Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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The incidence and prevalence of heart failure (HF) and chronic kidney disease (CKD) are increasing, and as such a better understanding of the interface between both conditions is imperative for developing optimal strategies for their detection, prevention, diagnosis, and management. To this end, Kidney Disease: Improving Global Outcomes (KDIGO) convened an international, multidisciplinary Controversies Conference titled *Heart Failure in CKD*. Breakout group discussions included (i) HF with preserved ejection fraction (HFpEF) and nondialysis CKD, (ii) HF with reduced ejection fraction (HFrEF) and nondialysis CKD, (iii) HFpEF and dialysis-dependent CKD, (iv) HFrEF and dialysis-dependent CKD, and (v) HF in kidney transplant patients. The questions that formed the basis of discussions are available on the KDIGO website http://kdigo.org/conferences/heart-failure-in-ckd/, and the deliberations from the conference are summarized here.

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KEYWORDS: cardiovascular disease; chronic kidney disease; congestive heart failure; hemodialysis; transplantation

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HF and CKD represent concurrent chronic disease epidemics.[1,2] Both conditions have increasing incidence and prevalence in older age groups as well as persons with hypertension, diabetes mellitus, or other cardiovascular and kidney disease risk factors.[3] The presence of one condition appears to accelerate the presentation and progression of the other; having both conditions increases the risk of hospitalization, rehospitalization, need for intensive care or kidney replacement therapy, and death.[4–9] In addition, patients with HF and CKD may fail to respond as predicted to conventional therapies or experience increased toxicity to them.[10,11]

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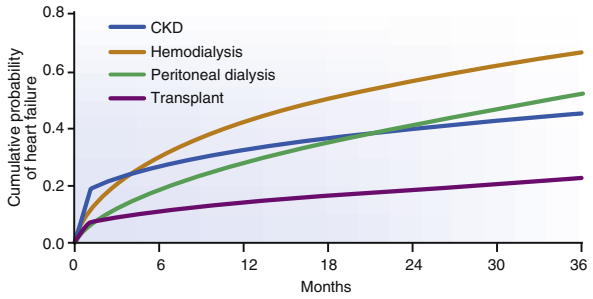
DEFINITIONS, PATHOPHYSIOLOGY, AND EPIDEMIOLOGY

The 2016 European Society for Cardiology guidelines for managing HF define it on the basis of signs and symptoms owing to structural and/or functional cardiac abnormalities, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[12] Subsets of HF include preserved ejection fraction, ≥50% (HFpEF); reduced ejection fraction, <40% (HFrEF); and mid-range ejection fraction, 40% to 49% (HFmrEF). Comorbid conditions make the diagnosis challenging, such as CKD and end-stage kidney disease (ESKD), as sodium and water retention contribute to HF manifestations.[13]

CKD is defined on the basis of persistently reduced estimated glomerular filtration rate (eGFR) of <60 ml/min per 1.73 m^2 or at least 1 marker of kidney damage for >3 months.[14] The latter markers include albuminuria, urine sediment abnormalities, histological, or structural abnormalities. HF as the primary syndrome can experience secondary CKD, and *vice versa*, or both can coexist on the basis of shared risk factors or systemic disorders. The distinction of which disease is primary and which is secondary may be challenging.

The incidence of *de novo* HF in known CKD is in the range of 17% to 21%.[15] The emergence of HF varies depending on the degree of CKD and the modality of kidney replacement therapy, including transplantation (Figure 1). Reduced eGFR is associated with increased risk of all-cause mortality, cardiovascular mortality, and hospitalization in patients with HFpEF or HFrEF.[16–18] Elevated urine albumin is prognostic for HF outcomes, albeit to a lesser extent than reduced eGFR. Both reduced eGFR and albuminuria can develop as a result of HF. Thus, HF and CKD occur in a bidirectional fashion with considerable overlap. A large meta-analysis of patients with HFrEF and HFpEF found that ∼55% of both groups had CKD G3a or higher (eGFR < 60 ml/min per 1.73 m^2), with a stepwise increase in mortality risk with the stage of CKD.[19] As severity of CKD increases, so does the prevalence of HF. An estimated 44% of patients on hemodialysis have HF (10% with HFpEF, 13% with HFrEF, and 21% with unspecified).[20] The complex and integrated pathophysiology is depicted in Figure 2.



CKD: Incident general Medicare CKD patients, age 66 & older, 2001–2003 combined
ESKD: Incident ESKD patients, age 20 & older
Patients with CHF at baseline excluded. Probabilities unadjusted

Figure 1 | Cumulative probability of heart failure in populations with chronic kidney disease (CKD), dialysis, and a kidney transplant. CHF, congestive heart failure; ESKD, end-stage kidney disease. Reproduced with permission from Collins AJ, Foley R, Herzog C, et al. Excerpts from the United States Renal Data System 2007 annual data report. *Am J Kidney Dis.* 2008;51(1 suppl 1):S1–S320.[130]

In CKD and ESKD, risk factors for HF include long-standing hypertension with often worsened blood pressure (BP) control as CKD worsens, salt and water retention causing excessive preload, and cardiomyopathic factors including left ventricular (LV) hypertrophy and fibrosis. In addition, there are CKD- and ESKD-specific factors that affect afterload (increased arterial stiffness and high output shunting through arteriovenous fistulae or grafts) as well as load-independent factors (neurohormonal activation, impaired iron utilization, anemia, demand ischemia, profibrotic factors [e.g., fibroblast growth factor 23 {FGF-23}], inflammation, etc.).[21] Arteriovenous fistulae or grafts have been reported to worsen right ventricular hypertrophy, increase pulmonary pressures, associate with significant right ventricular dilatation, and reduce right ventricular function, which are closely linked to survival.[22,23]

The association of CKD with mortality in HFrEF is independent of age, functional class, duration of HF, hemoglobin, or diabetes mellitus.[18] Patients with CKD are less likely to receive guideline-directed medical therapy, likely because of concerns about hypotension, kidney function, and hyperkalemia.[24]

The epidemiology of HFpEF appears to differ from that of HFrEF, where two-thirds of cases in the general population are due to ischemic cardiomyopathy and the remainder is due to nonischemic and/or idiopathic cardiomyopathy. In HFpEF there appears to be a strong influence of age, obesity, diabetes mellitus, and poor fitness.[25] In ∼25% of cases of HFpEF in the general population, there is superimposed cardiac ischemia; however, its role in the development of HFpEF is unknown.[26,27] All-cause mortality in HFpEF with CKD is elevated.[16,17,28]

DIAGNOSIS

There are no accepted definitions or criteria for HF diagnosis in CKD, and intravascular and extravascular volume overload can occur in the absence of structural heart disease, especially in patients with dialysis-dependent CKD. Echocardiography can support the diagnosis of HF by providing information on chamber volumes, ventricular systolic and diastolic function, wall thickness, valve function, and filling pressures.[12]

HFpEF in nondialysis CKD

As in the general population without CKD, the diagnosis of HFpEF in patients with nondialysis CKD is difficult and should be supported by multiple objective measures including impaired cardiac function with rest and exercise. Echocardiography with assessment using the American Society of Echocardiography grade of diastolic function (grades 1–4) should be performed. Biomarkers such as B-type natriuretic peptide (BNP) or N-terminal pro-BNP have a high negative predictive value.[29] The effect of worsening eGFR on levels of BNP and especially N-terminal pro-BNP relates to both impaired renal clearance and underlying cardiac abnormality.[30,31] Obesity can lead to modestly lower levels of BNP and N-terminal pro-BNP in those with HF.[32] Cystatin C may

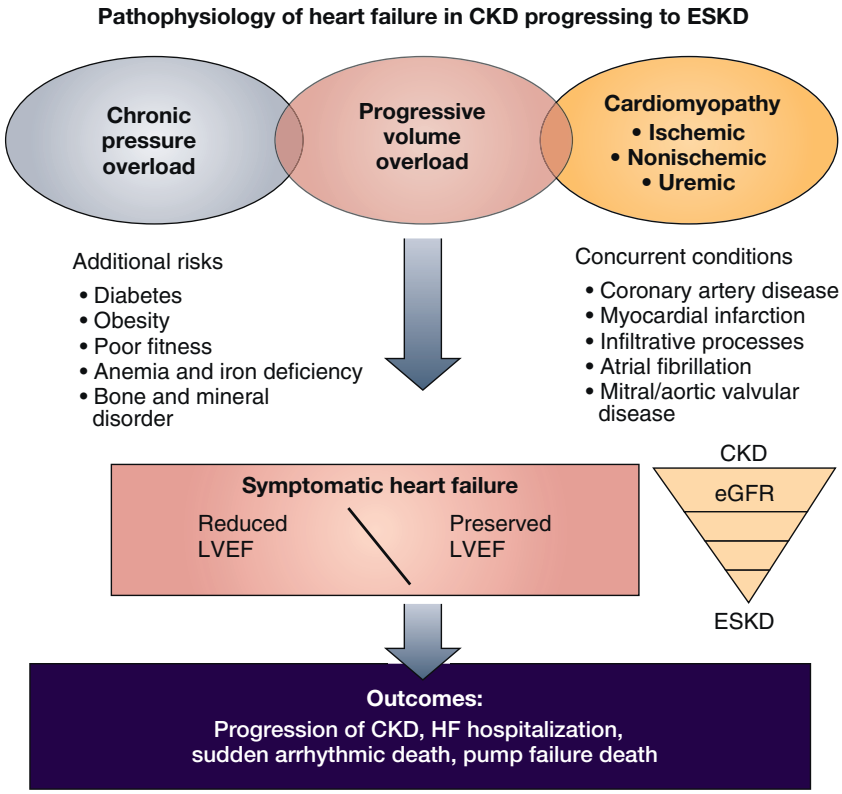


Figure 2 | Pathophysiology of heart failure (HF) in chronic kidney disease (CKD) progressing to end-stage kidney disease (ESKD). Pressure overload implies systemic hypertension. eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.

provide better estimates of eGFR than does creatinine because of its relative independence of muscle, hepatic, and dietary contributions of creatinine. Prognostic biomarkers include natriuretic peptides, cardiac troponins, soluble ST2 (Suppressor of Tumorgenicity 2), and galectin-3.[33] Biomarkers are complementary in terms of prognostic value and may give insight into HF phenotype. In critically ill patients, invasive assessment of hemodynamics including measurement of the pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, and LV end-diastolic pressure may be required to distinguish HFpEF from other diagnoses such as obesity-associated deconditioning, primary pulmonary hypertension, high output from arteriovenous shunting, and lung disease. Cardiopulmonary stress testing with measurement of the peak oxygen consumption can be a helpful adjunct for objectively assessing the degree of functional impairment and discerning between cardiac and pulmonary dyspnea.

HFrEF in nondialysis CKD

The diagnosis of HFrEF in the population with nondialysis CKD parallels that of the population without CKD. Monitoring of HFrEF in CKD includes the usual standards of care: evaluating sodium, potassium, creatinine (eGFR), albumin-to-creatinine ratio, BNP or N-terminal pro-BNP, troponin I or T, ST2, and galectin-3 levels, and, as is the case in HFpEF, some select cases may justify advanced physiological measurements such as pulmonary artery pressure monitoring and/or bioimpedance techniques. Changes in volume status can be detected on physical examination, chest radiography, and lung ultrasonography.

HFpEF or HFrEF in dialysis-dependent CKD

In patients on dialysis, symptoms typical of HF, such as paroxysmal nocturnal dyspnea, orthopnea, dyspnea, fatigue, ascites, and dependent edema, may be intermittent. It is important to consider other causes of dyspnea, such as chronic obstructive pulmonary disease, pulmonary hypertension, anemia, or obstructive sleep apnea. The Acute Dialysis Quality Initiative has proposed a functional classification system for HF symptoms in patients with ESKD.[34]

Patients with dialysis-dependent HF should undergo the same evaluation as patients with non−dialysis-dependent HF. However, there may be additional evaluation or considerations for dialysis-dependent patients.

Chest radiograph. Overall, radiographic signs are specific but only moderately sensitive in diagnosing HF.[35] The chest radiograph can be used to screen for other sources of dyspnea, such as pulmonary and diaphragmatic abnormalities. Given the high rates of pneumonia in acute hospitalizations in ESKD, the chest radiograph is prudent. Prompt resolution of radiographic findings of interstitial infiltrates after dialysis and/or ultrafiltration supports extracellular fluid overload as a cause of signs and symptoms of HF, but whether this is the

result of structural and/or functional cardiac abnormality may require additional diagnostic testing.

Echocardiography. Measurements of LV ejection fraction, LV hypertrophy, right ventricular ejection fraction, chamber dimensions, and valvular function are fundamental in managing ESKD. Approximately 87% of patients with ESKD have major abnormalities on echocardiography before initiating treatment with dialysis.[36] When possible, imaging should be carried out when patients on dialysis are close to dry weight, and preferably on a nondialysis day for patients on hemodialysis. In addition to reduced LV ejection fraction, indicators for LV dysfunction include LV diastolic volume index of >86 ml/m^2 or LV systolic volume index of >37 ml/m^2.

Electrocardiography. Electrocardiography can be used to detect rhythm disturbances or evidence of prior myocardial damage or pericardial disease.

In specific clinical scenarios, evaluation may include cardiac magnetic resonance imaging, global longitudinal strain analysis, whole-body bioimpedance technique, and extended cardiac rhythm monitoring through wearable and implantable monitors. Emerging diagnostic options include pulmonary artery ambulatory monitoring and thoracic impedance monitoring. In the setting of dialysis, the role of natriuretic peptides is unclear.[37]

Newly discovered HFrEF in patients undergoing dialysis should prompt full risk stratification for an ischemic versus nonischemic etiology. Revascularization in patients with HFrEF in the general population is supported by 10-year outcome data,[38] but no such data exist for patients with ESKD.

TREATMENT

Prevention of incident HF

Hypertensive and glycemic control. Tight BP control, defined as targeting systolic BP to <120 mm Hg, reduces incident HF with LV ejection fraction ≥ 35%, even in the presence of CKD.[39,40] In the RENAAL (Reduction in End Points in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan) diabetic nephropathy trial, a risk reduction of 32% was observed for the first hospitalization for HF in the losartan patient group versus the placebo group.[41]

In patients with CKD and diabetes, poor glycemic control is a risk factor for developing HF[42] and improved glycemic control is associated with a reduced risk of HF. In particular, sodium-glucose cotransporter 2 inhibitors have been shown to not only slow the progression of CKD in such patients but also reduce the risk of hospitalizations for HF in both those with and without a history of HF.[43,44] In the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) study, empagliflozin resulted in a 39% relative risk reduction in hospitalization for HF in patients with type 2 diabetes mellitus and CKD G3a or higher and/or urine albumin-to-creatinine ratio >300 mg/g.[45,46] A similar effect was seen with canagliflozin[47] and dapagliflozin.[48] Whether glycemic control has a direct effect in preventing HF is unclear, as sodium-glucose cotransporter 2 inhibitors also lead to reductions in BP and body weight, promote diuresis, and have strong off-target effects on the cardiac Na^+/H^+ exchanger.[49]

Treatment of existing HF

There are no proven treatments for HFpEF, including in the setting of CKD.[50] Medications that can reduce adverse outcomes associated with HFrEF include angiotensin-converting enzyme inhibitors (ACEis),[51] angiotensin II receptor blockers (ARBs), angiotensin receptor neprilysin inhibitors, β-blockers, and mineralocorticoid receptor antagonists (MRAs).[52] However, it cannot be assumed that drugs with proven efficacy in HFrEF have the same benefits in HFpEF.[51–55]

Although strategies for treating HF are the same in patients with or without CKD, its presence raises special considerations, particularly for patients with eGFR < 30 ml/min per 1.73 m^2 (serum creatinine level ≥2.5–3.0 mg/dl), who have largely been excluded from clinical trials, and in whom the risk of toxicity may significantly complicate therapy. Therapy for HFrEF can cause eGFR to vary, so when eGFR declines from >60 to <60 ml/min per 1.73 m^2 (i.e., CKD G3a or higher) it can be unclear if this truly represents CKD versus a transient decline due to hemodynamic and neurohormonal factors. In addition, serum creatinine levels do not solely reflect kidney function, thus further complicating the interpretation of eGFR measurement. As such, measurement of cystatin C levels can assist with the interpretation given the variability in creatinine levels. It is likely that biomarkers of true kidney damage in addition to functional markers will play an important role in the future. Identification of true kidney injury versus transient azotemia would dramatically aid in decisions on diuretics and other agents in goal-directed medical therapy.

β-Blockers. The Metoprolol CR/XL Randomized Intervention Trial in Chronic HF (MERIT-HF) trial randomized patients with symptomatic HFrEF to metoprolol or placebo and included many patients with eGFR < 45 ml/min per 1.73 m^2. The hazard ratio for total mortality was 0.41 in favor of metoprolol for the CKD subgroup and demonstrated higher risk reduction than did the reference group with eGFR > 60 ml/min per 1.73 m^2.[56] A similar analysis was performed in the CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) study, which included patients having a serum creatinine level up to 300 μmol/l (3.4 mg/dl) and demonstrated sustained benefit of bisoprolol with worsening kidney function.[57] A small study of carvedilol in patients with dialysis-dependent CKD and HFrEF also conferred a mortality benefit.[58] Therefore, it seems reasonable to use β-blockers for managing HFrEF in patients with CKD, except for β-blockers that have significant renal excretion and have the potential for overexposure, such as atenolol, nadolol, or sotalol.[59] Atenolol can be used as part of the management approach for hypertension and coronary disease if given 3 times per week in ESKD during hemodialysis.[60] Consideration should be given to the potential for dialyzability of certain β-blockers, as a 1.4-fold

increased mortality risk was observed in the group treated with highly dialyzable β-blockers such as metoprolol.[61]

Angiotensin blockade. Both ACEis and ARBs can lead to decreased GFR in patients with HFpEF or HFrEF. In patients with HFrEF, the benefit of angiotensin blockade in terms of mortality and other important outcomes is maintained[62]; however, observational trials in patients with HFpEF and worsening kidney function due to ACEis or ARBs have an increased mortality risk without experiencing improved outcome,[63,64] although these results have not been consistent.[65] ARBs can be considered for those who are ACEi intolerant. The Survival And Ventricular Enlargement (SAVE) study of captopril versus placebo post–myocardial infarction enrolled patients with HFrEF and serum creatinine level ≤2.5 mg/dl at baseline, of whom approximately one-third and one-tenth of patients had eGFR < 60 and < 45 ml/min per 1.73 m^2, respectively. The superiority of captopril was maintained in patients with CKD.[66] Other trials of ACEis and ARBs reported similar results in patients with CKD G3a and HFrEF.[67] The angiotensin receptor neprilysin inhibitor LCZ696 has also demonstrated a hemodynamic effect in preserving GFR, with 1 study reporting smaller eGFR decline in patients with HFpEF on LCZ696 versus valsartan after 36 weeks of treatment.[68] However, urinary albumin-to-creatinine ratios showed increases with LCZ696 versus valsartan. Figure 3 presents considerations for individualized treatment of HF in CKD.

Azotemia alone in the setting of diuresis should not necessarily result in changes to or withdrawal of ACEis or ARBs because their removal may lead to worse outcomes.[69,70]

Diuretics. Thiazide diuretics are a mainstay of BP control in the general population and commonly advanced to loop diuretics in the setting of CKD. Important considerations in patients hospitalized for decompensated HF on a twice daily, chronic oral loop diuretic regimen include (i) dosing, (ii) duration, and (iii) whether to change from oral to i.v. Increased i.v. doses of furosemide and continuous infusions may be used to relieve congestion. The Diuretic Optimization Strategies Evaluation (DOSE-AHF) study demonstrated that a high-dose strategy could improve dyspnea scores, weight change, and net fluid loss at 72 hours whereas a low-dose group was less likely to convert from i.v. to oral and more likely to require a dose increase. There was an increased frequency of early increased serum creatinine level of ≥0.3 mg/dl in the high-dose group, but no appreciable difference in kidney function over 60 days between any of the study groups.[71] Torsemide may have an advantage over furosemide, with longer half-life, better bioavailability, and potential for reducing myocardial fibrosis,[72,73] but this requires confirmation.

MRAs. In patients with HF and CKD G3a-G3b, MRAs are generally as effective as they are in patients without CKD,[74] but trials of MRAs for HF have systematically excluded patients with more advanced CKD. For instance, the

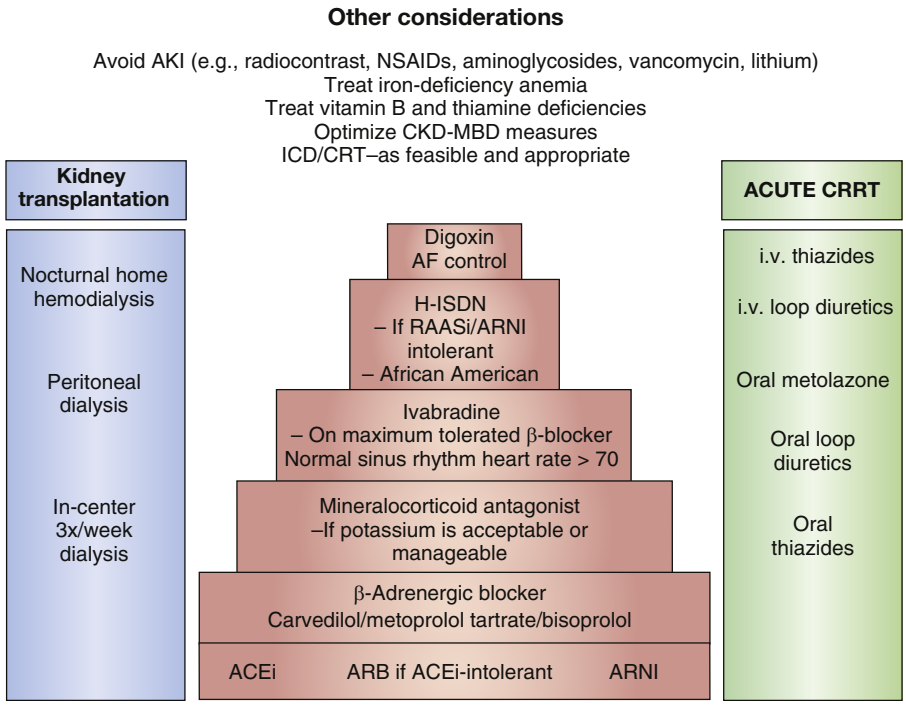


Figure 3 | Pharmacotherapy for the prevention and treatment of heart failure with reduced ejection fraction in chronic kidney disease (CKD) progressing to end-stage kidney disease (ESKD). ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CKD-MBD, chronic kidney disease–mineral bone disorder; CRT, cardiac resynchronization therapy; CRRT, continuous renal replacement therapy; H-ISDN, hydralazine-isosorbide dinitrate; ICD, implantable cardioverter-defibrillator; NSAID, nonsteroidal anti-inflammatory drug; RAASi, renin-angiotensin-aldosterone system inhibitor.

Randomized Aldactone Evaluation Study (RALES) examined subjects with ejection fraction < 35% but excluded patients with serum creatinine level ≥ 2.5 mg/dl or serum potassium level > 5.0 mEq/l.[75] However, a sizable subgroup of patients in RALES had eGFR < 60 ml/min per 1.73 m^2, and these patients experienced a similar reduction with spironolactone in all-cause death or hospitalizations for HF as with those who had eGFR > 60 ml/min per 1.73 m^2,[76] although they more frequently had hyperkalemia, reduction of >30% in eGFR, dose reduction, or discontinuation. Similar results have been shown with eplerenone.[67] Data on the use of MRAs for the treatment of HF (either HFrEF or HFpEF) in patients with CKD G4-G5 or patients on dialysis are of limited quality.[77] One observational study identified a significantly increased adjusted risk of death or hospitalization for HF in patients with CKD G5 treated with spironolactone.[78] An ongoing randomized clinical trial (RCT) of spironolactone in patients with HFrEF undergoing hemodialysis should inform practice in the future (ClinicalTrials.gov identifier: NCT01848639).

In a study of patients with HFrEF and type 2 diabetes mellitus and/or CKD G3a who were randomized to 1 of 5 different doses of finerenone (a nonsteroidal MRA) versus eplerenone, patients randomized to the highest dose of finerenone experienced a decrease in the secondary composite endpoint of death, cardiovascular hospitalization, or emergency department visit for worsening HF without worsening hyperkalemia or kidney function.[79] Confirming these promising results in a larger study of patients with CKD G4 would be valuable.

Hyperkalemia. Because of concerns about hyperkalemia, there is a strong underutilization of renin-angiotensin-aldosterone system inhibitors and a high rate of discontinuation in patients with HF and CKD.[69,80] In a small study of patients with CKD and HF who were hyperkalemic and on renin-angiotensin-aldosterone system inhibitors, 4 weeks of treatment with patiromer led to a mean reduction of 1.06 ± 0.05 mEq/l in serum potassium levels and lower rates of recurrent hyperkalemia as compared with placebo.[81] In another study that included 69% patients with eGFR <60 ml/min per 1.73 m^2, 48 hours of open-label treatment with sodium zirconium cyclosilicate resulted in normokalemia in 98% of patients. In a subsequent study, the serum potassium level was significantly lower during days 8 to 29 with sodium zirconium cyclosilicate.[82] However, edema was observed more frequently at the highest dose (15 g).[82,83] It remains unproven that pharmacological control of potassium levels can lead to increased ACEi/ARB/MRA utilization and in turn improve HF or CKD outcomes. It is also unknown whether deliberately lowering potassium levels would be helpful or harmful in the context of HF. Some have suggested that MRA may be beneficial on the basis of increasing serum potassium level, whereas others argue that the high serum potassium level causes further compensatory increase in aldosterone, which in turn is implicated in the pathophysiology of both HF and CKD. Only long-term RCTs will determine the merits of potassium reduction in this setting.

LV assist devices. Renal dysfunction is common in patients referred for mechanical circulatory support (MCS), and there are currently no diagnostic tests to distinguish

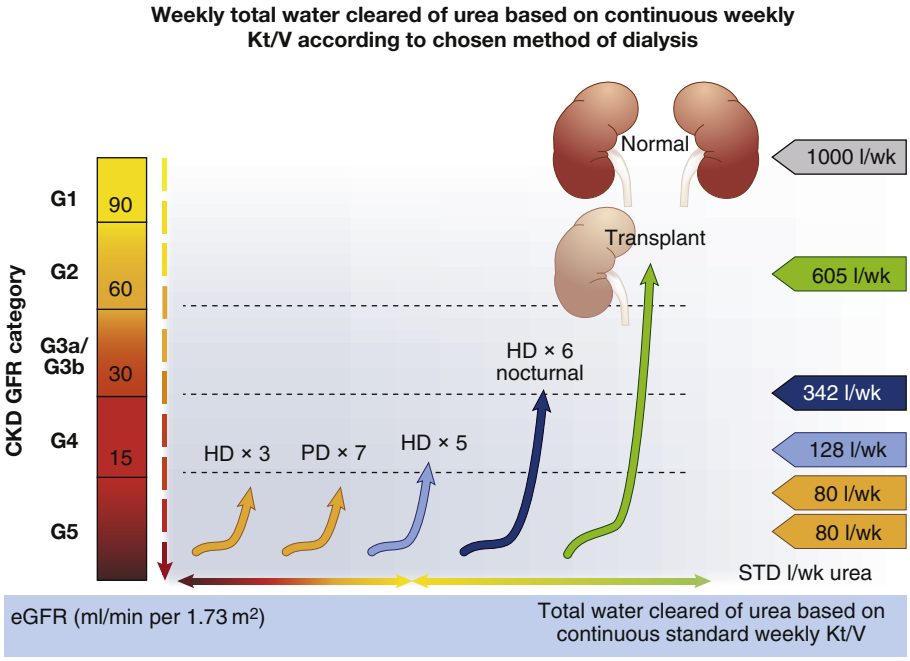


Figure 4 | Total water cleared of urea according to various dialysis modalities and in normal and kidney transplant recipient populations. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HD, hemodialysis; Kt/V, clearance of urea multiplied by dialysis duration and normalized for urea distribution volume; PD, peritoneal dialysis; STD, standardized.

Table 1 | Available evidence of the prevalence of HF before kidney transplantation and outcomes after transplantation

Reference	Design and participants	Measure to identify HF	Prevalence of HF or LV systolic dysfunction before kidney transplantation	Outcomes after HF[a]
Wu *et al.*[99]	• Retrospective, longitudinal • 712 recipients of KTx at 1 U.S. center (1998–2003)	• Extraction of comorbidities data from EMRs	• HF 11.9% at the time of KTx	
Faravardeh *et al.*[100]	• Retrospective, longitudinal • 4482 recipients of KTx at 1 U.S. center (1963–2012)	• Details of local clinical data collection unknown	• 5.8% at the time of KTx • 3.9% in patients aged <50 yr, 8.4% in patients aged 50–64 yr, 12.1% in patients aged ≥65 yr	• HF increased mortality after KTx (HR, 1.84; 95% CI, 1.20–2.83 in patients aged ≥65 yr; HR, 1.63, 95% CI, 1.24–2.15 in patients aged <50 yr; no increased mortality observed in patients aged 50–64 yr • HF: an independent risk factor for graft failure in patients aged <50 and ≥65 yr
Siedlecki *et al.*[101]	• Retrospective, longitudinal • 653 recipients of KTx at 1 U.S. center (1998–2005)	• Recipients of KTx who had SPECT perfusion scans for KTx evaluation • Clinical database	• 18% with LVEF ≤45% (mean LVEF, 36.7% ± 6.7%)	• LVEF ≤45% was associated with increased cardiac mortality (HR, 4.8; 95% CI, 2.1–11.2), total mortality (HR, 2.0; 95% CI, 1.2–3.5), and cardiac complications (HR, 1.7; 95%, CI 1.1–2.8) after KTx • Mean time to cardiac-related death: 1.5 ± 1.7 yr after KTx
Lentine *et al.*[102]	• Retrospective, longitudinal • 27,011 Medicare-insured U.S. recipients of KTx (1995–2001) without indication of HF before transplantation	• Diagnosis codes on Medicare billing claims (inpatient and outpatient HF)	• Development of HF on the transplant waiting list: 6.5%, 12%, and 32% at 6, 12, and 36 mo	
Lentine *et al.*[103]	• Retrospective, longitudinal • 1102 recipients of KTx at 1 U.S. center (1991–2004)	• Physician-reported diagnoses in the center's clinical database	• Development of HF on the transplant waiting list: 46% at 36 mo	

CI, confidence interval; EMR, electronic medical record; HF, heart failure; HR, hazard ratio; KTx, kidney transplant; LV, left ventricular; LVEF, left ventricular ejection fraction; SPECT, single photon emission computed tomography; U.S., United States.
[a]Reported HRs are multivariate.

irreversible from reversible forms of renal dysfunction in such patients. Although most patients, including those with renal dysfunction, experience early improvement in kidney function with MCS, this improvement is often transient.[84] Venous congestion, right ventricular dysfunction, and reduced pulsatility are potential mechanisms involved in resurgence of renal dysfunction after MCS. Although there is no clearly preferred method of kidney replacement therapy in MCS, peritoneal dialysis has advantages in MCS and non-MCS HF with sustained daily ultrafiltration, fewer volume-related preload issues, home accessibility, and reduced cost. Patients with ESKD undergoing MCS have significantly worse outcomes than do those without ESKD.[85]

Adjunctive and emerging approaches. Improved diagnosis and treatment of sleep apnea, obesity management, nutrition management, physical activity, sodium restriction (and possibly fluid restriction), and assessments for chronotropic incompetence may be helpful in reducing symptoms and improving functioning for patients with HF and CKD. In the setting of atrial fibrillation, permissive rate control and cardioversion are reasonable strategies.

Treatment of CKD-related conditions and dialysis

Iron deficiency and anemia. Erythropoiesis-stimulating agents have no effect on the prevention or treatment of HF in patients with CKD.[80,86] Yet for patients with chronic HF and iron deficiency with or without anemia, treatment with i.v. ferric carboxymaltose improves symptoms, functional capacity, and quality of life.[87] In the CONFIRM-HF (Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure) study of patients with LV ejection fraction ≤45%, treatment of iron deficiency with ferric carboxymaltose for >1 year was associated with a significant reduction in the risk of hospitalization for worsening HF.[88] In the FAIR-HF (Ferinject Assessment in patients with IRon deficiency and chronic Heart Failure) trial in patients with HF and iron deficiency, treatment with ferric carboxymaltose was associated with an increase in eGFR compared with placebo.[89] A recent meta-analysis showed that hospitalizations for HF and mortality were significantly decreased in the iron-treated group, of whom >40% had eGFR < 60 ml/min per 1.73 m^2 and iron

deficiency (ferritin level <100 μg/l, or < 300 μg/l if transferrin saturation is <20%) irrespective of hemoglobin level.[90] Patients with HF and CKD can be considered for receiving parenteral iron given the proven safety record in patients with advanced CKD.[91]

Hypoxia-inducible factor prolyl hydroxylase inhibitors are being evaluated for their ability to treat anemia in CKD, and intriguing data suggest a possible role for the prevention or attenuation of cardiac ischemic injury.[92]

Mineral and bone disorders. There are limited data from RCTs, but cinacalcet treatment has been associated with modest reductions in the time to first episode of HF in patients on hemodialysis.[93]

Macro- and micronutrients. Maintenance of lean tissue through adequate macronutrient intake of protein, essential amino acids, and essential fatty acids is viewed as desirable, and adequate levels of micronutrients including water- and fat-soluble vitamins, trace minerals, and cofactors are also considered to be important.

Mode of dialysis. There are no studies of interventions that use the development of *de novo* HFrEF or HFpEF as an outcome in the population on dialysis. To date, it has not been feasible to randomize patients to modality type.[94] Increasing the frequency of dialysis sessions, as in short daily hemodialysis, reduces LV mass and lowers the risk of cardiovascular death and hospitalizations.[95] Patients undergoing home dialysis have a markedly reduced risk of hospitalization for HF and cardiovascular mortality (41% lower risk of HF, fluid overload, and cardiomyopathy).[95] As shown in Figure 4, home nocturnal hemodialysis 6 times per week is next best after kidney transplantation and normal functioning kidneys for clearance of urea from water. These benefits are juxtaposed against a higher risk of vascular access issues and infection-related hospitalization.[96] Recurrent dialysis-induced ischemic injury is associated with regional wall motion abnormalities and the development and worsening of HF,[97] and therefore conditions of the dialysis treatment itself may influence HF. Evidence from a small study suggests dialysate cooling may slow the progression of hemodialysis-associated cardiomyopathy by reducing recurrent ischemic injury.[98] Thus far there are no RCTs to inform the benefits of peritoneal dialysis versus hemodialysis. Management of the sodium concentration in dialysis solutions requires careful consideration in dialysis-dependent patients with HF, as it may present an additional sodium load. Strategies to maintain, where possible, residual kidney function are desirable, as this can mitigate some of the significant hemodynamic and fluid shifts that occur with volume removal during dialysis.

PATIENTS WITH A KIDNEY TRANSPLANT

Incidence and prevalence of HF in recipients of kidney transplant

In patients with a kidney transplant, HF has been most commonly defined and identified in administrative and clinical databases and less frequently identified with diagnostic testing such as echocardiography. Data on pretransplant HF prevalence and prognosis are sparse, but the prevalence of HF/LV systolic dysfunction in patients referred or wait-listed for transplantation may be as high as 25% (Table 1).[99–103] HF at the time of transplantation is associated with a higher risk of mortality, cardiovascular events, and graft failure.[100–102]

On the basis of Medicare billing claims data, the incidence of posttransplant *de novo* HF is ∼18% at 3 years.[102] Several risk factors have been shown to be associated with clinical HF after

Table 2 | Risk factors for HF after kidney transplantation

Risk factor	Rigatto *et al.*[104]	Abbott *et al.*[105]	Lentine *et al.*[102]	Risk factors for HF in the general population[42,106–108]
Increased age	X	X	X	X
Sex			X	Increased in male patients (increased in female patients in the absence of MI)
Increased BMI		X	X	X
Unemployment			X	
CVD before KTx		X	X	Prevalent coronary heart disease and prior MI
MI after KTx		X	X	Prevalent coronary heart disease and prior MI
Smoking history			X	X
Diabetes	X	X	X	X
Anemia	X		X	X
Hypoalbuminemia	X			X
Hypertension	X		X	X
African American race		X		X
Increased duration of dialysis before KTx		X		NA
Deceased donor kidney	X			NA
Increased donor age			X	NA
Delayed graft function		X	X	NA
Graft failure		X	X	NA
Allograft rejection		X	X	Chronic kidney disease
Donor CMV positive		X		NA

BMI, body mass index; CMV, cytomegalovirus; CVD, cardiovascular disease; HF, heart failure; KTx, kidney transplant; MI, myocardial infarction; NA, not applicable.

transplantation (Table 2).[102,104–108] *De novo* HF is also associated with lower patient and graft survival (Supplementary Table S1).[102–105,109]

Diagnosis and screening of HF in recipients of kidney transplant

There is little or no evidence of whether to obtain a screening echocardiogram to assess LV function for all transplant candidates. However, it is reasonable to obtain an echocardiogram if there are symptoms of HF, history of cardiovascular disease, or hemodynamic instability on dialysis. The approach to *de novo* HF in transplant recipients is the same as that for the general population, including evaluation for coronary artery disease.[110]

HF treatment in recipients of kidney transplant

Transplant recipients with HF should be treated as they would be treated in the general population. There have been no definitive interventional studies of ACEis or ARBs, MRAs, β-blockers, calcium channel blockers, nitrates, vasodilators, or angiotensin receptor neprilysin inhibitors in the treatment of HF in recipients of kidney transplant. In a small RCT of recipients of kidney transplant with LV hypertrophy, lisinopril reduced LV mass index compared with placebo.[111] There are no reports evaluating interventions that could possibly prevent or delay development of *de novo* HF in patients with a kidney transplant, nor are there trials in patients with a kidney transplant that have included HF as an endpoint. In some patients with a kidney transplant, management of HF is

Table 3 | Future research recommendations

- ***Acquire a better understanding of the pathophysiology of HF in CKD.*** Physiological and imaging tests are needed for kidney disease. Reliance on the plasma serum creatinine, blood urea nitrogen, and limited urine tests is inadequate to advance the field. Methods to assess the kidney functional reserve, or the ability of the kidneys to increase filtration, are needed. An understanding of when reduced renal filtration is adaptive or maladaptive is needed. Conversely, methods of assessing inflammation, irreversible fibrosis, and loss of functioning nephrons would assist in understanding the recoverability of AKI superimposed on CKD. The clinical examination can be improved by objective measurements of volume status including plasma volume and red blood cell volume, degree of pulmonary congestion, and venous capacitance. Studies to unveil the determinants of plasma refill after treatment with i.v. loop diuretics or ultrafiltration are needed. Variation in plasma refill likely explains why some patients respond favorably after the first few doses while others do not. Investigating possible systemic mechanisms of both heart and kidney disease and gaining a better understanding of the processes by which the kidneys retain salt and water and how this relates to myocardial dysfunction in systole and diastole would be worthwhile.
- ***Reevaluate the pathophysiology of the progression of HF.*** This includes examining the role of serial imaging of right/left ventricular function and biomarkers (e.g., neurohormonal activation, bone metabolism, inflammation, fibrosis, and kidney injury) in prognosis and treatment in asymptomatic and symptomatic patients.
- ***Identify appropriate kidney outcomes for HF trials and position them as prespecified endpoints*** (i.e., progression of CKD and eGFR slopes). Future trials of HF interventions should focus on prespecified subgroups with eGFR $<$ 30 ml/min per 1.73 m^2.
- ***Refine detection of AKI using measures of kidney filtration and markers of kidney damage.***
- ***Examine and include patient-oriented outcomes, especially for symptom control, and design shared decision-making aids.***
- ***Develop and test better markers of initiation, persistence, and recovery of AKI.*** AKI biomarkers have not been adequately studied in acute HF. Understanding the role of AKI in the prediction and management of diuretic resistance will be important for acute HF.
- ***Study novel diuretic strategies in patients with HFrEF with more accurate methods to detect volume overload in order to avoid both hypotension and continued congestion.***
- ***Identify the best means for adjusting loop diuretics, whether by blood biomarker measurement or hemodynamic assessment.*** This will help guide use of diuretics in HF with CKD in the hope of reducing hospitalizations for HF and perhaps cardiovascular death.
- ***Examine new potassium-binding drugs in patients with eGFR $<$ 30 ml/min per 1.73 m^2.*** It would also be useful to know whether the potassium-binding drugs allow higher use or doses of RAAS blockers and whether this leads to improved outcomes. It would also be important to examine whether and how potassium-lowering agents can reduce potassium swings when patients are undergoing hemodialysis.
- ***Compare various dialysis modalities and their frequency for optimizing ultrafiltration and maintaining euvolemia.***
- ***Address and overcome the difficulty in randomizing patients to peritoneal dialysis or ultrafiltration trials.***
- ***Determine the optimal timing for initiating dialysis in the setting of HFrEF and HFpEF.*** There is reason to hypothesize that the subgroup that will develop diuretic resistance could benefit from starting dialysis early.
- ***Find methods of achieving volume control during dialysis while still ensuring patients receive optimal cardioprotective medications.***
- ***Evaluate wearable devices that monitor fluid status, heart rhythm, etc.***
- ***Design and conduct an adequately powered observational study of clinical and echocardiographic determinants of HF in patients referred for transplantation.***
- ***Determine which patients should undergo a simultaneous heart-kidney transplant versus a heart transplant alone with watchful waiting for renal recovery posttransplant.***
- ***Investigate the degree to which the following comorbid conditions contribute to HF physiology in patients with ESKD: hypertension, coronary artery disease, valvular disease, diabetes, atrial fibrillation, sleep apnea, cachexia/sarcopenia, anemia, iron deficiency, mineral metabolism, chronic lung disease, and hypertension.***
- ***Investigate technologies to better phenotype patients and target them for specific interventional strategies.*** Such domains of phenotypic assessment could include genomics, metabolomics, cardiovascular hemodynamics, myocardial energetics, neurohormonal milieu, salt and water metabolism including plasma refill, and heart-kidney signaling and regulation.
- ***Evaluate the effects of exercise, weight loss, diet, and possibly treatment of sleep apnea in the prevention of HF in patients with CKD.***
- ***Ascertain approaches to reduce protein energy wasting, sarcopenia, and cachexia.*** Research is needed to better understand the role of nutrition in the prevention of HF and the attenuation of both HF and CKD.
- ***Obtain a better understanding of best practices for ligating AV fistulas for high output cardiac failure: location, flow, determining when to ligate.***

AKI, acute kidney injury; AV, arteriovenous; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; RAAS, renin-angiotensin-aldosterone system.

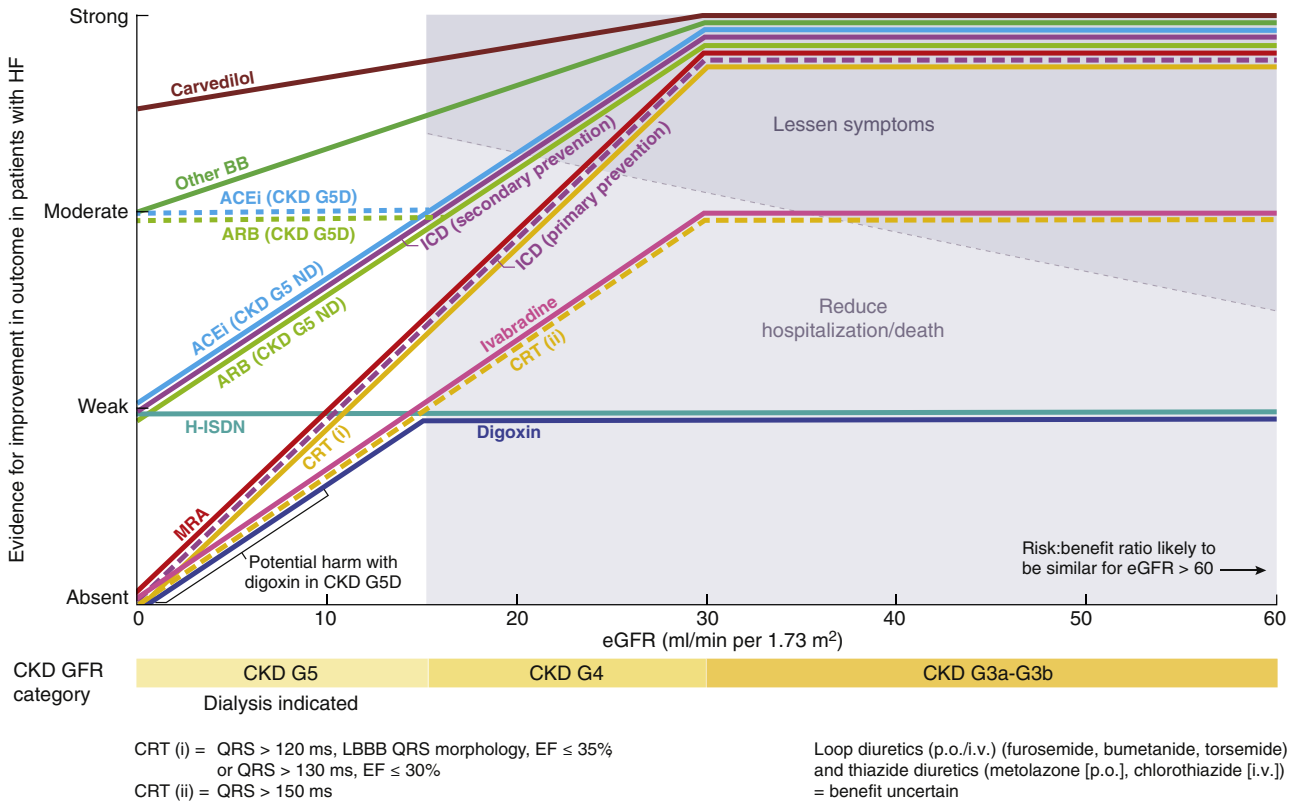


Figure 5 | Positioning of heart failure (HF) therapies according to left ventricular ejection fraction and renal filtration function. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, β-blocker; CKD G5D, chronic kidney disease glomerular filtration rate category 5 patient on dialysis; CKD G5 ND, chronic kidney disease glomerular filtration rate category 5 patient not on dialysis; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; H-ISDN, hydralazine-isosorbide dinitrate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonist.

complicated by persistent, severe hyperkalemia, which may prevent the use of ACEis, ARBs, and MRAs. Counteracting therapies such as patiromer or sodium zirconium cyclosilicate will require evaluation in this population, as there is potential for interference with absorption of certain medications.

Concern about reduction in eGFR should not automatically lead to withholding of otherwise beneficial treatments of HFrEF. A unique exacerbating factor may be the ongoing presence of an "unnecessary" arteriovenous fistula, the ligation of which should be considered in recipients with symptoms of HF, a high cardiac output hemodynamic profile, and high arteriovenous fistula flow (1.5–2.0 l/min and arteriovenous fistula flow > 30% cardiac output).[112]

Effects of kidney transplantation on cardiac structure and function

Reports have documented reversal of clinical cardiac dysfunction and improvement in echocardiographic parameters after kidney transplantation,[113–127] supporting the notion of a potentially reversible "uremic cardiomyopathy" (Supplementary Table S2). Reversal is less likely in patients who have been dialyzed for long periods of time.[114] Transplant candidates should thus not be excluded solely on the basis of LV systolic dysfunction and, in some circumstances, should be considered for priority wait-listing. However, there exists a need for more long-term studies with prospective follow-up of LV structure and function before and after kidney transplantation to evaluate consecutive patients in an unbiased fashion.

Simultaneous kidney-heart transplant

Patients with severe HF who are dependent on chronic dialysis may benefit from a simultaneous kidney-heart transplant. In an analysis of U.S. registry data, 5-year posttransplant survival was higher in dialysis-dependent patients with end-stage HF who received a simultaneous kidney-heart transplant compared with heart transplant alone (75% vs. 51%).[128] Survival benefits were present, although to a lesser extent, in patients with renal dysfunction and end-stage HF not dependent on dialysis who received a kidney-heart transplant.[129] Given the absence of robust data on patient selection for simultaneous kidney-heart transplantation, it is reasonable to state that transplantation of both organs must be weighed against the possibility of recovering kidney function with heart transplantation alone, and selection bias must be considered in interpreting these observational data.

RESEARCH PRIORITIES

Table 3 outlines the prioritized research recommendations whose outcomes would most likely improve future clinical practice.

CONCLUSION

A multidisciplinary approach is vital for understanding the mechanistic and clinical data concerning HF in CKD. Clearly, high-quality data are lacking on all aspects of HF (pathophysiology, epidemiology, diagnosis, prevention, and treatment) specific to the population of patients with advanced nondialysis CKD as well as patients undergoing dialysis and transplantation. Figure 5 depicts a representation of the relative benefits of evidence-based therapy of HF across a continuum of kidney function. It is highly recommended that nephrologists and cardiologists partner to design and conduct clinical trials and that trials be as integrative as possible. Because HF in CKD appears to be a complex disease or set of syndromes, it is prudent to integrate clinical history, phenotypic assessment with biomarkers and high-quality imaging, and treatment paradigms that are both comparable and sustainable. It is important to avoid medication toxicity and complications with cardiovascular or renal procedures in the setting of HF and CKD. The interpretation of azotemia as representing kidney damage versus transient worsening kidney function is one of the great challenges facing clinicians today and calls for a strong mandate for use of biomarkers beyond serum creatinine and blood urea nitrogen. In the future, it will be beneficial to include patient-oriented outcomes as well as end-of-life preferences when evaluating therapeutic strategies, particularly in patients who are dialysis dependent.

APPENDIX

Other conference participants

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SUPPLEMENTARY MATERIAL

Table S1. Available evidence on the incidence and outcomes of HF after kidney transplantation.

Table S2. Selected studies evaluating kidney transplantation and reversal of structural and functional cardiac dysfunction.

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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