to help address these knowledge gaps (Figure 4) and harmonize the approach to clinical investigation across disciplines.[86]

It is encouraging that specific cardiorenal trials evaluating cardiovascular and renal outcomes are now underway.[87]

Specific training in cardiorenal medicine and the emergence of a new generation of cardiorenal specialists may be justified given the complexity of interactions between the renal and cardiovascular systems. This may apply to both the basic research level and the usual care setting. Closer collaboration between nephrologists and cardiologists has been encouraged as a mechanism to advance clinical research efforts in cardiorenal syndrome.[84,86,88] Such a collaboration may, for instance, lead to better persistence in the long-term use of lifesaving drugs (ie, RAAS inhibitors), with improved management of recurrent worsening renal function or hyperkalemia
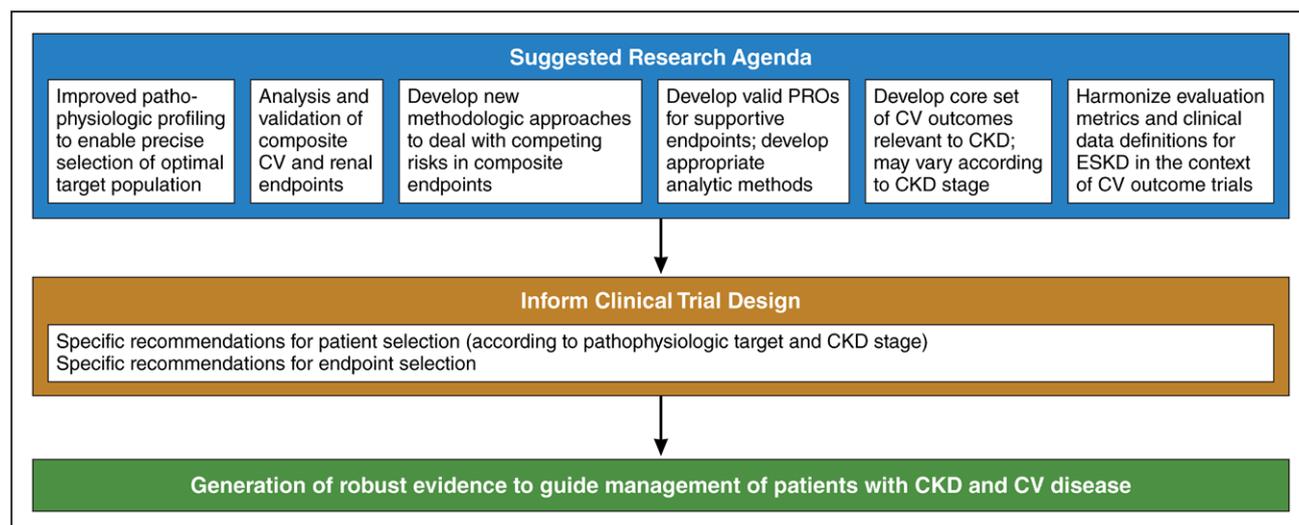
Figure 4. Research agenda.
Completing the priorities outlined in the Cardiovascular and Renal Clinical Trialists (CRCT) research agenda will inform clinical trial design for future clinical trials and will enable specific recommendations to be made on patient selection and end point selection, which will in turn enable robust evidence to be generated that will guide the management of patients with chronic kidney disease (CKD) and cardiovascular (CV) disease. ESKD indicates end-stage kidney disease; and PRO, patient-reported outcome. Reprinted from Rossignol et al[86] with permission of the publisher. Copyright ©2017, Oxford University Press.
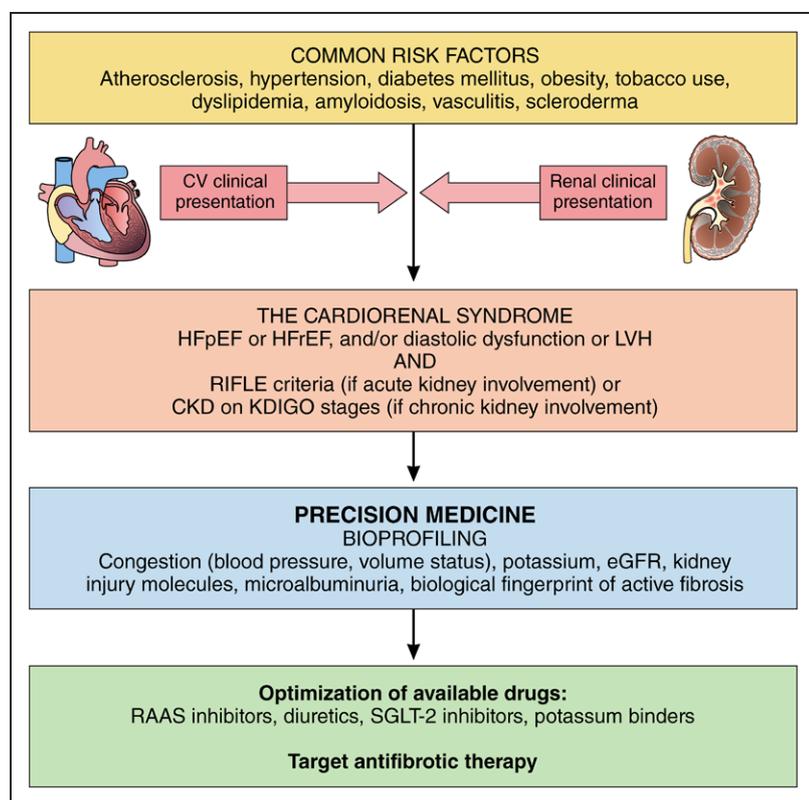
Figure 5. Cardiorenal syndrome.
This figure depicts a proposed new paradigm in which common risk factors lead to cardiorenal syndrome that may have either a cardiovascular (CV) or a renal clinical presentation. Bioprofiling with clinical and biomarker information will enable precision medicine, optimized to the specific profile. CKD indicates chronic kidney disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KDIGO, Kidney Disease Improving Global Outcomes; LVH, left ventricular hypertrophy; and RIFLE, Radial Versus Femoral Randomized Investigation.

episodes. Evolution of a new cardiorenal subspecialty may be an effective approach to promote scientific advances, to achieve coordinated care, to enhance quality of life, and to improve patient outcomes.[89]

CONCLUSIONS

The 2008 classification of cardiorenal syndromes has broadened interest in cardiorenal interactions, but it has produced little change so far, with no specifically derived therapeutic interventions shown to improve outcomes since the release of the classification. Although still a hypothesis, we propose a single cardiorenal syndrome with a new pragmatic and dynamic cardiorenal integrative concept (Figure 5) that combines documentation of fibrotic pathophysiology using companion diagnostic biomarkers with therapeutic management aimed at potential common fibrotic biotargets (eg, RAAS inhibitors, MRA, novel molecules) and patient-centered monitoring tools (eg, markers of congestion and kidney function, hypertension). A series of studies are ongoing to evaluate this strategy, which, if effective, can be applied across the continuum of patients exhibiting cardiorenal syndrome.

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Acknowledgments

Disclosures

Dr Zannad reports personal fees for Steering Committee membership from Janssen, Bayer, Pfizer, Novartis, Boston Scientific, Resmed, Takeda, General Electric, and Boehringer Ingelheim, as well as consultancy fees from Amgen, CVRx, Quantum Genomics, Relypsa, ZS Pharma, AstraZeneca, and GSK. Dr Zannad is the founder of Cardiovascular Clinical Trialists and CardioRenal. Dr Rossignol reports personal fees (consulting) from Novartis, Relypsa, AstraZeneca, Grünenthal, Stealth Peptides, Fresenius, Vifor Fresenius Medical Care Renal Pharma, Vifor, and CTMA, as well as lecture fees from Bayer and CVRx. Dr Rossignol is a cofounder of CardioRenal.

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