Circulation

AHA SCIENTIFIC STATEMENT

# Evaluation and Management of Kidney Dysfunction in Advanced Heart Failure: A Scientific Statement From the American Heart Association

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**ABSTRACT:** Early identification of kidney dysfunction in patients with advanced heart failure is crucial for timely interventions. In addition to elevations in serum creatinine, kidney dysfunction encompasses inadequate maintenance of sodium and volume homeostasis, retention of uremic solutes, and disrupted endocrine functions. Hemodynamic derangements and maladaptive neurohormonal upregulations contribute to fluctuations in kidney indices and electrolytes that may recover with guideline-directed medical therapy. Quantifying the extent of underlying irreversible intrinsic kidney disease is crucial in predicting whether optimization of congestion and guideline-directed medical therapy can stabilize kidney function. This scientific statement focuses on clinical management of patients experiencing kidney dysfunction through the trajectory of advanced heart failure, with specific focus on (1) the conceptual framework for appropriate evaluation of kidney dysfunction within the context of clinical trajectories in advanced heart failure, including in the consideration of advanced heart failure therapies; (2) preoperative, perioperative, and postoperative approaches to evaluation and management of kidney disease for advanced surgical therapies (durable left ventricular assist device/heart transplantation) and kidney replacement therapies; and (3) the key concepts in palliative care and decision-making processes unique to individuals with concomitant advanced heart failure and kidney disease.

**Key Words:** AHA Scientific Statements ■ heart failure ■ heart-assist devices ■ kidney diseases ■ kidney transplantation ■ renal replacement therapy



Optimal management of kidney function is crucial in the comprehensive care of patients with advanced heart failure (HF) to improve clinical outcomes and quality of life. Abnormal kidney function, either chronic kidney disease (CKD) or acute kidney injury (AKI), leads to retention of uremic solutes, which can have direct cardiotoxic effects. In addition, kidney dysfunction affects water, sodium, and other electrolyte homeostasis; leads to hormonal dysregulation (eg, renin-angiotensin-aldosterone system [RAAS] pathway, erythropoietin); and often leads to inappropriate and reactive adjustments of guideline-directed medical therapies in this high-risk population. Recent data estimate that more than two-thirds of patients with advanced HF have kidney dysfunction,[1] in part as a result of shared comorbidities, hemodynamic insults, dysregulation of neurohormonal pathways, and other biological derangements seen in both kidney disease and HF. This process can be further exacerbated if other systemic insults accompany HF disease progression (eg, hypotension, hypoxia, toxic exposures). The pathophysiology of cardiorenal syndrome has been reviewed extensively elsewhere and is summarized in Supplemental Figure 1.[2] The latest clinical guidelines and scientific statements have recognized the importance of this topic.[3–9]

This scientific statement focuses on the clinical management of patients experiencing kidney dysfunction through the trajectory of advanced HF, with specific focus on (1) the conceptual framework for appropriate

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evaluation of kidney dysfunction within the context of clinical trajectories in advanced HF, including in the consideration of advanced HF therapies; (2) preoperative, perioperative, and postoperative approaches to the evaluation and management of kidney disease for advanced surgical therapies (durable left ventricular assist device [LVAD]/orthotopic heart transplantation [HTx]) and kidney replacement therapies; and (3) the key concepts in palliative care and decision-making processes unique to advanced heart/kidney medical interventions for all individuals with concomitant advanced HF and kidney dysfunction (Supplemental Table summarizes key points addressed in this scientific statement).

## CONCEPTUAL FRAMEWORK FOR ASSESSING KIDNEY FUNCTION IN ADVANCED HF

### Evaluation of Kidney Function in Patients With Advanced HF

Clinicians frequently assess kidney dysfunction by estimated glomerular filtration rate (eGFR) using biomarker-based formulas. Each methodology of estimating eGFR, whether by incorporating serum creatinine, serum cystatin C, or timed urine collection, assumes a steady-state assessment, which may not be reliable in the context of advanced HF in all settings. Particularly during hospitalizations for decompensated HF, serum creatinine (not eGFR) is preferred in assessing day-to-day changes in kidney function. However, the use of serum creatinine to quantify longitudinal kidney function has significant limitations. For example, there may be a risk of underestimating the burden of kidney disease among patients with lower creatinine levels due to low muscle mass (or sarcopenia, a common scenario in advanced HF).[10] Alternatively, cystatin C could be measured in patients in whom there is concern about the accuracy of creatinine because of low muscle mass. Meanwhile, in the chronic setting, there may be an eGFR decline or rise in serum creatinine after the initiation and uptitration of several guideline-directed medical therapies. Particularly for sodium-glucose cotransporter-2 inhibitors, the initial eGFR decline was paradoxically associated with improvement in cardiovascular outcomes and a reduction in major kidney events.[11] Some research also suggested that urinary biomarkers of tubular injury may be discordant with dynamic changes in serum creatinine in acute HF.[12,13] Hence, using multiple testing modalities is the preferred approach (Figure 1).

To better characterize kidney dysfunction in the setting of advanced HF, we propose a conceptual framework with a more holistic assessment of the ability of the kidneys to adequately maintain solute and volume homeostasis and excretory and endocrine functions, as well as ascertaining whether there is any reversibility of kidney dysfunction (Figure 1). Although no formal protocols exist, assessing reversibility of kidney dysfunction entails a staged process in which contributing cardiovascular (hemodynamic) factors are alleviated (eg, congestion, kidney hypoperfusion, intra-abdominal hypertension) and the kidney response in several domains (glomerular function, tubular function) is objectively quantified (Figure 1). Patients with advanced HF may have acute chronic kidney injury, as well as both reversible and irreversible causes of kidney injury.

### Identifying the Extent of Irreversible Intrinsic Kidney Disease

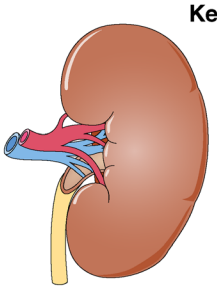
Intrinsic kidney disease is characterized by loss of nephron mass or individual nephron dysfunction involving the kidney tubule, glomerulus, interstitium, or its vasculature (Figure 1). In general, injury to these nephron components is not reversible. Evidence for this can be gleaned by functional and structural assessments. Parameters such as microscopic hematuria, acanthocytes, or cellular casts on urinalysis and urine sediment are key to identifying the causes of AKI or CKD (glomerulopathies, tubular injury), which may not be reversible after hemodynamic optimization. Proteinuria and albuminuria, both of which can be quantified from spot urine samples or 24-hour urine collections, are important markers of loss of glomerular integrity and intrinsic kidney disease and are independently associated with CKD progression, cardiovascular disease (especially HF), and mortality.[14,15] Kidney biopsies may provide prognostic information on the burden of irreversible atrophy and fibrosis; however, the risks (including bleeding and pain) versus benefits should be considered because obtaining a biopsy is an invasive and potentially high-risk procedure.

### Identifying Potentially Reversible Hemodynamics-Related Changes in Kidney Function

Hemodynamic derangements encountered in advanced HF such as reductions in forward flow with decreases in kidney arterial perfusion, increased venous congestion, external compression from elevated intra-abdominal pressures, and changes in drug therapy (eg, diuretics or RAAS inhibitors) can cause acute changes in kidney function, clinically measured by declines in eGFR, sodium excretion, and urine output (Supplemental Figure 1).[16] However, rises in serum creatinine in the context of decongestion do not necessarily carry adverse prognostic value in the acute setting and often reverse after hospitalization.[17] It is important to note that hemodynamics-driven changes in glomerular function should be distinguished from true tubular injury.[13] For example, with decline in kidney function during the course of treatment for advanced HF, placement of a pulmonary artery catheter

**Key concept for assessing kidney function and potential reversibility before LVAD and transplant**

**Key concept 1: assessing reversibility of GFR before LVAD and transplant**



$$\text{Total GFR} = \#\text{nephrons} \times \overbrace{[K_f \times (P_{gc} - P_B) - (\pi_{gc} - \pi_b)]}^{\text{Single nephron GFR}}$$

**a.** Permanent loss of #nephrons points towards CKD and is not reversible by LVAD implant and points to poor prognosis

**b.** Low single nephron GFR might relate to altered hemodynamics in advanced HF and are reversed by LVAD and do not indicate poor prognosis necessarily

**Favoring chronicity (low #nephrons)**

- Low GFR despite hemodynamic optimization of RAP, CI, and MAP
- Proteinuria/albuminuria: YES
- Altered kidney morphology on renal imaging

**Favoring reversibility (low Single nephron GFR)**

- Improved GFR with hemodynamic optimization of RAP, CI, and MAP
- Proteinuria/albuminuria: NO
- Normal kidney morphology on renal imaging

**Key concept 2: assessment of kidney function = more than GFR**

| Clinical assessments | Kidney Function | | | |
|---|---|---|---|---|
| | Glomerular structure and function | Nephron mass | Tubular function | Neuro-endocrine |
| eGFR based on serum creatinine and/or cystatin C | ✓ | | | |
| Measured GFR | ✓ | | | |
| 24 hour urine creatinine and urea clearance | ✓ | | | |
| Urine albuminuria and proteinuria | ✓ | | ✓ | |
| Kidney ultrasound | | ✓ | | |
| Urinalysis with sediment evaluation | ✓ | | ✓ | |
| Urine biomarkers (NGAL, KIM-1, NAG) | | | ✓ | |
| Urine Na avidity* | | | ✓ | ✓ |
| Serum electrolytes | | | ✓ | ✓ |
| Kidney biopsy | ✓ | | ✓ | |

**Figure 1. Assessing kidney function and potential reversibility before advanced HF therapies.**
CI indicates cardiac index; GFR, glomerular filtration rate; HF, heart failure; $K_f$, ultrafiltration coefficient; KIM-1, kidney injury marker-1; LVAD, left ventricular assist device; MAP, mean arterial pressure; NA, sodium; NAG, N-acetyl-β-d-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; NO, nitric oxide; $P_b$, hydrostatic pressure in the Bowman space; $P_{gc}$; hydrostatic pressure in glomerular capillary; $\Pi_b$, oncotic pressure in the Bowman space; $\Pi_{gc}$; oncotic pressure in glomerular capillary; and RAP, right atrial pressure. *Urine Na avidity can be assessed by fractional excretion of sodium or spot urine sodium (depending on clinical situation).

may better define the hemodynamic profile.[6,18,19] An acute increase in serum creatinine >1.5 times the baseline value or >50% drop in eGFR (especially with rising NT-proBNP [N-terminal pro-B-type natriuretic peptide] levels or elevated lactate levels) may identify a high-risk patient population who may benefit from hemodynamic evaluation.[20] Once such hemodynamic insults can be corrected, their kidney consequences should be theoretically reversible. Maintaining transkidney perfusion pressure (estimated by the difference between mean arterial pressure and central venous pressure) >60 mm Hg has been suggested as a reasonable goal.[21]

Hemodynamic abnormalities may trigger multiple neurohormonal pathways, including the RAAS and sympathetic and arginine vasopressin systems, resulting in declines in eGFR and electrolyte abnormalities and poor response to diuretics. Arginine vasopressin also stimulates urea nitrogen reabsorption, leading to a high

ratio of blood urea nitrogen to creatinine, which is independently associated with higher risk of mortality.[22,23] A salt- and water-avid state will tend to manifest in hyponatremia, which has been associated with higher risk of mortality among patients with HF.[24,25] Inadequate urinary sodium excretion, before or after loop diuretics (<50–70 mEq/L), may reflect heightened kidney sodium avidity.[26–28] In addition, patients with abnormalities in sodium handling by the kidneys tend to also have abnormalities in chloride handling, with observations that hypochloremia confers a strong risk for mortality.[29–31] In the kidney, decreased chloride delivery in the tubules to the macula densa triggers renin release from the juxtaglomerular apparatus, further exacerbating maladaptive RAAS stimulation with ever more sodium retention downstream (Supplemental Figure 1). Improvements in the neurohormonal milieu should be reflected in improvements in these clinical parameters and thus suggest reversibility of neurohormone-mediated kidney dysfunction.

Pharmacologically mediated eGFR reduction seen with various disease-modifying HF therapies (eg, RAAS inhibitors or sodium-glucose cotransporter-2 inhibitors) may instead be associated with long-term protective kidney effects through an acute reduction in intraglomerular pressure (manifested in the acute decrease in eGFR), which may attenuate functional nephron loss.[32] Therefore tolerating a modest eGFR decline and preventing unnecessary dose reduction or cessation of guideline-directed medical therapies (including loop diuretics in congested patients) are important strategies to reduce clinical cardiovascular events and CKD progression. De-escalating or withholding diuretic therapy to preserve eGFR can also lead to worsening congestion and adverse consequences. On the other hand, if the eGFR decline is sustained with other accompanying abnormalities despite substantial improvements in cardiac output, decongestion, and mean arterial blood pressure, later improvements in kidney function are unlikely and may portend further kidney injury with advanced HF surgical treatments and immunosuppressive drugs.

Kidney imaging can potentially be used to assess kidney function. The use of kidney sonography to assess kidney venous flow in congested states may provide insights into how systemic hemodynamics may affect changes in kidney blood flow because venous congestion may have a greater but reversible impact on eGFR decline than decreases in cardiac output.[33] However, there can be interindividual variability, and specialized training is needed for accurate assessment of kidney vein flow. Therefore, this is not currently considered standard of care. Moreover, changes in kidney venous flow have been associated with decreased diuretic responsiveness independently of eGFR[34] (Figure 1).[35] Last, other anatomic characteristics on kidney sonography can provide additional clues on reversibility. For example, if the kidneys are echogenic with cortical thinning or are small, this indicates chronicity and nephron loss.

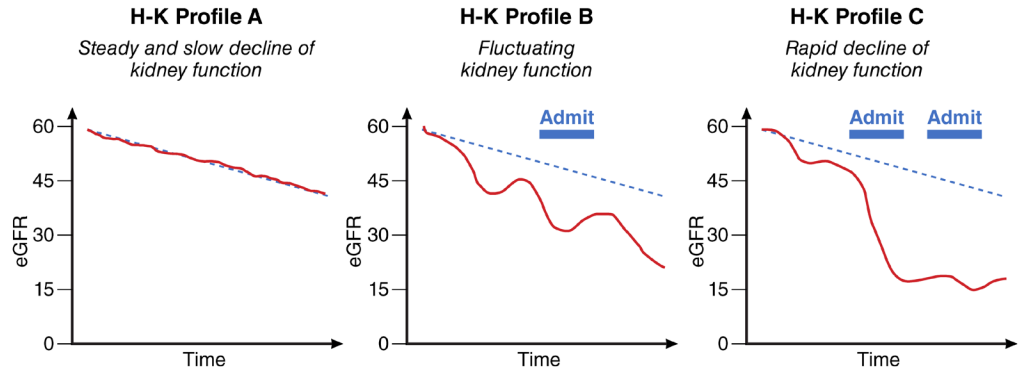
### Clinical Trajectories and Profiles of Kidney Dysfunction in Advanced HF

There is uncertainty about how to best incorporate prior trends of kidney function into the evaluation of candidacy for advanced HF surgical therapies. A baseline (eg, at the time of presentation) low eGFR is a clear and powerful prognostic predictor for adverse clinical outcomes in HF. However, current prediction models such as the Kidney Failure Risk Equation[36] have not been validated in advanced HF. In addition, variability in eGFR may identify a higher-risk patient population with diminished kidney reserve and permanent nephron loss in the context of worsening HF. Fluctuations in kidney function from visit to visit may reflect the kidney sensitivity of remaining functional nephrons to congestion or RAAS activity and may be seen as a sign of more advanced disease associated with worse outcome.[37–39] This fluctuation might stabilize with appropriate advanced HF therapies.[40] Different clinical heart-kidney profiles that leverage clinical features or laboratory abnormalities and their responses to medical therapy over time may serve as a useful construct to incorporate eGFR trajectories into prognostication and clinical decision-making (Figure 2). For example, patients may present with no kidney dysfunction (Profile A) or transient (HF-related) kidney dysfunction that is reversible with hemodynamic and medical optimization (Profile B) or persistent kidney dysfunction despite vasoactive drug or temporary mechanical circulatory support and necessitate kidney replacement therapy KRT (Profile C). Identification of such profiles may allow timelier referral of patients for appropriate medical or surgical treatment options to stabilize and maximize recovery of kidney function for the best long-term outcomes; however, future research is needed (Figure 2).

## CANDIDACY AND PERIOPERATIVE CONSIDERATIONS OF KIDNEY DYSFUNCTION FOR DURABLE LVAD

### Kidney Dysfunction Before LVAD Implantation

Kidney dysfunction before or at the time of durable LVAD implantation is strongly linked to poor outcomes, including postoperative kidney dysfunction, need for kidney transplantation (KTx), and mortality. A systematic review of 7 studies of patients who underwent LVAD implantation demonstrated a significant increase in all-cause mortality in patients with impaired preoperative kidney function,[41,42] especially when kidney dysfunction is severe enough to require KRT.[43–46] For example, lower preoperative eGFR as measured by iothalamate clearance and higher 24-hour urine protein levels were




| | H-K Profile A | H-K Profile B | H-K Profile C |
|---|---|---|---|
| Preserved eGFR/Cr | Yes | Fluctuating/reversible | No |
| Reversibility | N/A | Yes | Maybe |
| GDMT tolerance | Yes | Maybe | Maybe |
| Low cardiac output | No | No | Maybe |
| Venous congestion | No | Maybe | Maybe |
| HypoNa/HypoCl | No | Maybe | Maybe |
| Abnormal acid-base | No | Maybe | Maybe |
| Hemodynamic support | Adequate | Adequate | Inadequate |
| Kidney Replacement Therapy (KRT) | No | Maybe | Yes |

Moderate risk → High risk

Risk of poor kidney and heart failure outcomes

**Figure 2. Proposed heart-kidney (H-K) profiles related to kidney function trajectories, hemodynamics, and treatment responses and requirement.**

Cr indicates creatinine; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; H-K, heart-kidney; HypoCl, hypochloremia; HypoNa, hyponatremia; and KRT, kidney replacement therapy.

independent predictors of the need for postoperative KRT,[47] a finding that has been replicated in other studies.[48,49] Although no high-quality data exist with validated protocols for kidney function optimization before LVAD implantation (especially with more advanced CKD), a strategy of improving circulatory hemodynamic support with inotropes, vasodilators, diuretics, and temporary mechanical circulatory support to optimize kidney function to test reversibility in patients with questionable kidney function impairment before LVAD implantation may be reasonable (Figure 3).[50,51] This could allow identification of patients with reversible kidney function impairment who might have favorable outcomes after LVAD implantation. However, given the lack of data in this area, it is also possible that kidney function may worsen after mechanical circulatory support. A major challenge is differentiating whether preimplantation kidney dysfunction is related to hemodynamic derangements in advanced HF (affecting kidney perfusion pressure and single nephron ultrafiltration kinetics) or whether preexisting kidney dysfunction reflects irreversible loss of nephrons, as discussed previously (Figure 1). This uncertainty results in significant variability among centers in the tolerance of preexisting kidney dysfunction before durable LVAD implantation. Hence, systematic evaluation of the underlying mechanisms of kidney dysfunction may guide appropriate interventions to minimize postsurgical KRT (Figure 4).

The need for chronic KRT before LVAD implantation is associated with poor outcomes after LVAD implantation, including high perioperative and postoperative mortality and higher risk of complications such as thrombosis, bleeding, and infections. Therefore, decisions to proceed with LVAD in patients with irreversible severe kidney dysfunction or receiving KRT should be carefully considered, weighing the possible benefits versus risks and using a

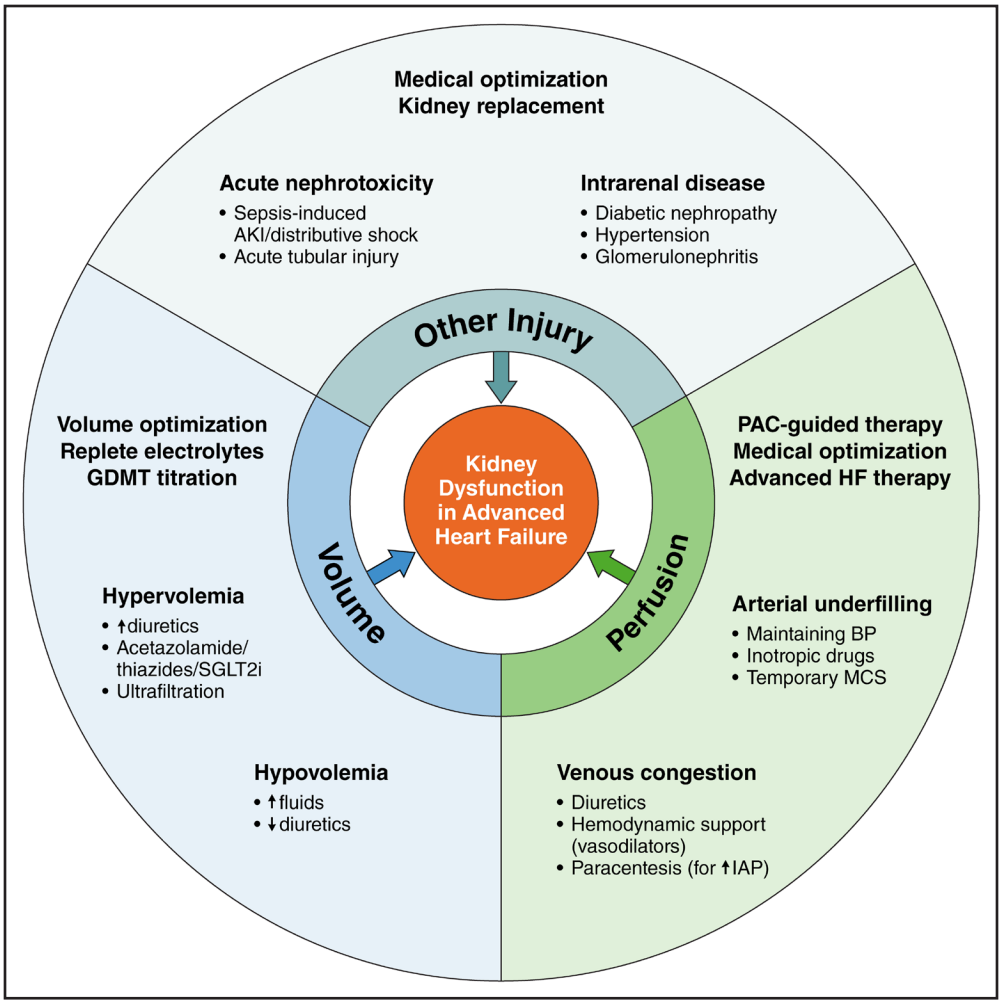



**Figure 3. Approach to assessment of kidney dysfunction in advanced HF.**
AKI indicates acute kidney injury; BP, blood pressure; GDMT, guideline-directed medical therapy; HF, heart failure; IAP, intra-abdominal pressure; MCS, mechanical circulatory support; PAC, pulmonary artery catheter; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

model of shared decision-making, especially without HTx candidacy.[7]

## Recovery of Kidney Function With LVAD

There is considerable heterogeneity in post-LVAD kidney function trajectories determined largely by baseline kidney function, hemodynamic versus intrinsic kidney disease before LVAD implantation, severity of HF before LVAD implantation, intraoperative factors, and change in muscle mass. An early improvement in eGFR after LVAD implantation followed by long-term decline in kidney function was reported in an INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) analysis, with poor survival associated with both marked improvement and worsening in eGFR that is illustrative of this conundrum.[52] In another INTERMACS analysis of kidney function trajectories after LVAD, early and transient improvement in eGFR was identified in 85% of 4615 patients. The remaining 15% of patients experienced sustained worsening of eGFR (10.1%), sustained improvement in eGFR (3.3%), or worsening eGFR followed by a variable course (1.7%) at 12 months.[53] Younger patients presenting in cardiogenic shock manifest a phenotype of sustained kidney function recovery after LVAD implantation, perhaps to larger preserved nephron mass.[54] A recent United Network of Organ Sharing analysis indicated that patients who underwent LVAD implantation as a bridge therapy to HTx did not have a higher risk of worse kidney outcomes after HTx or multiorgan transplantations compared with those who underwent HTx or multiorgan transplantation directly, regardless of baseline kidney function.[55]

## Post-LVAD Kidney Dysfunction

Postoperative AKI may present as new-onset kidney dysfunction or worsening of preexisting kidney dysfunction, especially with venous congestion.[56] AKI occurs in 11% to 45% of patients after durable LVAD implantation. Postimplantation AKI is associated with a higher risk of 30-day mortality, with particularly high risk in those who

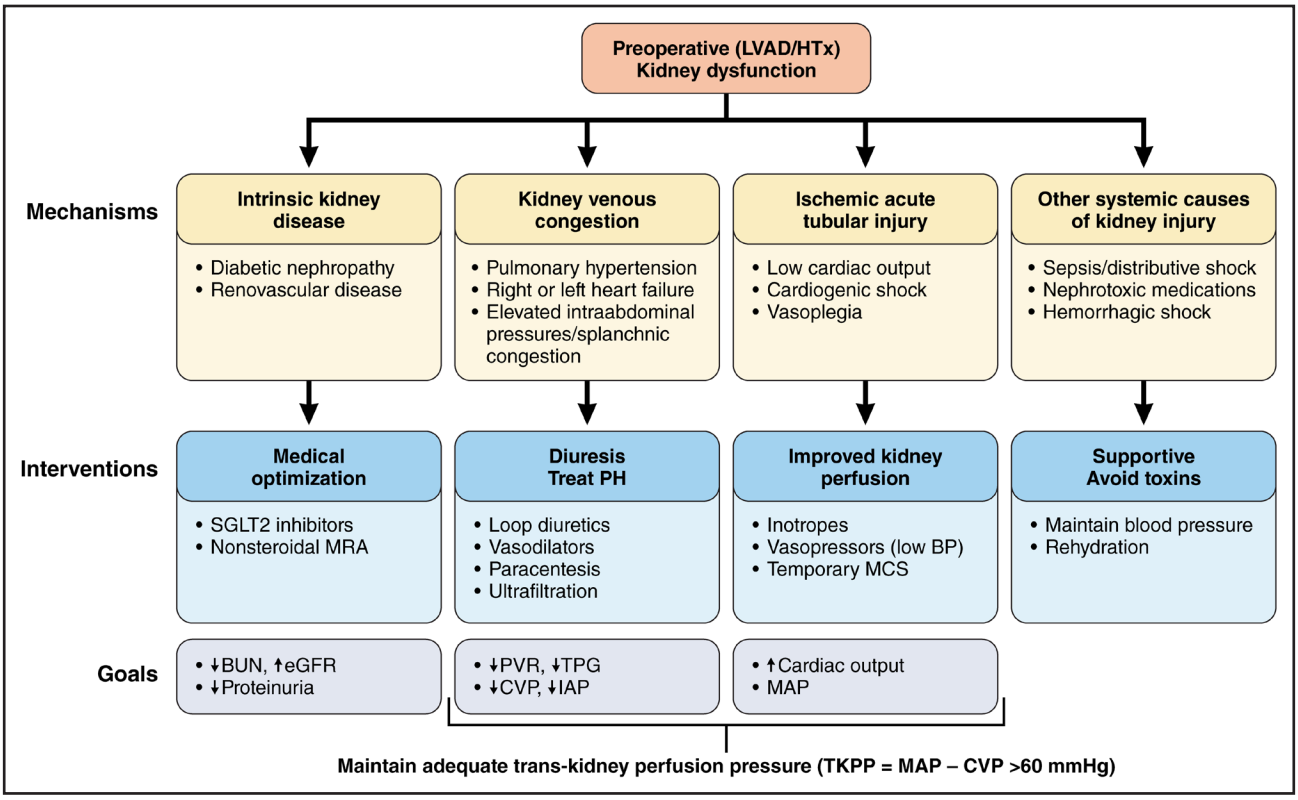



**Figure 4. Preoperative management of kidney dysfunction in advanced HF according to pathophysiological mechanisms.**
BP indicates blood pressure; BUN, blood urea nitrogen; CVP, central venous pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HTx, heart transplantation; IAP, intra-abdominal pressure; LVAD, left ventricular assist device; MAP, mean arterial pressure; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; SGLT2, sodium-glucose cotransporter-2; TKPP, transkidney perfusion pressure; and TPG, transpulmonary gradient.

required KRT. A recent meta-analysis estimated the incidence of AKI (using standardized criteria) in >63 000 LVAD recipients at 37%, with 13% of patients requiring KRT after LVAD implantation.[45] Given the dependency of glomerular filtration and tubular function on kidney blood flow, numerous factors can be associated with the development of AKI that can be classified into perioperative or postoperative factors (Figure 5). Perioperative factors associated with post-LVAD implantation AKI include duration of cardiopulmonary bypass, bleeding with need for transfusion, postoperative re-exploration, and intraoperative hypotension. Therefore, a balanced choice of whether to operate on additional valvular lesions (increasing cardiopulmonary bypass duration) and preoperative optimization of anemia and intraoperative hemodynamics is essential. Postoperatively, myriad surgical and medical complications may be associated with AKI, ranging from persistent volume overload/kidney venous congestion, infection, and bleeding driving acute tubular injury/necrosis to right ventricular (RV) dysfunction, postoperative pulmonary hypertension, external kidney compression (kidney tamponade) from intra-abdominal hypertension in the setting of volume overload, nephrotoxin exposure, congestive hepatopathy, and postoperative ileus.[51]

Preventing RV dysfunction is of particular importance because its presence will result in persistent venous congestion and the inability of the LVAD to generate sufficient systemic perfusion, both of which are hemodynamic factors that strongly influence kidney perfusion pressure. Data from the INTERMACS registry indicate that up to 24% of LVAD-implanted patients develop RV failure over time. Preventing and treating RV failure through hemodynamics-guided titration of inotropes and diuretics (targeting central venous pressure <10–12 mm Hg), use of pulmonary vasodilators, avoidance of hypotension, and early use of KRT and RV mechanical support (RV assist device) is important in the management of postoperative RV failure[57] and associated AKI.[58] Use of upfront RV assist device support in patients at risk of RV failure may be associated with a better outcome compared with the use of rescue RV assist device.[59]

## Maintenance KRT After LVAD Implantation

The need for KRT after LVAD implantation is associated with a poor prognosis compared with no need for KRT. A study of patients treated with dialysis from the US Renal Data System demonstrated a median

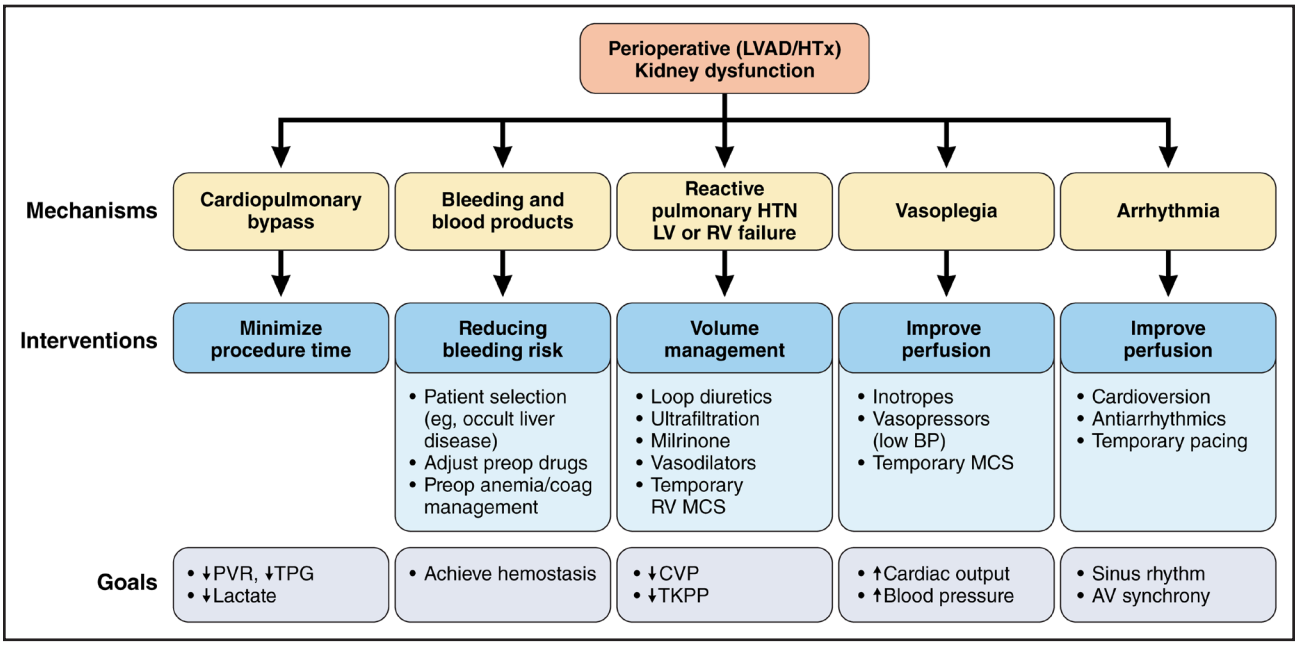



**Figure 5. Perioperative management of kidney dysfunction in advanced HF according to pathophysiological mechanisms.**
AV indicates atrioventricular; BP, blood pressure; CVP, central venous pressure; HF, heart failure; HTN, hypertension; HTx, heart transplantation; LV, left ventricular; LVAD, left ventricular assist device; MCS, mechanical circulatory support; PVR, pulmonary vascular resistance; RV, right ventricular; TKPP, transkidney perfusion pressure; and TPG, transpulmonary gradient.

survival of ≈3 weeks after LVAD implantation.[43] There are also small series reporting the outpatient hemodialysis in-center experience, which is challenging but feasible, and adjustments such as extended dialysis sessions or slower-volume removal may be needed.[60,61] Besides extremely poor survival, patients on hemodialysis have other increased risks associated with LVADs. First, there is increased risk of infections, likely related to central catheter placement for hemodialysis access. Other options such as arteriovenous grafts and fistulas could be considered, and the continuous flow of the current LVADs is not a contraindication for this. In addition, patients treated with dialysis have a paradoxical increased risk of bleeding (from platelet dysfunction) while also being prothrombotic (attributable to endothelial dysfunction). Last, patients treated with hemodialysis are at higher risk of hemodynamic disturbances given the high ultrafiltration rates needed to maintain euvolemia when hemodialysis is administered 3 or 4 times weekly. Meanwhile, peritoneal dialysis represents an attractive alternative dialysis option for patients with an LVAD given the smaller hemodynamic shifts, the lack of need for venous catheters, a more patient-centric approach, and perhaps a better chance at renal recovery given fewer repeated ischemic insults to kidneys compared with hemodialysis.[62–64] Although there are limited data, case reports have demonstrated that peritoneal dialysis, even in the absence of kidney failure, may decrease hospitalization days and lead to symptomatic improvement after LVAD.[63,65] Earlier LVAD models were less compatible with peritoneal dialysis given the need to sometimes surgically breach the peritoneum, risk of peritonitis, and subsequent driveline infections. With the current generation of LVADs, the risk of a direct device infection is much lower given the intrapericardial placement.[66]

The development of KRT-dependent kidney failure also results in lengthy hospitalizations and challenges in transition of care to the outpatient setting given the unpreparedness of most outpatient hemodialysis centers and outpatient home dialysis programs to manage KRT in patients with LVADs. Possible accepting dialysis units need to be identified early (ideally even before LVAD implantation) because not all geographic regions have dialysis units that are able to care for these patients. Furthermore, variability in staff training, unfamiliarity with pressure and flow alarms in LVAD machines, and appropriate responses to modify hemodialysis prescriptions, insurance coverage, and education on monitoring Doppler-based blood pressures during treatments contribute to delays in transitions of care for these patients. Often, the dialysis unit staff will undergo training from the LVAD team in preparation for accepting patients with LVAD. Furthermore, because many of the dialysis centers equipped to care for these patients are in select geographic regions or urban centers, transportation to and from the dialysis unit 3 to 4 times a week can be challenging for patients in certain locations. Home modalities, including peritoneal dialysis and home hemodialysis, may help bridge this gap but also require supportive home dialysis programs.

## CANDIDACY AND PERIOPERATIVE CONSIDERATIONS OF KIDNEY DYSFUNCTION FOR HTX

### Pretransplantation Kidney Dysfunction and Simultaneous Heart-Kidney Transplantation

Many patients being considered for HTx have preexisting kidney disease or develop kidney disease in their HF pre-HTx or post-HTx course. Early post-HTx instability precluding KTx is a poor prognostic marker, and median survival in these patients is only 2.9 years, with most mortality occurring within the first 30 days after transplantation.[67] In patients with preexisting kidney disease, a key decision is whether to proceed with HTx alone or simultaneous heart-kidney transplantation (sHKTx). Consensus statements recommend that all patients with advanced HF with a screening eGFR <45 mL·min$^{-1}$·1.73 m$^{-2}$ may be evaluated for sHKTx, especially with evidence of intrinsic kidney disease.[9,68] Although ≤30 mL is the criterion set forth by the United Network of Organ Sharing, owing to the challenges in estimating eGFR accurately and fluctuating eGFR in the setting of advanced HF, a closer evaluation by a combined nephrology and cardiology team is warranted. This will also provide a chance for more nuanced counseling on the risk of dialysis-requiring kidney failure after HTx and safety net versus living donor KTx. Retrospective data analyses suggested that in patients with eGFR <30 mL·min$^{-1}$·1.73 m$^{-2}$ or requiring KRT, sHKTx was associated with better survival than HTx alone.[67,69–71] The timing and decision to proceed with KTx after HTx depend on patient stability, hemodynamic status, and inotropic and vasopressor requirements. However, kidney outcomes after sHKTx remain suboptimal, especially when bridged with LVAD,[72,73] with a delayed kidney graft function rate of 27% to 37%[74] and a primary kidney nonfunction rate of 14% to 33%.[75,76] Risk factors for early kidney graft failure include difficult HTx surgery (eg, prior sternotomy, retransplantation), unfavorable hemodynamics (eg, elevated RV pressure), and delay (eg, long cold ischemia time).[75,77] Recently, the United Network of Organ Sharing has established eligibility criteria for sHKTx based on the severity and chronicity of kidney dysfunction (Supplemental Figure 2). These criteria serve as minimal eligibility criteria, and the decision to list a patient for sHKTx still depends on other factors such as the likelihood of kidney recovery without transplantation and overall transplantation candidacy.

The HTx and KTx teams should jointly develop immunosuppression, surveillance, and follow-up protocols (Table 1). In sensitized patients, a lymphodepleting induction regimen appears to be efficacious.[78] Some differences in maintenance immunosuppression exist between the 2 organ groups. For instance, mammalian target of rapamycin inhibitor–based immunosuppression is gaining widespread acceptance in HTx because of the favorable effects on transplantation vasculopathy,[79] whereas in KTx, mammalian target of rapamycin–based, non–calcineurin inhibitor (CNI)–containing regimens have been associated with increased rejection and proteinuria compared with the standard CNI-based regimens.[80]

### Outcome and Management of Kidney Dysfunction After HT

Kidney failure requiring dialysis complicates 13.4% of HTx within 90 days.[81] Post-HTx kidney failure is often associated with poorer long-term survival; independent predictors of post-HTx kidney failure include the use of preoperative extracorporeal membrane oxygenation, intra-aortic balloon pump and ventilators, and longer ischemia times.[82] Immediate perioperative and early postoperative causes of kidney failure are predominantly hypoxic tubular injury from a combination of arterial hypotension, venous congestion, vasopressor use, and anemia (Figure 3 and Table 2). Kidney recovery is negatively associated with the severity and duration of the insult, with hemodynamic optimization and reversal of anemia being key to this success. CNI nephrotoxicity is a contributing factor, and CNI-delaying induction protocols can be considered.[83] The clearance of certain active mycophenolate mofetil metabolites is reduced in kidney failure.[83,84] In the intermediate post-HTx course, enhanced recovery after surgery protocols (including standardized

**Table 1. Management Considerations for Kidney Dysfunction in Heart Transplant Recipients**

| Pretransplantation management | Perioperative management | Long-term management |
|---|---|---|
| Consideration and patient counseling for sHKTx candidacy if eGFR <45 mL·min$^{-1}$·1.73 m$^{-2}$, especially with intrinsic kidney disease<br>Pretransplantation optimization, including inotropes, vasodilators (maintaining adequate systemic blood pressure), or even temporary mechanical circulatory support | Early induction therapy to delay initiation of CNI<br>Pulmonary vasodilator for postoperative pulmonary hypertension<br>Early KRT to improve venous congestion in postoperative AKI and oliguria<br>Establishment of criteria to decide whether to proceed with kidney implantation in patients approved for sHKTx who experienced a complicated HTx | Avoid nephrotoxins and limit contrast exposure (PET scan for CAV surveillance instead of coronary angiography)<br>CNI-sparing protocols and early downtitration of CNI (or CNI-free protocol)<br>Tricuspid valve repair/replacement for severe tricuspid regurgitation and volume overload<br>Comprehensive evaluation of kidney function (including biopsy if needed) and consideration for KTx for progressive CKD |

AKI indicates acute kidney injury; CAV, cardiac allograft vasculopathy; CKD, chronic kidney disease; CNI, calcineurin inhibitor; eGFR, glomerular filtration rate; HTx, heart transplantation; KRT, kidney replacement therapy; KTx, kidney transplantation; mTOR, mammalian target of rapamycin; PET, positron emission tomography; and sHKTx, simultaneous heart-kidney transplantation.

**Table 2. Practical Considerations for Volume Management of Patients With Advanced HF Ineligible for Surgical Therapies**

| | Advantages | Disadvantages |
|---|---|---|
| Intravenous or subcutaneous loop diuretics | Can augment oral diuretics<br>Can be used daily or intermittently<br>Better bioavailability and patient response<br>Subcutaneous injection; limited dose of 80 mg furosemide | All require some frequent monitoring of electrolytes<br>Some kidney function required<br>Requires indwelling line or frequent insertion of peripheral catheters for intravenous delivery<br>Requires home health care<br>Site irritation<br>Expensive |
| Hemodialysis | Requires less patient autonomy<br>Ability to titrate ultrafiltration and clearance precisely | Intravascular access (fistula or tunneled line)<br>High rates of complications (bleeding, infections)<br>Hemodynamic fluctuations<br>Often need for heparin in dialysis circuit, which increases risk of bleeding<br>Less patient control<br>Time consuming/resource intensive |
| Peritoneal dialysis | Helps maintain residual kidney function<br>No need for intravascular access (lower infection risk)<br>Fewer large hemodynamic swings with ultrafiltration<br>No need for heparin with dialysis circuit<br>Able to liberate diet more<br>Able to be performed at home, avoiding need to travel to a dialysis center several times a week | Surgical catheter insertion/maintenance<br>Risk of peritonitis<br>Space needed at home to store supplies<br>Needs to be performed by patient or caregiver |

perioperative care pathways, optimized pain management, early mobilization, and early enteral nutrition) may help prevent additional insults to the kidney arising from systemic infections and other complications.

In the longer term, CKD may manifest in the form of hypertension, decreased kidney reserve, frequent acute kidney injuries, and progressively declining eGFRs. Management of CKD risk factors and CNI minimization should be utilized when possible in HT recipients.[85] A comprehensive kidney evaluation may include kidney ultrasound and urine studies. There should be a low threshold to perform kidney biopsies in these patients who have persistent signs of kidney dysfunction, and treatable causes (eg, BK virus infection) need to be ruled out.

Because of the high incidence of kidney failure and lack of certainty around sHKTx, patients accepted for HTx and sHKTx listing should be counseled on all the possible posttransplantation trajectories and prepare for the need for posttransplantation KRT and possible KTx evaluation. Despite advanced CKD, the majority of carefully selected sHKTx recipients demonstrate recovery of kidney function, and United Network for Organ Sharing data suggest that <10% will experience kidney failure requiring KRT in 5 years.[86] Similar to the liver transplantation experience,[87,88] a safety net policy is in place, granting priority access to deceased donor kidneys for HTx recipients who meet KTx eligibility criteria and are listed for KTx at 60 to 365 days after HTx, which provides a possibility for HTx candidates to rapidly receive a KTx even without potential living kidney donors.

## DECISION-MAKING AND COMANAGEMENT OF ADVANCED HF AND KIDNEY DYSFUNCTION

Early identification of patients with advanced HF and kidney disease is critical for timely interventions. The core elements include (1) engaging the patient and their family/caregivers, cardiologist/nephrologists, and all team members; (2) focusing on information and knowledge sharing and building consensus about treatment options; (3) clarifying goals of care and reaching agreement on treatment implementation; and (4) adapting care models within the context of health equity and consideration of social determinants of health. Patient and family engagement, including elicitation of patients' preferences, beliefs, and values, should be prioritized, especially in complex decision-making for advanced therapies, to achieve outcomes relevant to the patient. Cultural considerations and the patients' and families' values and beliefs should guide patient decision-making to foster communication, enhance clinician-patient relationships, and improve patient satisfaction.

Decision aids may be helpful in discussing treatment options with patients, and guided decision-making that aligns with patients' values and preferences is important throughout the continuum of disease. Options to pursue or not pursue advanced therapies should be presented,

although there are no specific decision aids for patients with concomitant advanced HF and kidney disease. Yet, approaches from each field individually may be applicable here. In nephrology, for example, the decision to pursue a nondialysis approach to manage kidney failure, called conservative care, is now presented side by side with more intense treatment options. Treatment de-escalation and deactivation, including withdrawal of dialysis or LVAD support, may be necessary in some cases and can be uncomfortable for patients and clinicians alike but should be considered in accordance with ethics guidelines. Involvement of palliative care specialists can assist with sensitive and candid discussions with the patient and caregivers before the initiation of advanced HF therapies or dialysis inclusive of time-limited trials and stopping rules to ensure patients' values, preferences, and comfort drive care as disease progresses.

### Palliative Management for Patients Ineligible for Advanced Surgical Therapies

The focus of care for patients with advanced HF and kidney dysfunction is to improve the quality of life, which can be challenging because of uncertain clinical trajectories. Palliative care is recommended for individuals with advanced HF and comorbid conditions such as kidney dysfunction, preferably from the time of initial diagnosis.[89] Palliative care involves interdisciplinary, patient- and family-centered care, symptom management, and decision support and can be provided by an interdisciplinary team of palliative care specialists in collaboration with trained specialty clinicians.[90,91] In concomitant heart and kidney failure, palliative care consultation assists with illness and prognosis understanding, symptom control, treatment decision-making, and advance care planning. Notably, management of symptoms of volume overload is important and can be achieved through either diuretics or dialysis. The availability of home, caregiver, and social support is also an important consideration in treatment decision-making. Palliative care, home care, and hospice can be valuable resources to improve patients' quality of life and alleviate caregiver burden, although financial resources and home care and hospice eligibility criteria may influence available treatment choices.[92] Some practical considerations for volume management of patients with advanced HF and kidney dysfunction deemed ineligible for advanced surgical therapies are listed in Table 2.

### Social Determinants of Health in Patients With Advanced HF and Kidney Dysfunction

People of underrepresented races and ethnicities and disenfranchised populations have a high burden of chronic HF and CKD.[93,94] Compounding this is limited access to treatment modalities for patients with advanced HF and kidney disease and the cost of medical therapies, even when such resources are available. Patients from underrepresented groups often do not receive early referrals to advanced HF and transplantation centers. Race and gender bias results in delayed referral and lack of acceptance into treatment programs for eligibility when LVAD and HTx evaluations are conducted, leading to the widening disparities in the allocation of advanced HF therapies.[95] An interdisciplinary team–based approach to care may be effective in addressing social determinants of health, especially for patients from historically underrepresented groups and patients in resource-limited health care settings.[96,97] Patient and family engagement and their preferences, beliefs, and values should be prioritized, especially for complex decision-making for advanced therapies.

## CONCLUSIONS AND KNOWLEDGE GAPS

Clinical evidence of kidney dysfunction in advanced HF calls for an interdisciplinary approach with longitudinal assessments to ensure individualized care. This may require careful evaluation of reversibility of heart and kidney dysfunction through timely drug and device therapies, appropriate considerations for risk-benefit assessment of advanced therapies, and early involvement of palliative care to aid in patient-centered decision-making. With clear knowledge gaps and the lack of standardization in

**Table 3. Future Research Directions for Patients With Advanced HF With Kidney Dysfunction**

| |
|---|
| Standardized approach and novel diagnostic tools, including use of kidney biopsies, for determining reversibility of kidney dysfunction in the setting of advanced HF |
| Best practices and standardization of hemodynamic optimization for stabilizing kidney function preoperatively |
| Better understanding of the other potential mechanisms contributing to kidney dysfunction in preclinical and clinical models of HF |
| Newer serum and histological biomarkers that may shed light on the presence of intrinsic kidney disease, AKI, AKI-to-CKD transition, and noninvasive markers of kidney fibrosis may help with more accurate prognostication and risk-benefit discussions in patients with kidney dysfunction in need of durable LVAD or transplantation |
| Use of peritoneal dialysis and home hemodialysis as a KRT modality in patients with LVADs |
| Strategies for non–catheter-based accesses for patients requiring hemodialysis with LVAD, including best practices for healing and maturation of arteriovenous graft |
| Prediction tools to predict kidney function trajectory more accurately after LVAD implantation and after HTx |
| Evaluation of HTx rejection risks with CNI-sparing immunosuppressive regimens such as belatacept |
| Decision aids to guide shared decision-making specific to patients with concomitant kidney disease and advanced HF |
| Interventions to improve access to specialized advanced HF care and transplantation for individuals from underrepresented backgrounds |

AKI indicates acute kidney injury; CKD, chronic kidney disease; CNI, calcineurin inhibitor; HF, heart failure; HTx, heart transplantation; KRT, kidney replacement therapy; and LVAD, left ventricular assist device.

diagnosing and managing kidney dysfunction in patients with advanced HF, further research efforts are needed to serve this patient population (Table 3).

## ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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