Kidney disease and heart failure: recent advances and current challenges: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Heart failure (HF) and chronic kidney disease (CKD) frequently coexist, which elevates the risks of hospitalization, disease progression, and death. Despite advances in treating each condition independently, many challenges remain in diagnosing and managing them in combination. In March 2024, Kidney Disease: Improving Global Outcomes (KDIGO) held the Controversies Conference on Kidney Disease and Heart Failure: Recent Advances and Current Challenges. Discussions highlighted the complex, bidirectional relationship between HF and CKD, including shared risk factors and overlapping pathophysiology as well as nuances in interpreting biomarkers such as natriuretic peptides and serum creatinine. Sodium-glucose cotransporter-2 inhibitors, renin-angiotensin-aldosterone system inhibitors, and emerging agents such as finerenone and glucagon-like peptide-1 receptor agonists can have benefits in both populations of patients with HF and CKD, though evidence in advanced CKD remains limited. Importantly, small declines in kidney function after initiating guideline-directed HF therapies generally do not require discontinuation, as these declines are often hemodynamic in nature and not associated with poor outcomes. The group highlighted the need for CKD-specific HF diagnostic thresholds and refined acute kidney injury definitions in HF. It is important for future cardiovascular and kidney trials to include relevant end points, such as kidney function trajectories, symptom burden, and quality of life. To improve care for individuals with HF and CKD, a more integrated approach to management, rooted in individualization, clinical context, and shared therapeutic goals, is needed.

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Heart failure (HF) and kidney disease share similar risk factors, present with overlapping symptoms, and commonly coexist.[1–3] Approximately 10%–30% of patients with chronic kidney disease (CKD) have HF, whereas approximately 30%–60% of patients with HF have CKD.[4–8] There is a graded association of the severity of CKD with the risk of HF,[9] and vice versa.[6] This population of patients with concurrent HF and kidney disease, which

continues to grow, is at elevated risks of loss of kidney function, frequent hospitalizations, and death.[9]

In recent years, there have been significant advances in understanding HF pathophysiology and refining approaches to earlier diagnosis and intervention.[10,11] Yet much remains unknown regarding the unique pathophysiology, diagnosis, and treatment of patients with *both* HF and kidney disease, leaving critical knowledge gaps.[12] In particular, prior pathophysiological classifications of concomitant HF and kidney disease focused on HF with reduced ejection fraction (HFrEF), largely ignoring the increasingly prevalent HF subtype with preserved ejection fraction (HFpEF).[13] Despite advancements in diagnostic testing, there are unique challenges in applying these tests to patients with kidney disease, including distinguishing fluid overload due to HF from that due to kidney disease.

Therapies are now available to improve both HF and kidney outcomes,[3,14,15] but there are particular considerations related to efficacy, safety, and implementation of these therapies in patients with both HF and kidney disease. Notably, therapies with proven kidney-protective effects in dedicated CKD trials have failed to consistently show benefits on traditional kidney outcomes in HF trials.[16–19] It is unclear why therapies proven to be kidney protective in CKD do not appear to have the same kidney effects in HF trials. Potential reasons include a lower risk of CKD progression in unselected HF trial populations (Figure 1), limitations of estimated glomerular filtration rate (eGFR) fluctuations as surrogate markers of kidney disease progression in HF, competing risks from death or worsening HF events, or insufficient duration of traditional HF clinical trials to affect changes in conventional clinical kidney end points.[20]

In March 2024, Kidney Disease: Improving Global Outcomes (KDIGO) held the Controversies Conference on Kidney Disease and Heart Failure: Recent Advances and Current Challenges to consider novel evidence and advances in the context of clinical care and to identify key knowledge gaps and priority research strategies (Table 1). Plenary presentations (which can be viewed at https://kdigo.org/conferences/controversies-conference-on-heart-failure-in-kidney-disease/) and breakout group discussions addressed pathophysiology, diagnosis, treatment, and clinical trial approaches, which are all summarized in this report.

PATHOPHYSIOLOGY OF HF AND KIDNEY DISEASE

Lower eGFR is a strong risk factor for adverse outcomes in both HFpEF and HFrEF, whereas albuminuria independently predicts incident HFpEF and worse outcomes in prevalent HF.[4,5,21–25] Clinical trial data suggest that eGFR declines approximately 1.5–2.3 ml/min per 1.73 m^2 in HF, whereas changes in albuminuria in both HFpEF and HFrEF are generally small.[26–30] Rates of eGFR decline are broadly similar between HFpEF and HFrEF,[31] though some studies report faster loss with HFpEF.[32]

The temporal relationship between HF and CKD is often unclear, with shared comorbidities—obesity, diabetes, and hypertension—promoting inflammation, endothelial dysfunction, neurohormonal activation, and hemodynamic stress in both organs (the "common soil" hypothesis) (Figure 2).[13] For most of these comorbid conditions, the associations are similar for HFrEF and HFpEF, although the association with obesity is more pronounced in HFpEF.

Hemodynamic perturbations in HF and kidney disease

In patients with HF, the relative roles of changes in arterial pressure, decreased cardiac index, and increased central venous pressures as drivers of glomerular filtration rate (GFR) decline are likely important, but remain incompletely understood.[33] Changes in blood pressure, likely one of the more important hemodynamic predictors of GFR decline, only explain a small percentage of the variance in changes in serum creatinine.[34] As patients with HFpEF are generally considered more preload dependent, blood pressure fluctuations may affect kidney function more profoundly. Higher central venous pressure is a strong risk factor for reductions in GFR on the basis of evidence in animal models[35] as well as some,[36] but not all,[34,37,38] clinical studies. Future human mechanistic studies are needed to determine whether elevations in central venous pressure are in fact causative or a marker of more severe HF. Furthermore, reductions in cardiac output/index may lead to reductions in renal blood flow, contributing to kidney hypoperfusion.[39]

Kidney tubular health in HF

Tubules regulate fluid, electrolytes, and endocrine functions and adapt in HF to hemodynamic and neurohormonal stress. Reduced blood pressure triggers efferent vasoconstriction, lower renal blood flow, higher filtration fraction, and increased proximal sodium reabsorption.[40] Sodium transporters are upregulated throughout the nephron, and proximal tubular function, assessed by tubular maximum phosphate absorption capacity/GFR, may be impaired in HF and linked to hospitalization and mortality.[41]

Data on tubular injury markers are conflicting regarding prediction of CKD progression, acute kidney injury (AKI), decongestion, HF outcomes, or mortality.[42–47] Their relationship to tubular function in HF is unclear, and large-scale studies of proximal tubular function, endocrine activity, and secretion are lacking. Developing validated measures of tubular health could improve understanding of kidney decline in HF.

DIAGNOSTIC DILEMMAS IN HF AND KIDNEY DISEASE

Diagnosis of kidney disease in patients with HF

Routine and repeated assessment of kidney function is important in patients with HF for prognosis and therapy selection and titration. In addition to eGFR (estimated by serum creatinine or cystatin C), measurement of urinary albumin-to-creatinine ratio (UACR) is important to identify kidney disease and screen for cardiovascular risk. In individuals with HF, elevated UACR is common[48–50] and

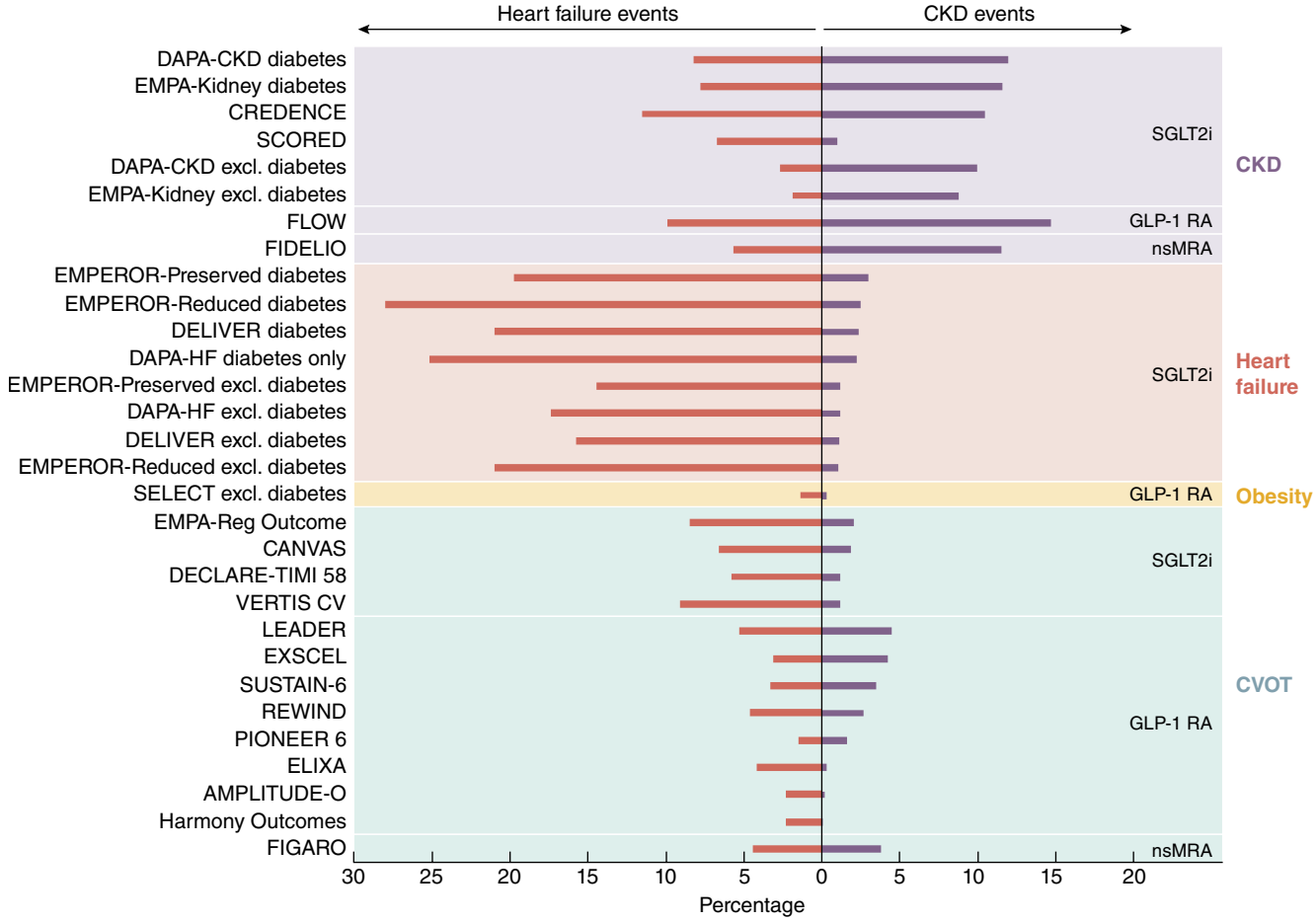

Figure 1 | Chronic kidney disease (CKD) progression or heart failure (HF) events among participants receiving placebo in large trials of sodium-glucose cotransporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and nonsteroidal mineralocorticoid receptor antagonists (nsMRA). Percentages represent the number of participants with an event/total number of participants in the placebo group for a selected set of trials. *For kidney disease progression,* outcomes are a composite of a reduction in estimated glomerular filtration rate (eGFR; 50% for SGLT2i,[16] mostly 50% for GLP-1 RA,[18] and 57% for nsMRA[17,19]), plus kidney failure (eGFR <15 ml/min per 1.73 m^2), plus kidney replacement therapy, plus kidney death. *For HF events,* in trials of SGLT2i, the outcome was a composite of cardiovascular death or hospitalization for heart failure[16]; in trials of GLP-1 RA[18] and nsMRA (FIGARO [Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease][17] and FIDELIO [Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease][19]), the outcome was hospitalization for HF. AMPLITUDE-O, Effect of Efpeglenatide on Cardiovascular Outcomes; CANVAS, CANagliflozin cardioVascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CVOT, cardiovascular outcomes trial; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; DELIVER, Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure; eGFR, estimated glomerular filtration rate; EMPA-KIDNEY, Study of Heart and Kidney Protection with Empagliflozin; EMPA-Reg, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EMPEROR, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide); EXSCEL, Exenatide Study of Cardiovascular Event Lowering Trial; FLOW, Evaluate Renal Function with Semaglutide Once Weekly; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial; PIONEER 6, A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SELECT, Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity; SCORED, Effect of Sotagliflozin on Cardiovascular and Renal Events in Participants With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; VERTIS CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

associated with HF markers such as B-type natriuretic peptide (BNP).[51] In this population, UACR is also a marker of HF risk, severity, and complications including hospitalizations, AKI, and mortality.[52–55] The level of UACR and the risk of hospitalization and rehospitalization have a similar predictive value as BNP.[51] Inclusion of UACR also improves risk prediction models for incident HF.

Despite its importance, combined UACR and eGFR testing in high-risk patients remains low. In a laboratory-based analysis in the United States, of more than 28

Table 1 | Key questions and research strategies for HF and CKD

HF and CKD	Key questions and knowledge gaps	Priority strategies for research
Pathophysiology	• Are there differences in risk factors and outcomes in the development of CKD or HF by age and biological sex? • Do reduced eGFR or albuminuria confer different risks in HF, depending on the cause of CKD? • In the development of HF and CKD, can certain patients have a single causal pathway for pathogenesis, or are there usually or always shared risk factors (the "common soil" hypothesis)? • What is the effect of systemic hemodynamics relative to other important risk factors? • How important are neurohormones, kidney capsular pressures, and lymphatics in contributing to abnormal kidney function, including GFR and tubular function? • Are there different mechanisms for declines in GFR in HFpEF versus HFrEF? • What clinical markers can be used to distinguish between reversible/hemodynamic versus intrinsic kidney injury? • Would more sophisticated modeling (such as machine learning) result in a better understanding of the pathophysiology of declines in kidney function in HF?	• Evaluate cardiac and HF phenotyping and assessment of risk factors in cohort studies across the spectrum of CKD. Conduct epidemiological studies incorporating sex-specific cut points and analysis stratified by biological sex. • Conduct additional pathological (biopsy) kidney studies in patients with HF and declines in GFR to gain further insight into underlying mechanisms. The available data are currently limited by selection bias. • Incorporate novel statistical methods that include dynamic changes into study design to help improve our understanding of the pathophysiology of kidney function decline in HF. • Evaluate the dominant drivers of declines in kidney function (e.g., decreased eGFR or albuminuria) in patients with HF through mechanistic large animal and human studies. Studies may incorporate hemodynamic data obtained through right heart catheterization, kidney plasma flow or filtration fraction, measurement of neurohormones, kidney capsular pressures, and lymphatic function. • Conduct studies on markers of tubular health to understand pathogenesis, assess prognosis, serve as surrogates for treatment response, inform treatment decisions, or provide novel targets for therapy. • Evaluate reversible versus injury-associated declines in kidney function in HF through mechanistic and epidemiological studies.

Diagnostic dilemmas	• How should clinicians attribute fluid overload symptoms or signs to HF versus CKD? Is fluid overload a single clinical syndrome?
	• In the acute HF setting, what kidney biomarkers can be used to:
	  ○ guide HF management and help prognosticate?
	  ○ distinguish between intrinsic and hemodynamic kidney injury?
	• How do we best measure kidney health in HF? Is there a need to assess tubular health in HF?
	• Are current biomarkers (e.g., NT-proBNP, troponin, and cystatin C) reliable in the presence of both HF and CKD?
	• What are the barriers to assessing kidney health in patients with HF?
	• What are the barriers to assessing HF risk and diagnosing HF in patients with CKD?
	• What is the most clinically applicable measure of intrinsic kidney function that is accessible to HF cardiologists (imaging markers and biomarkers)?
	• What is the most clinically applicable measure of cardiac function or HF risk that is accessible to nephrologists (imaging markers and biomarkers)?
		• Test use of HF diagnostic tools in a population with CKD and kidney failure.
		• Evaluate existing and new kidney biomarkers for their use in distinguishing between intrinsic and hemodynamic AKI as well as reliably guiding HF management.
		• Develop new diagnostic tools and symptom scores to distinguish HF from CKD-caused volume overload.
		• Develop guidance to ensure consistency and harmonization among measures of kidney health (eGFR, serum creatinine, UACR, and cystatin C).
		• Develop guidance on natriuretic peptide thresholds of risk in the presence of CKD.
		• Undertake efforts to increase public awareness and health care professional awareness of the importance of testing and following UACR.
		• Incorporate CKD and UACR into HF diagnostic recommendations.

Treatment	• What are the optimal dosing and safety profiles of standard HF therapies in CKD? What constitutes acceptable standard of care? • Can GDMT for HF be used consistently and safely across the spectrum of CKD? • Does rapidity of GDMT optimization matter in CKD in the same way as it does in HF? • What is the best way to operationalize a faster, better approach to GDMT optimization and individualize treatment approaches on the basis of inpatient versus outpatient setting, risk of adverse outcomes, or degree of kidney disease? • Should ARNI be included as GDMT for CKD independent of HF?	• Increase the representation of patients with CKD in HF trials and representation of patients with HF in CKD trials. • Conduct focused studies on the subset of patients with the most advanced kidney disease and heart disease where limited data exist, specifically kidney failure and HF stage D. • Conduct trials of GDMT for outpatients with HF and CKD and inpatients with HF and AKI. • Evaluate rapid GDMT initiation factors such as timing and order of starting drug, especially in individuals with eGFR < 30 ml/min per 1.73 m^2. • Evaluate targets for optimal GDMT in the presence of CKD, with careful attention to adverse effects.

(*Continued on following page*)

Table 1 | (Continued) **Key questions and research strategies for HF and CKD**

HF and CKD	Key questions and knowledge gaps	Priority strategies for research
	• What are therapeutic targets for novel agents in patients with HF and CKD? • Can disruptive strategies, such as polypills, improve administration, safety, and outcomes? • What is the optimal approach to successfully decongest patients with worsening HF and CKD? For example, which diuretic or combination of diuretics to use, in what order, and via which delivery approach (e.g., s.c.)? • What is the best method to evaluate or anticipate diuretic resistance, and does implementation of systematic risk-based scoring approaches help improve outcomes? • Does sodium administration help with diuresis in acutely congested patients with HF? • What are the optimal tools to assess fluid status and diuretic response in hospitalized inpatients, outpatients, or even home-based patients? • How should we use PACs (including in exercise-based monitoring): in whom, when, and for how long? • Does implantable cardiovascular monitoring influence kidney outcomes in patients with concomitant CKD? • Do noninvasive measures of hemodynamic status (such as intra-abdominal pressure measurement) improve outcomes, and are they cost-effective? • For dietary potassium and sodium, what is the association with serum concentrations, and does restriction of either improve outcomes in patients with HF and CKD? • What are the optimal approaches to exercise (aerobic, resistance training, physical therapy, and cardiac rehabilitation) to improve quality of life and outcomes and prevent frailty? • Can efforts of care coordinators or support persons improve implementation and sustainability of healthy dietary patterns and physical activity? • Can integrated care models improve care of patients with HF and CKD?	• Determine appropriate indications to discontinue therapy and how to guide rechallenging when therapy is paused or stopped. • Evaluate the safety of ARNI in individuals with HFrEF and CKD. • Test new therapies to treat HF and CKD, given the novel mechanisms that contribute to both diseases. • Evaluate whether implementation of diuretic protocols improves outcomes in patients with HF and CKD or AKI. • Test the use of diagnostic tools, including imaging, to guide implementation of therapies. • Test dietary and lifestyle interventions, such as sodium restriction and exercise. • Evaluate integrated care models to improve clinical outcomes.
Clinical trial design	• How should inclusion criteria be structured to increase representation of patients with HF and CKD, particularly advanced stages of disease? • How should trials be designed to be more inclusive of patients, considering the high burden of health care disparities in patients with CKD and HF? • How can trials be designed to enrich selection of patients who would benefit from the intervention as well as increase the efficiency of the trial? • How should end points be selected in this population with dual disease? • How can surrogate end points be applied to patients with CKD and HF? • What trial designs offer advantages in studying the same investigational treatment in both HF and CKD?	• Apply an interdisciplinary approach to clinical trial design. • Develop strategies for greater community participation in the design of clinical trials. • Develop low-burden, pragmatic clinical trials to address disparities in clinical trial participation. • Develop validated surrogate end points for HF and kidney disease trials. • Explore the importance of other important end points, including eGFR slope. • Develop and validate PROs to reflect patients with kidney disease and HF. • Develop core data sets for cardiovascular and kidney trials to aid efficiency and assist interpretation.

AKI, acute kidney injury; ARNI, angiotensin receptor–neprilysin inhibitor; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; GFR, glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; PAC, pulmonary arterial catheter; PRO, patient-reported outcome; s.c., subcutaneous; UACR, urinary albumin-to-creatinine ratio.
Sex refers to biological attributes.

million individuals at risk for CKD, 80% did not receive guideline-concordant assessment during a study period of 6 years.[56] In cases where testing was performed, 90% had eGFR evaluation, whereas only 20% had UACR evaluation. CKD assessment occurred at least once in 29% of patients with diabetes and 11% of those with hypertension. Clinical decision support tools and reimbursed prevention strategies may be needed to boost kidney disease screening.

In the setting of acute decompensated HF, interpreting elevations in serum creatinine to distinguish between intrinsic and hemodynamic kidney injury remains controversial. In some patients with acute decompensated HF, rises

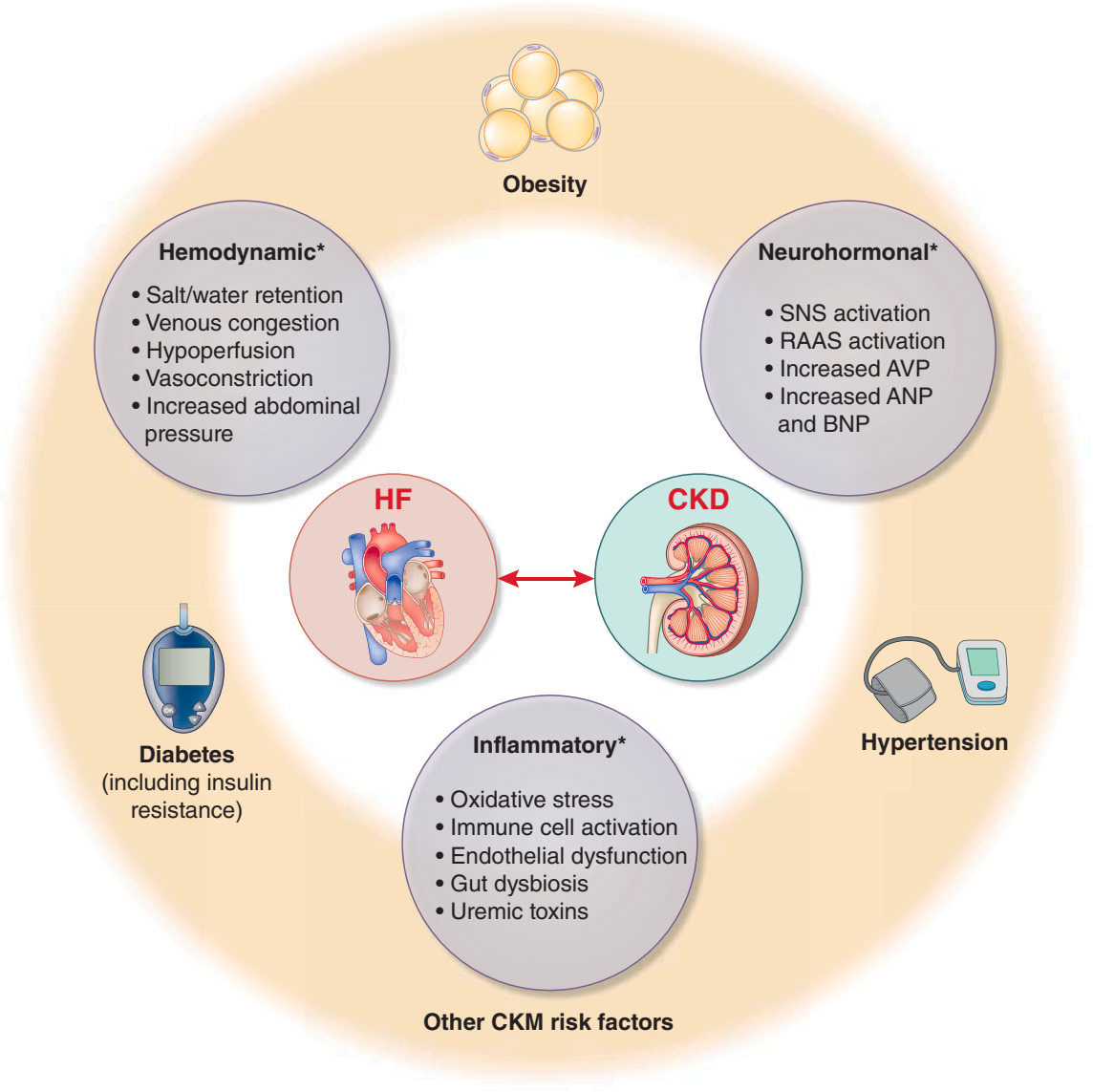

Figure 2 | Pathophysiology of heart failure (HF) and chronic kidney disease (CKD). Comorbid conditions such as obesity, diabetes, and hypertension have all been associated with incident CKD and HF. In the "common soil" hypothesis, shared comorbidities lead to inflammation, endothelial dysfunction, neurohormonal stimulation, and hemodynamic perturbations in both the kidneys and the heart. Some of these pathways may lead to end-organ fibrosis. ANP, atrial natriuretic peptide; AVP, arginine vasopressin; BNP, B-type natriuretic peptide; CKM, cardio-kidney-metabolic; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

in serum creatinine signal worsening kidney injury and worse outcomes; however, in others, increases in creatinine may reflect an appropriate hemodynamic shift with decongestion and may be associated with *better* outcomes.[57,58] In a *post hoc* analysis of the Diuretic Optimization Strategies Evaluation (DOSE) trial, which compared high- versus low-dose loop diuretics,[59] worsening of serum creatinine was *not* associated with adverse outcomes. In another trial, increases in serum creatinine were associated with improved survival.[60] These paradoxical findings may be due, in part, to the inherent limitations of serum creatinine as a biomarker in the setting of acute decompensated HF: its production is affected by muscle mass; it is intended to be interpreted in steady state; and it may manifest a delayed response to dynamic changes in kidney function. Therefore, the evidence for using serum creatinine to guide therapy in acute decompensated HF to improve clinical outcomes is modest at best, and studies have shown that both improvement and worsening of serum creatinine are associated with poor clinical outcomes.[37,61,62] Furthermore, other studies have suggested that urinary biomarkers of tubular injury may be discordant with dynamic changes in serum creatinine in acute HF.[46,63] The lack of reliable kidney markers that reflect congestion or decongestion may also contribute to persistent

congestion on hospital discharge, which is linked with the increased risk of rehospitalization and mortality.[64,65]

Assessment of AKI in acute decompensated HF remains an important area of future investigation. The limitations of creatinine rise for the definition of AKI are well established. More accurate and timely reflections of kidney function perturbations in HF and other conditions are needed, either through novel biomarkers or through other creatinine-based assessments, such as dynamic kidney function changes.

Diagnosis of HF in patients with kidney disease

By definition, HF is a clinical syndrome with current or prior symptoms or signs caused by a structural or functional cardiac abnormality.[66,67] HF is corroborated by elevated levels of natriuretic peptide or objective evidence of cardiogenic pulmonary or systemic congestion by diagnostic modalities such as imaging (e.g., chest radiography or elevated filling pressures by echocardiography) or by hemodynamic measurement (e.g., right heart catheterization or pulmonary artery catheter) at rest or with provocation (e.g., exercise).[66,67] Typical symptoms are often not specific for HF and can overlap with many other conditions, including kidney disease. Certain symptoms, such as paroxysmal nocturnal dyspnea and orthopnea accompanied by signs (jugular vein distention, S3 heart sound, and cardiomegaly), are more likely—though not reliably—attributable to HF.[66,67] In the setting of CKD, objective evidence of elevated filling pressures, either by elevated natriuretic peptide levels, by imaging, or by hemodynamic assessment with right heart catheterization, may be helpful for distinguishing HF from other etiologies.[66,67]

Role of natriuretic peptide levels. Natriuretic peptide level thresholds for diagnosis vary according to the indication for evaluation: lower cutoff points are used for population-based screening for HF risk or diagnosis in ambulatory symptomatic patients (e.g., BNP $\geq$ 35 pg/ml and N-terminal prohormone of B-type natriuretic peptide [NT-proBNP] $\geq$ 125 pg/ml), whereas higher cutoff points are used in the acute hospital or emergency department setting (e.g., BNP $\geq$ 100 pg/ml and NT-proBNP $\geq$ 300 pg/ml). In both HF and CKD, natriuretic peptide levels can be elevated, which informs diagnosis and prognosis and indicates disease trajectory. However, the interpretation of natriuretic peptides remains challenging in the context of CKD. Prognostically, elevation correlates with severity of CKD (due to decreased kidney clearance) and worse outcomes for HF and CKD. Conversely, natriuretic peptide levels are lower in individuals with obesity and are commonly lower in patients with HFpEF, possibly reflecting a natriuretic peptide deficiency.[68] In patients with CKD, higher BNP values can rule in the diagnosis of HF, whereas normal natriuretic peptide levels can be helpful in excluding HF. Decline in natriuretic peptide levels or other signs of successful decongestion (i.e., resolution of symptoms) after the initiation of guideline-directed medical therapy (GDMT) are associated with better outcomes, even in the presence of a rise in serum creatinine.[69–71]

Despite epidemiological data supporting the association of higher BNP with poor outcomes in patients with kidney disease, the cutoffs that should be used in this population are unknown. It is unclear whether thresholds used in the general population can be applied.[72] In the absence of defined CKD-specific BNP thresholds, individual baseline levels of BNP may be obtained during an asymptomatic ambulatory state.[73] Rising or declining natriuretic peptide levels can indicate disease trajectory and help with prognosticating or evaluating response to therapy.

Role of imaging in the diagnosis of HF. In patients suspected to have HF symptoms, echocardiography and other cardiac imaging methods, such as cardiac magnetic resonance imaging, can indicate the presence of a cardiac abnormality, help support the diagnosis of HF, or help with the assessment of the etiology of HF. However, some findings, such as left ventricular hypertrophy, are common in patients with CKD and may not be a specific finding for HF in the setting of advanced CKD.

Echocardiography can be helpful in determining cardiac filling pressures (mitral inflow, E wave/e′ wave ratio, and inferior vena cava) and in attributing symptoms (edema and shortness of breath) to elevated filling pressures due to HF. It should, however, be kept in mind that in patients with advanced CKD or kidney failure requiring hemodialysis, filling pressures may be affected by severity of fluid retention due to kidney failure. Echocardiography can also help determine HF phenotype (HFrEF or HFpEF) as well as detect abnormalities in structure (e.g., valvular abnormality, chamber enlargement, and wall motion abnormality) or function (e.g., diastolic abnormality), which can help discern etiology. Other imaging modalities, such as cardiovascular magnetic resonance, are useful when specific etiologies such as cardiac amyloidosis, sarcoidosis, adult congenital heart disease, or myocarditis are suspected. In patients on hemodialysis, cardiac imaging should ideally be performed on nondialysis days.

Attributing fluid overload to HF or kidney disease. In ambulatory patients, attribution of fluid overload depends on the severity of CKD and HF and also the proximate (preceding) cause (e.g., New York Heart Association functional class IV HF with CKD G2 vs. CKD G4 with New York Heart Association functional class II HFpEF); however, it may be difficult to determine which organ dysfunction is causing fluid overload.

In patients with acutely decompensated HF presenting with congestion, hypoperfusion, suspected shock, and acute kidney failure, hemodynamic assessment with right heart catheterization can help confirm cardiogenic shock due to HF. Similarly, if a patient presents with AKI, hemodynamic assessment with right heart catheterization is helpful for determining volume status if these are difficult to discern by physical examination or noninvasive methods (e.g., echocardiography).

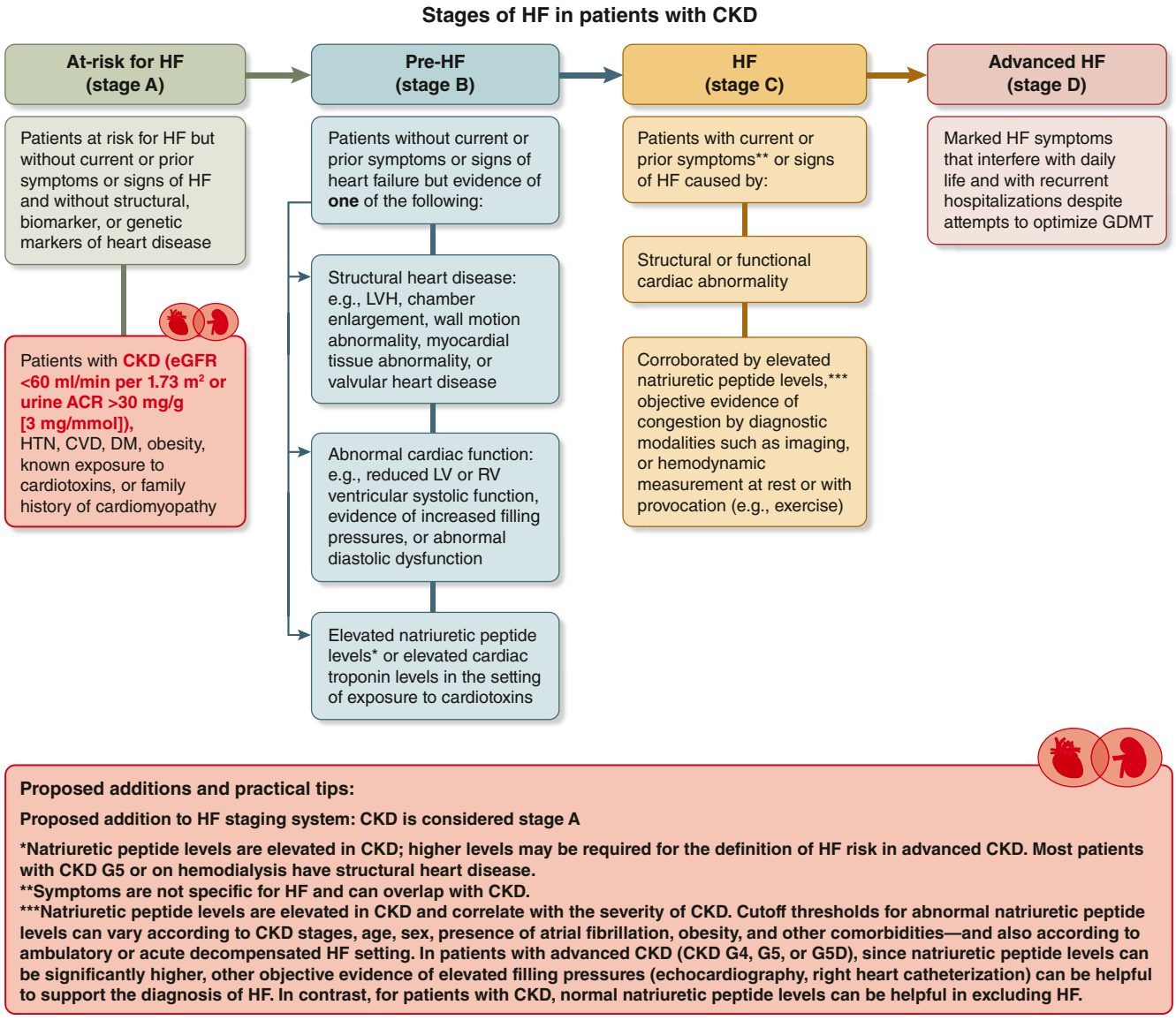

Figure 3 | Stages in the development and progression of heart failure (HF) with inclusion of chronic kidney disease (CKD). The Heart Failure Society of America, the Heart Failure Association of the European Society for Cardiology, and the Japanese Heart Failure Society have proposed a staging system to capture the range of HF severity, with stage A inclusive of patients at significant risk for HF.[66] Although CKD was not explicitly listed as a risk factor, conference participants propose including both reduced estimated glomerular filtration rate (eGFR) and elevated urinary albumin-to-creatinine ratio (ACR) in HF stage A because CKD is a significant risk factor with high relative risk and population-attributable risk for incident HF.[66,75] CKD G4/G5, CKD category G4 or G5; CKD G5D, CKD G5 receiving dialysis; CVD, cardiovascular disease; DM, diabetes mellitus; GDMT, guideline-directed medical therapy; HTN, hypertension; LV, left ventricular; LVH, left ventricular hypertrophy; RV, right ventricular. Modified from Bozkurt B, Coats AJ, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J Card Fail.* 2021;27:387–413.[66]

Staging and prediction of HF in patients with kidney disease

When investigating for HF, it is important to determine eGFR and UACR in addition to NT-proBNP. Cardiovascular risk should ideally be assessed using validated risk tools.[74] The Heart Failure Society of America, the Heart Failure Association of the European Society of Cardiology, and the Japanese Heart Failure Society have proposed a staging system for HF analogous to staging for other conditions such as cancer (Figure 3).[66,75] HF stage A (At risk for HF) reflects those patients at significant risk for HF who may develop preclinical structural cardiac changes (stage B: Pre-HF) before showing overt symptoms of HF (stage C) progressing to advanced HF (stage D). Although CKD is not explicitly listed as a risk factor, both reduced eGFR and

elevated UACR should be included in HF stage A (highlighted in red in Figure 3). Because CKD is a significant risk factor with high relative risk and population attributable risk for incident HF,[66,75] all patients with CKD should be considered in the HF staging system.

The new American Heart Association PREVENT (Predicting Risk of Cardiovascular Disease EVENTs) calculator estimates total CVD risk (including HF).[76] This model includes eGFR in the base model and UACR and hemoglobin A1c as add-on variables when available. The implementation of the American Heart Association PREVENT model may increase the assessment of kidney function in patients at risk for HF.

TREATMENT OF HF AND KIDNEY DISEASE

Given the interrelatedness of HF and CKD, treatment of each condition may have shared benefits, and therapeutic options may even overlap. However, there is also the potential for treatment of HF to worsen CKD and patient outcomes if kidney health is not prioritized and monitored closely in HF management, and vice versa. Moreover, evidence-based guidelines for the treatment of CKD versus HF may not completely align, even when referring to the same medications (e.g., different eGFR thresholds for treatment using renin-angiotensin-aldosterone system inhibitors) (Table 2).[77–80]

Pharmacological interventions

Figure 4 provides a conceptual framework for managing HFrEF or HFpEF and CKD according to eGFR.

HFrEF and CKD. Patients with both HFrEF and CKD have poor cardiovascular outcomes and survival. However, patients with advanced CKD (G4–G5) are often excluded from randomized controlled trials (RCTs), which has led to gaps in evidence for optimal management of HFrEF in this very high-risk subgroup. Current multinational guidelines recommend rapid initiation and titration to target doses of 4

Table 2 | Thresholds for initiating guideline-directed medical therapy in HF and kidney disease

Therapy	Eligibility based on kidney function		Management of adverse effects
	CKD guidance[a]	HF guidance[b]	
SGLT2i	eGFR > 20 ml/min per 1.73 m^2 in those with CKD and DM eGFR > 20 ml/min per 1.73 m^2 in those with CKD and UACR > 200 mg/g (20 mg/mmol) eGFR 20–45 ml/min per 1.73 m^2 in those with CKD and UACR <200 mg/g (20 mg/mmol)	eGFR > 20 ml/min per 1.73 m^2	Hyperkalemia with RAASi, steroidal and nsMRA, and ARNI may be mitigated by • Concomitant SGLT2i • Potassium binders • Correction of acidosis • Moderation of dietary potassium intake • Review and adjustment of concurrent medications • Diuretics
nsMRA (finerenone)	Type 2 diabetes, eGFR > 25 ml/min per 1.73 m^2, and UACR > 30 mg/g despite standard care	(As for the treatment of comorbid diabetic CKD)	eGFR "dip" with SGLT2i, RAASi, steroidal and nsMRA, and ARNI: • Hemodynamic fluctuations in eGFR up to 30% can be seen and should not lead to discontinuation • If >30%, other causes of AKI should be evaluated
GLP-1 RA	Type 2 diabetes, eGFR ≥ 25 ml/min per 1.73 m^2, and elevated UACR despite standard care Initiation for glycemia lowering down to 15 ml/min per 1.73 m^2	(As for the treatment of comorbid type 2 diabetes)	
ARNI	If eGFR <30 ml/min per 1.73 m^2, reduced dose should be started and titrated up	eGFR > 30 ml/min per 1.73 m^2	
ACEi or ARB	All persons with CKD, and moderate or severe albuminuria in persons with and without diabetes Should be continued in CKD even when eGFR declines to <30 ml/min per 1.73 m^2	Serum creatinine <221 μmol/l (<2.5 mg/dl) or eGFR > 30 ml/min per 1.73 m^2	
Steroidal MRA	May be used for the treatment of HF in CKD but have a higher risk of adverse effects (nsMRA preferred)	Serum creatinine <221 μmol/l (<2.5 mg/dl) or eGFR > 30 ml/min per 1.73 m^2	

ACEi, angiotensin-converting enzyme inhibitor(s); AKI, acute kidney injury; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; GLP-1 RA, glucagon-like peptide-1 receptor agonist(s); HF, heart failure; MRA, mineralocorticoid receptor antagonist; nsMRA, nonsteroidal mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor(s); SGLT2i, sodium-glucose cotransporter-2 inhibitor(s); UACR, urinary albumin-to-creatinine ratio.

[a]CKD-based guidance for SGLT2i, finerenone, ACEi, ARB, and steroidal MRA is from the KDIGO 2024 CKD guideline[77]; for GLP-1 receptor agonists, based on meeting participant opinion informed by clinical trial data; and for ARNI, from the 2024 American College of Cardiology consensus statement on treating HF with reduced ejection fraction.[80]

[b]HF-based guidance is from the European Society for Cardiology's 2021 HF guideline[78] and 2023 focused update.[79]

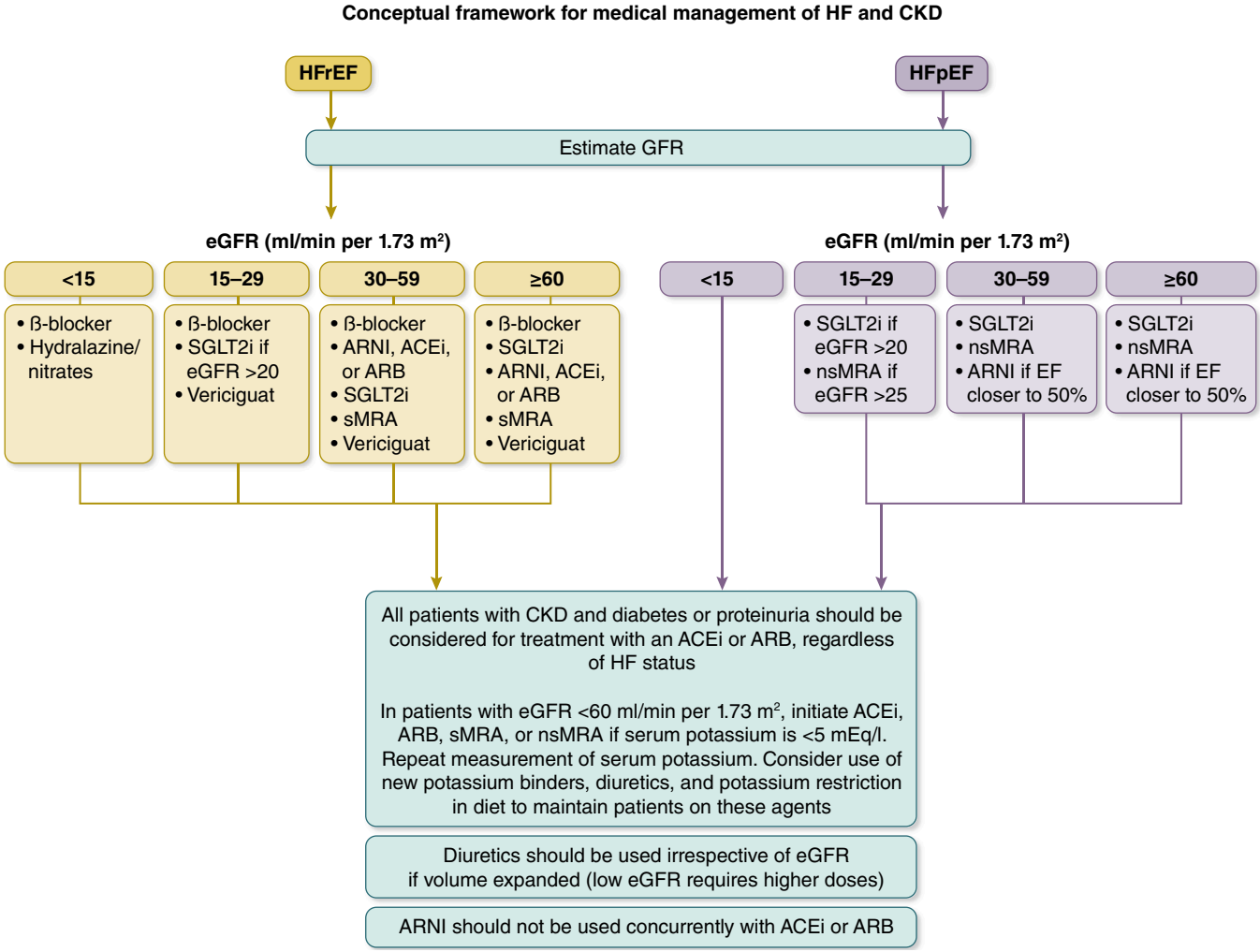

Figure 4 | Conceptual framework for the medical management of heart failure (HF) with reduced or preserved ejection fraction (HFrEF or HFpEF) and chronic kidney disease (CKD). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; nsMRA, nonsteroidal mineralocorticoid receptor antagonist; sMRA, steroidal mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

key medication classes for HFrEF[81]: angiotensin receptor–neprilysin inhibitors, sodium-glucose cotransporter-2 inhibitors (SGLT2i), mineralocorticoid receptor antagonists, and β-blockers.[82,83] However, many barriers exist for GDMT initiation and titration that uniquely affect individuals with CKD, such as elevated serum creatinine, hypotension, and hyperkalemia, which may worsen with initiation and titration of GDMT. Many therapies may be inappropriately discontinued when kidney function fluctuates. The current European Society of Cardiology HF guideline recommends continuing renin-angiotensin-aldosterone system agents unless there is a >50% increase in serum creatinine (and serum creatinine is < 3 mg/dl, eGFR is > 25 ml/min per 1.73 m^2, and there is no hyperkalemia).[78] Strategies to address some of the challenges for optimizing GDMT, such as the use of potassium binders, ensuring concomitant use of SGLT2i and loop diuretics to mitigate hyperkalemia, and slower dose titration of medications, may be helpful, but further research is needed to optimize implementation and prevent inappropriate discontinuation. Ultimately, an individualized approach is needed while prioritizing maximal GDMT in terms of timing (faster is better; https://www.gdmt.org/HFrEF.php) and dosing as high as tolerated (serum creatinine cutoffs in GDMT provided in Gilstrap and Vest[84]). However, in CKD G5D, the efficacy and safety of GDMT remain knowledge gaps.

HFpEF and CKD. Compared with patients with HFrEF, those with HFpEF are more likely to be older, be female, and have more cardiometabolic comorbidities. As a result, they are often more likely to have concomitant CKD, experience diuretic agent resistance, and exhibit decline in kidney function with enhanced diuresis. In 2023, the American College of Cardiology published the "Expert consensus decision pathway on management of heart failure with preserved ejection fraction,"[85] which highlighted SGLT2i therapy for HFpEF. Emerging data from the FINEARTS-HF

study (FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure) demonstrate benefit of finerenone in patients with HF and mildly reduced or preserved ejection fraction, with a lower rate of a composite outcome including total worsening HF events and death from cardiovascular causes than placebo.[86] Among the study population, the median (interquartile range) baseline eGFR was 61 (47–77) ml/min per 1.73 m^2, and 2785 people (48%) had eGFR levels $<$ 60 ml/min per 1.73 m^2. The median (interquartile range) baseline UACR was 18 (7–67) mg/g, and 2256 individuals (39%) had UACR levels $\geq$ 30 mg/g. These results are generalizable to populations with HFpEF and CKD.[87] As in patients with HFrEF, eGFR, serum potassium, and blood pressure need to be considered when prescribing these agents. Robust evidence also supports the use of glucagon-like peptide-1 receptor agonists in HF and CKD. In a recent trial of 529 patients with HFpEF and obesity, treatment with semaglutide (2.4 mg once weekly) led to larger reductions in symptoms and physical limitations, greater improvements in exercise function, and greater weight loss than with placebo.[88] Similar to HFrEF, GDMT for HFpEF has not been well studied in patients with advanced CKD, including those with kidney failure treated with dialysis or kidney transplantation.

Changes in kidney function with GDMT

One of the unique challenges in the comanagement of HF and CKD is that many of the shared therapies result in laboratory-based changes in serum creatinine that are *not* associated with adverse clinical outcomes. First and foremost, the etiology of the change in creatinine or eGFR upon initiation of therapy should be considered. Continuous declines in eGFR are generally more concerning than a single mild (10%–15%) decrease that remains stable in subsequent measurements. Declines can represent hemodynamic effects alone or direct kidney injury (transient vs. persistent) and should be contextualized with age-anticipated decline in GFR and with anticipated eGFR changes in specific disease states. There is increasing recognition that declines in eGFR do not always associate with adverse prognosis in patients with HF,[21,89–91] particularly in the context of HF therapies. For example, renin-angiotensin-aldosterone system inhibitors, angiotensin receptor–neprilysin inhibitors, mineralocorticoid receptor antagonists, and SGLT2i cause an acute "dip" in GFR,[91–93] but these declines are not associated with poor clinical outcomes. Urinalysis can be useful in detecting tubular injury if it is suspected. Treatments should target symptoms, volume status, and hemodynamics—not serum creatinine. However, controversy remains regarding how to interpret meaningful changes in kidney function in HF and whether markers other than creatinine, such as NT-proBNP, should also be considered in the setting of decongestion or hemodynamic therapy initiation. Furthermore, angiotensin receptor–neprilysin inhibitor therapy is associated with a slower rate of eGFR decline but may be associated with a modest increase in UACR compared with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers[71]; the clinical significance and long-term kidney effects of this increase remain unclear and require further study.

Guideline-specified definitions of AKI may not necessarily apply to patients with HF.[94] Patients with HF often have dynamic serum creatinine levels because of day-to-day changes in volume status, blood pressure, and initiation and titration of GDMT that are not representative of an adverse phenotype of AKI. A decline in kidney function can occur in the setting of decongestion and is not associated with worse outcomes in patients with HF.[95,96] Worsening kidney function alone is not an independent determinant of outcomes in patients with acute HF.[96] This suggests that the definition of AKI itself should differ for patients with HF who are initiating GDMT and should be refined on the basis of the clinical scenario.

Iron therapy

Iron deficiency is common in patients with both HF and CKD and is frequently associated with greater burden of symptoms and adverse cardiovascular outcomes. Although oral iron is likely not useful in either HF or CKD, i.v. iron may be particularly beneficial for symptom management with concomitant iron deficiency and HF.[97] Although early trials of i.v. iron repletion in patients with HF found improvements in symptoms and functional capacity, 4 large RCTs failed to confirm the benefit of i.v. iron with hard cardiovascular outcomes.[98,99] In a recent trial including ambulatory patients who had HFrEF and iron deficiency, there was no apparent difference between ferric carboxymaltose and placebo with respect to the hierarchical composite of death, hospitalizations for HF, or 6-minute walk distance.[100] Modeling data from 1 study in Europe and the United States indicated i.v. iron therapies may be cost effective[101]; however, side effects of and alternatives to i.v. iron repletion warrant careful consideration.

Nonpharmacological interventions

Historically, sodium restriction has been a cornerstone of HF management to control blood pressure and fluid overload. However, recent evidence has challenged this long-standing approach. Several randomized and observational studies have shown that strict sodium restriction (often below 1500–2500 mg daily) does not consistently reduce mortality or HF hospitalizations, with some studies even suggesting harm.[102–105] There remains controversy regarding whether dietary sodium restriction may still be appropriate for selected patients, not as a means to improve hard outcomes but potentially to enhance quality of life. Moving forward, well-designed, large-scale clinical trials are needed to clarify which patients may benefit from low-cost strategies, such as sodium restriction.

Regular physical activity is recommended in both HF and CKD. Exercise is beneficial and important in preventing and slowing the progression of disease. For HF, both the American College of Cardiology/American Heart Association/Heart Failure Society of America[82] and the European Society

of Cardiology[78] have class 1 guideline recommendations for exercise for all patients who are able. For CKD, the KDIGO 2024 CKD guideline recommends moderate-intensity exercise for patients with CKD (1D grade).[74] Social determinants of health and environmental context (e.g., neighborhood safety and heat exposure) can limit opportunities for physical activity. The specific components and styles of exercise (aerobic, resistance training, physical therapy, and cardiac rehabilitation) for improving quality of life and outcomes and preventing frailty are unknown. Yet, quality of life is a clinically meaningful end point and an important consideration for individualized therapy.

Treatment of volume overload

Diuretics. Volume overload is common in patients with HF and kidney disease, driving symptoms and hospitalization. The goals for decongestion are achieving euvolemia, improving quality of life, and reducing adverse events (rehospitalization and death).[106–108] Although loop and thiazide diuretics effectively relieve congestion, they confer no survival benefit; thus, their use should be minimized, with priority placed on initiating or titrating disease-modifying therapies (angiotensin receptor–neprilysin inhibitor and SGLT2i) that improve hemodynamics, volume status, and kidney health.

In the acute decompensated setting, time to euvolemia or length of hospital stay are also meaningful outcomes. Process-based approaches (urine output, urine sodium, and BNP) can be used for optimizing diuresis.[109] Figure 5 shows a conceptual framework modified from the European Society of Cardiology's algorithm for diuretic therapy in acute HF.[78] A spot urine sample 1–2 hours after loop diuretic administration has recently demonstrated an excellent

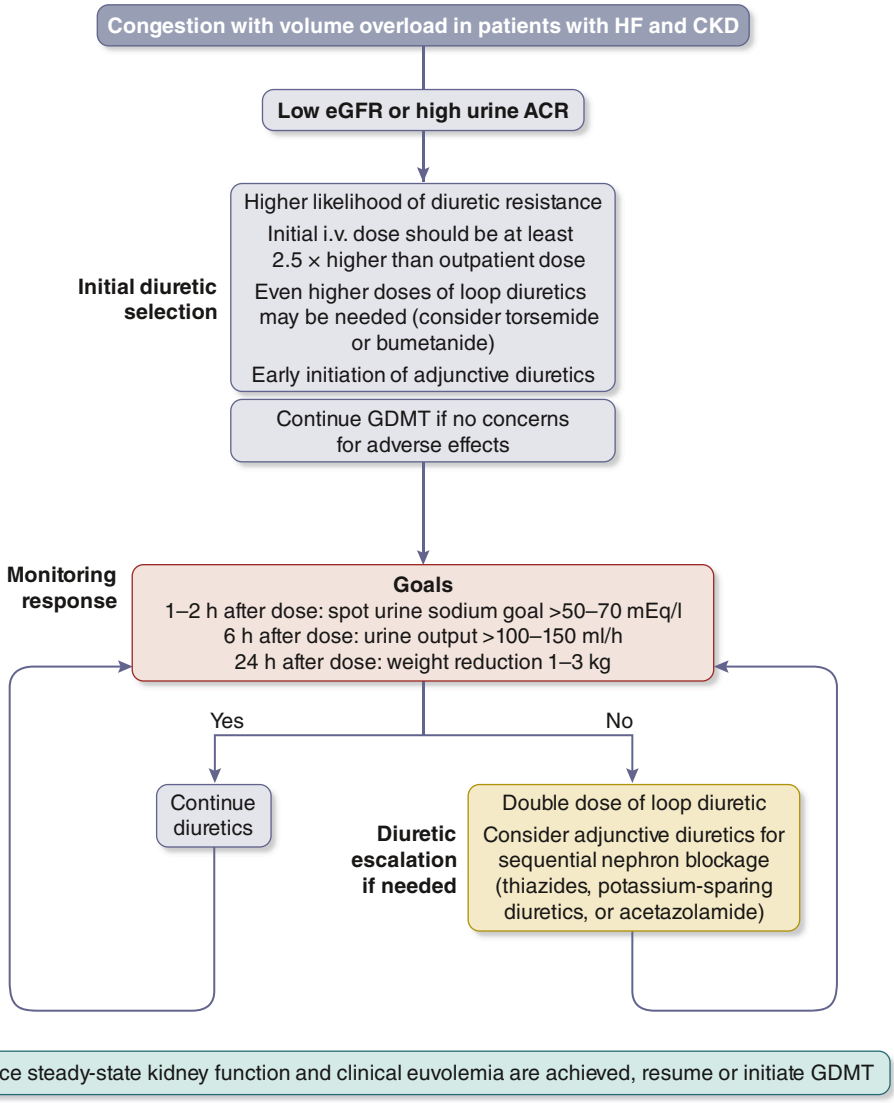

Figure 5 | Proposed framework for diuretic management in patients with reduced kidney function and acute heart failure (HF). ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy. Modified from McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599–3726.[78]

correlation with total urine sodium and urine output in a 6-hour urine collection,[110] and high spot urine sodium after the first diuretic administration identifies patients with HF likely to respond to an ambulatory diuretic infusion with lower rates of hospitalization or emergency department visits at 30 days.[111]

For hospitalized patients, diuretic strategies include sequential nephron blockade, combination therapy, and tailored delivery. In the CARRESS Study (Effectiveness of Ultrafiltration in Treating People With Acute Decompensated Heart Failure and Cardiorenal Syndrome), the addition of metolazone was an intrinsic part of the stepped pharmacological algorithm.[112] In the CLOROTIC trial (Combining Loop With Thiazide Diuretics for Decompensated Heart Failure), participants assigned to hydrochlorothiazide were more likely to lose weight at 72 hours than those assigned to placebo (−2.3 kg vs. −1.5 kg; $P = 0.002$), and those allocated to hydrochlorothiazide showed greater 24-hour diuresis.[113] Acetazolamide (500 mg once daily) or placebo added to standardized i.v. loop diuretics resulted in successful decongestion (primary end point, defined as the absence of signs of volume overload within 3 days) but did not reduce 3-month rates of death or HF rehospitalization.[106]

Ultrafiltration. Ultrafiltration and kidney replacement therapy are recommended in patients with advanced HF with refractory volume overload, defined as unresponsive to diuretic treatment. Evidence from the CARESS-HF trial (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) demonstrated no benefit, and a greater increase in serum creatinine, in early ultrafiltration versus maximum use of diuretics in patients with acute decompensated HF, persistent congestion, and worsening kidney function.[114] Different ultrafiltration treatment options in HF include isolated extracorporeal ultrafiltration (conventional devices vs. peripheral ultrafiltration [aquapheresis]) or peritoneal dialysis for chronic management of HF in diuretic–resistant patients. Peritoneal dialysis has several benefits over hemodialysis, including not requiring vascular access, a lower risk of bacteremia, and preservation of residual kidney function. Peritoneal dialysis offers more consistent volume control without rapid fluid shifts or changes in blood pressure. Peritoneal dialysis ultrafiltration has minimal impact on hemodynamics, results in sustained daily ultrafiltration, and is a home-based therapy, giving the patient independence and quality of life.

In addition to the ultrafiltration modalities, novel approaches and therapies are being developed to overcome diuretic resistance in HF. Some examples include increasing lymphatic flow into the venous system, inserting a catheter pump into the descending aorta, or using a transcatheter renal venous decongesting system.[115]

CLINICAL TRIALS IN HF AND KIDNEY DISEASE

There is growing interest in clinical trials testing interventions in persons with both CKD and HF, given the overlap in patient populations, bidirectional effects of each condition on the other in terms of clinical outcomes, and increasing availability of therapies. Traditionally, trials have focused on single diseases in isolation. Explicit categorization of trials as cardiac or kidney is typical and reflected in PICO (Population, Intervention, Comparison, Outcome) singular frameworks. Whether the purpose of a trial is to evaluate the primary or secondary prevention of HF or progressive CKD events, the recruited population is likely to be at elevated risk for both progressive CKD and cardiac events, so it is important to assess the impact of interventions on both types of events (Figure 6).

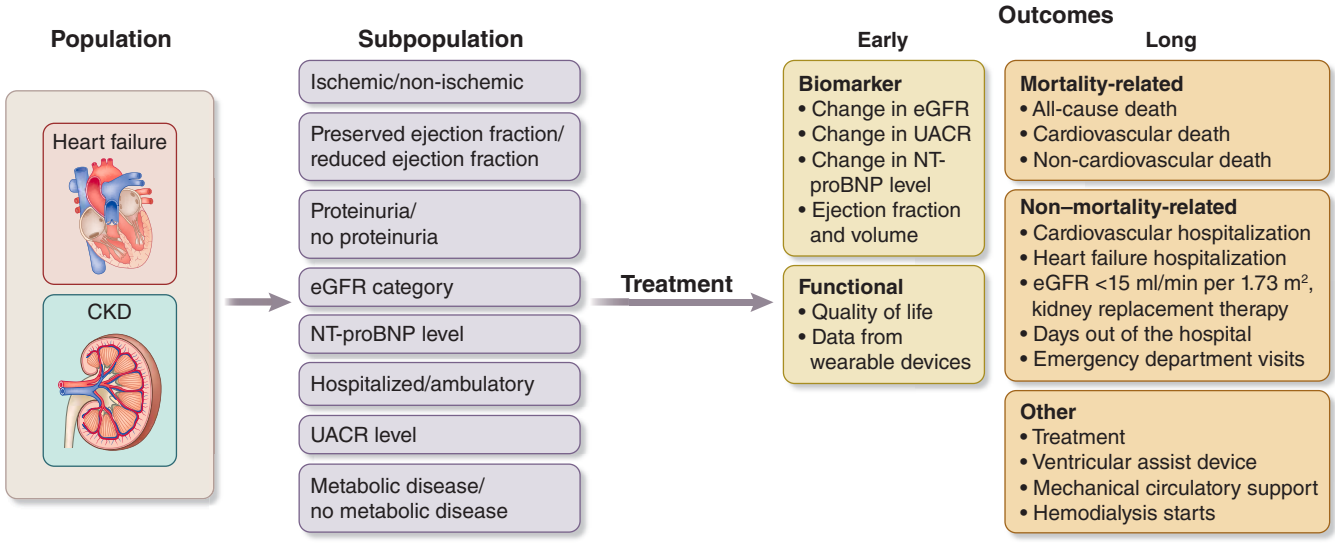

Figure 6 | Populations and outcomes to consider when designing trials of heart failure and chronic kidney disease (CKD). eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; UACR, urinary albumin-to-creatinine ratio.

Design considerations for HF and kidney disease trials

Trial inclusion: defining at-risk populations. Strategies to match risk or risk clusters include the use of biomarkers, clinical variables, and risk scores that integrate several additional factors.

Kidney biomarkers. Both eGFR and UACR should be measured for inclusion in trials. Definition of baseline kidney function (i.e., before hospitalization) can be challenging. If outpatient serum creatinine values are available, ideally 2 outpatient measures $>$ 90 days apart, but at least 7 days before the hospitalization, should be used. If outpatient measures are not readily available, strategies include the first available serum creatinine or the nadir serum creatinine during hospitalization. Prespecified subgroup analyses based on these definitions should be considered.

HF biomarkers. NT-proBNP can be helpful in defining higher risk for HF in people with relatively preserved kidney function, although thresholds would have to be carefully considered in those with CKD.[116]

Clinical variables. Enriching a population via clinical risk factors should be considered carefully, given the intersection of disease states as well as the potential for posttrial generalizability. For example, prior hospitalization due to HF or a comorbidity such as atrial fibrillation may be good risk predictors for both cardiovascular events and kidney events and may influence the efficacy of an intervention. Similarly, in kidney disease, UACR or diabetes may have the same impact. Trialists should think broadly when designing trials and consider both HF- and CKD-related factors.

Risk scores. There are several examples of risk scores to predict HF and CKD.[76] How these are applied to enrich a population and the performance (as well as the weaknesses) of a risk score should be considered carefully in the design of a clinical trial.

End points selection. Selection of kidney and HF end points can be challenging in the design of RCTs. Although increasing numbers of therapies are hypothesized to provide both cardiac and kidney benefits, the demonstration of both kidney and cardiovascular benefits in individual trials can be challenging because the timeline to the most clinically impactful events is longer for kidney disease than for HF events. The result could be that trials are terminated because of the demonstration of benefit for one type of event, preventing the demonstration of benefit for the other.

Composite outcomes that include elements of both cardiovascular and kidney events are a potential means for showing benefit over the 2 domains. Methods such as the win ratio can prioritize components by clinical importance, but ranking kidney versus cardiovascular events is challenging, especially because both (e.g., HF hospitalization vs. sustained eGFR decline) carry similar mortality risks. Other approaches, such as outcome weighting or competing risk analyses, also have limitations: weighting may be subjective, and rare kidney events remain difficult to capture effectively in trials of shorter duration.[117] Composite end points can also have the drawbacks of being considered nonspecific, inclusive of elements that may be less clinically relevant, or less efficient from a data science perspective. Surrogate end points are unlikely to lead to regulatory approval of new drug or device entities in patients with common diseases such as HF or CKD.

Kidney end points. The inherent compensatory capacity of the kidney means that the progression of CKD may be relatively slow to manifest clinically even while underlying pathophysiological processes continue. Recent kidney end point development has focused on meaningful surrogates that manifest earlier than traditional kidney end points. These considerations will be particularly important for minimizing time discrepancies between the accumulation of kidney events and the more rapid accumulation of HF events.[118–124] A traditional kidney composite end point includes a creatinine-based component such as a sustained doubling of serum creatinine (which equates to approximately 57% decline in eGFR) as well as *kidney failure* (defined as chronic receipt of dialysis, kidney transplant, or sustained eGFR $<$ 15 ml/min per 1.73 m^2, or death due to kidney disease). The earliest alternative kidney end points modified the eGFR requirement to a lesser threshold of 40% or 50% decline in eGFR but retained the composite format. A recent kidney end point development is the rate of decline in eGFR over a fixed time period, often referred to as GFR slope. Many kidney-protective agents, such as SGLT2i, manifest a biphasic eGFR response consisting of an initial reduction in eGFR followed by a stabilization of chronic eGFR loss. With kidney-protective agents, the initial eGFR drop is reversible on cessation and, in many cases, is presumed to be a glomerular hemodynamic effect associated with reduced intraglomerular pressure, resulting in lower hydrostatic forces across the filtration membrane. eGFR slope is thus often categorized as a total slope (from baseline to a specified time point) that includes the initial acute phase, followed by the chronic phase. These end points are designed to run over a fixed time period of generally 2–3 years, which shortens trial duration compared with traditional end points. Disadvantages include the influence of the acute eGFR drop on the outcome. Changes in UACR are also used as a traditional *surrogate* end point that has stood the test of time for albuminuria-associated glomerular conditions. Hierarchical composite end points are a form of rank outcomes that combine multiple outcomes, such as all-cause mortality, kidney failure, and various thresholds of eGFR decline, and are discussed further below. Unlike traditional composites, where participants are censored when they reach the first and usually least clinically meaningful event, the hierarchical ordering of the hierarchical composite end point weighs the most serious end points first.

Important caveats to consider when examining changes in kidney function over time may be particularly relevant to persons with HF. Kidney function is derived from changes in serum creatinine on the assumption that creatinine production is stable, and any changes are attributable to kidney function. However, this assumption may not hold with interventions that systematically lead to major changes in lean

body mass, such as regimens with higher doses of glucagon-like peptide-1 receptor agonists. Cystatin C–derived kidney function equations are useful and affected by weight loss to a lesser degree.[125] Accordingly, trials that include therapies that induce significant weight loss should consider inclusion of cystatin C–based eGFR estimates, because direct measured GFR levels pose logistic challenges in large-scale trials. Finally, as many therapies may cause acute hemodynamic changes in eGFR, chronic slope outcomes that exclude the initial treatment period may have appeal, although they do contravene the fundamental intention-to-treat principle of postrandomization follow-up.

HF end points. In phase 3 trials of chronic HF, the most frequently used end point is a composite of cardiovascular death or HF-related events (i.e., HF hospitalizations or urgent visits), including either the first HF event or first and recurrent (i.e., total) HF events. Historically, kidney outcomes in HF trials have mainly been detected from safety reports using inconsistent definitions and outdated measures. To date, no chronic HF trials to our knowledge have used a primary composite end point that integrates both cardiovascular and kidney outcomes.

Several challenges complicate the evaluation of kidney effects in HF trials today, including the early eGFR drop with some HF treatments that may not reflect long-term kidney effects, the slow rate of CKD progression in recruited populations with HF not enriched for albuminuria, the short follow-up period of typical HF trials (1.5–2.5 years, too brief to capture kidney outcomes that evolve slowly), and the frequent competing events of death and worsening HF that occur far more often than kidney outcomes in these trials.[20]

Nontraditional end points for kidney or HF events. Nontraditional end points should also be considered, and examples include the win ratio (and its varied methods of analysis),[107] win odds, z score,[126] weighted composite, recurrent events,[127] Finkelstein-Schoen methods,[128] organ-support–free days alive and out of hospital,[129] and days alive and out of hospital and quality of life adjusted.[130] Updated or refined analytical techniques should correspond to the needs of the specific RCT. With each technique, there are pros and cons, and choosing an end point involves balancing relevant perspectives from regulatory agencies as well as patient, clinical practice, and trial communities.

Patient-reported outcome measures

Patient-reported outcome measures (PROMs) are outcomes in and of themselves, and validated PROMs should be used in most, if not all, RCTs. Relevant competing events need to be accounted for when considering the timing and capture of PROMs. Full data collection and ascertainment are important, as there are some concerns that PROMs have more missing data than clinical outcomes, although this is largely overcome by thoughtful trial design. PROMs capture important outcomes not reflected in clinical or laboratory end points, such as physical or social functioning, and they complement other information that is not considered as accurate (e.g., New York Heart Association functional class). Regulators have recognized the need to anchor a PROM with single or serial patient global assessments to ensure that differences can be evaluated in the context of external comparators. Emphasizing the importance of PROMs, the U.S. Food and Drug Administration has approved the Kansas City Cardiomyopathy Questionnaire for use in studies evaluating therapies for patients with symptomatic HF[131]; its psychometric properties have been summarized in reviews.[132]

For both HF and CKD, there may be subtle variations in PROMs based on acute or chronic situations. However, PROMs should be captured in both scenarios, recognizing that many patients will have a chronic condition punctuated by acute episodes. A challenge for using PROMs in progressive CKD is the lower responsiveness of PROMs to chronic than acute changes in state. Further research in refining the appropriate PROM for patients with CKD for use in clinical trial settings should be considered.

Core data sets

The development of core data sets should be considered for trials that include both cardiovascular and kidney outcomes to aid efficiency and assist interpretation. Collection of core data sets is aided by standardized case report forms, such as the Heart Failure Collaboratory case report forms. There are no formalized kidney core data sets, although eGFR and some measure of urinary albumin or protein excretion are common elements in trials of progressive CKD. Where possible, the use of both creatinine- and cystatin C–based eGFR equations should be considered, particularly when agents may affect muscle metabolism, potentially increasing the variability of serum creatinine levels.

KEY FUTURE RESEARCH DIRECTIONS

There are numerous key future research directions to inform the clinical management and improve prognosis for patients with CKD and HF (Table 1), including, but not limited to, (i) identification of thresholds for natriuretic peptides to guide diagnosis for HF in persons with CKD, (ii) development of diagnostic markers to differentiate hemodynamic-induced AKI versus intrinsic AKI in persons with acute decompensated HF, (iii) standardization of kidney outcomes in HF trials, and (iv) and development of noninvasive tools for hemodynamic assessment to distinguish the primary cause of volume overload. In addition, greater focus on implementation of routine measurement of eGFR and UACR in persons with HF is needed.

SUMMARY AND CONCLUSIONS

The HF and CKD overlap is driven by shared risk factors and intertwined pathophysiology. Although their frequent co-occurrence is widely recognized, diagnostic uncertainty persists in distinguishing fluid overload due to HF from that attributable to kidney disease. Encouragingly, therapies now exist that improve both HF and kidney outcomes; yet their efficacy, safety, and implementation in patients with both

conditions require careful consideration. Moreover, therapies proven to protect kidneys in dedicated CKD trials have not consistently translated into kidney benefit in HF trials, underscoring the need for harmonized trial design and interpretation.

Management of HF and CKD demands an integrated, individualized, and collaborative approach that bridges diagnostic ambiguity, therapeutic complexity, and trial limitations. By advancing diagnostic precision, applying therapies thoughtfully across HF subtypes and CKD stages, and prioritizing inclusive, patient-centered trials (Table 1), the field can begin to close persistent care gaps. Moving forward, centering the patient voice in both treatment decisions and research design will be essential to delivering care that is not only evidence-based but also meaningful and responsive to patients' lived experiences. With a holistic and collaborative approach, we are poised to transform outcomes for individuals living with the dual burdens of HF and CKD.

APPENDIX

Other Conference Participants

Nancy M. Albert, USA; Lisa J. Anderson, UK; Linda Awdishu, USA; Marc Bains, Canada; Debasish Banerjee, UK; Sunita Bavanandan, Malaysia; Saul Blecker, USA; Christopher T. Chan, Canada; Josef Coresh, USA; François Dépret, France; Jaya Duncan, USA; Elke Eaton, USA; Hideki Fujii, Japan; Masafumi Fukagawa, Japan; João Pedro Ferreira, Portugal; Carmen Gray, USA; Jennifer E. Ho, USA; Richard Hobbs, UK; Jonathan G. Howlett, Canada; David W. Johnson, Australia; Vivek Kumar, India; Adeera Levin, Canada; Jolanta Małyszko, Poland; Patrick B. Mark, UK; Robert J. Mentz, USA; Brendon L. Neuen, Australia; Marlies Ostermann, UK; Ambarish Pandey, USA; Janani Rangaswami, USA; Dani Renouf, Canada; Gregory A. Roth, USA; Stephen Seliger, USA; Maria F. Slon Roblero, Spain; Manish M. Sood, Canada; John R. Teerlink, USA; Jeffrey M. Testani, USA; Katherine R. Tuttle, USA; Manvir Victor, Malaysia; Carl P. Walther, USA; Ken Wiecke, Canada; Wolfgang C. Winkelmayer, USA.

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