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Review

Management of heart failure in patients with end-stage kidney disease on maintenance dialysis: a practical guide

Megan S. Joseph[1], Maryse Palardy[1] and Nicole M. Bhave[1,*]

[1] *University of Michigan Medical School and Michigan Medicine, Department of Internal Medicine, Division of Cardiovascular Medicine, 1500 East Medical Center Drive, Ann Arbor, Michigan, 48109, USA*

*Correspondence: nbhave@med.umich.edu (Nicole M. Bhave)

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End-stage kidney disease (ESKD) and heart failure (HF) often coexist and must be managed simultaneously. Multidisciplinary collaboration between nephrology and cardiology is critical when treating patients with such complicated physiology. There is no "one-size-fits-all" approach to the evaluation of patients with new left ventricular systolic dysfunction, and diagnostic testing should be adapted to an individual's risk factors. Guideline-directed medical therapy (GDMT) for systolic heart failure should be employed in these patients. While limited randomized data exist, observational data and post hoc analyses suggest that GDMT, including renin angiotensin aldosterone system inhibitors, is associated with improved cardiovascular outcomes and can be safely initiated at low doses with close monitoring of kidney function in this population. Volume status is typically managed through ultrafiltration, so close communication between cardiology and nephrology is necessary to achieve a patient's optimal dry weight and mitigate intradialytic hypotension.Patient education and engagement regarding sodium and fluid restriction is crucial, and symptom burden should be reassessed following changes to the dialysis regimen.

Keywords

Heart failure; end-stage kidney disease; dialysis

1. Introduction

The prevalence of chronic kidney disease (CKD) and heart failure (HF) has been rising steadily over the past decade.The burden of HF in CKD is high, given the common soil of traditional cardiovascular disease risk factors such as diabetes, hypertension, and obesity, in conjunction with non-traditional risk factors unique to CKD such as inflammation, anemia, and disorders of bone and mineral metabolism. Rates of HF are higher in patients who have ESKD, with a point prevalence of close to 40% in Medicare beneficiaries. The presence of HF complicates the management of end-stage kidney disease (ESKD) and adds complexity to diagnosis, volume status assessment, and optimal pharmacologic management in these patients. Management of this patient population can be labor-intensive and requires collaboration between nephrology and cardiology, in addition to patient education and close clinical follow up. The goals of this review are to facilitate effective and safe guideline-directed medical therapy (GDMT) and to provide strategies for optimizing volume status, with a focus on heart failure with reduced ejection fraction (HFrEF) in ESKD.

2. Diagnostic considerations

Once it has been established that a patient has left ventricular (LV) systolic dysfunction, usually based on transthoracic echocardiogram (TTE) findings, further diagnostic testing should be tailored to the individual's risk factors. Ischemic heart disease is the most common etiology of cardiomyopathy in the population at large, though the test of choice to evaluate for coronary artery disease (CAD) depends on an individual's pre-test probability (He et al., 2001). In a young patient without other risk factors for CAD, coronary computed tomography angiography may be appropriate, as it has a high negative predictive value and can exclude anomalous coronary artery origins (Ponikowski et al., 2016). Nuclear imaging with positron emission tomography (PET) provides image quality superior to that of single-photon emission computed tomography (SPECT). Moreover, PET provides myocardial flow reserve data, which can be valuable in distinguishing normal myocardial perfusion from diffuse, multivessel ischemia (so-called "balanced ischemia" as can be seen on SPECT) (Sheikine and Di Carli, 2008). Myocardial flow reserve data can also identify coronary microvascular dysfunction, and in patients with moderate to severe kidney dysfunction, abnormal myocardial flow reserve has been associated with a higher rate of cardiovascular mortality (Murthy et al., 2012). However, cardiac PET is more expensive than SPECT and less widely available. Cardiovascular magnetic resonance (CMR) with vasodilator perfusion imaging and late gadolinium enhancement imaging is an excellent choice for comprehensive myocardial assessment, as it evaluates for ischemia, scar, and inflammation and is often considered the gold standard for LV and right ventricular systolic function quantification (Schwitter and Arai, 2011). Though group I gadolinium-based contrast agents were implicated as causative agents for nephrogenic systemic fibrosis among patients with CKD and ESKD in the past, group II agents such as gadobenate dimeglumine, gadobutrol, and gadoteridol appear to be safe for use in such patients (Soulez et al., 2015). The American College of Radiology recommends that ESKD patients receive dialysis as soon as possible after admin-

istration of gadolinium, though it remains uncertain whether this strategy provides additional benefit (ACR Committee on Drugs and Contrast Media, 2020). Stress echocardiography with exercise or dobutamine is often equivocal and therefore less helpful in patients with LV systolic dysfunction, as patients with non-ischemic cardiomyopathy may exhibit a less than normal hyperdynamic response to stress. Coronary angiography may be appropriate in patients with known CAD, angina or anginal equivalent symptoms, or abnormal noninvasive testing suggestive of CAD (Yancy et al., 2013). However, contrast-induced kidney dysfunction has been associated with increased all-cause mortality (Rihal et al., 2002). As such, in patients with advanced CKD who are not yet dialysis-dependent, strategies to minimize the use of contrast during percutaneous coronary interventions and pre-procedure hydration based on left ventricular end-diastolic pressure should be considered (Brar et al., 2014).

CKD is an important risk factor for valvular heart disease (VHD). In particular, patients with CKD tend to develop calcification of the aortic valve and mitral apparatus. In hemodialysis (HD) patients, the prevalence of VHD is estimated to be 14% versus 7% in the general Medicare population. Furthermore, aortic stenosis progresses more rapidly in patients with CKD (0.2 cm^2/year vs. 0.1 cm^2/year) (Perkovic et al., 2003). Valve lesions including aortic stenosis, aortic regurgitation, and mitral regurgitation can cause or exacerbate LV dilation and LV systolic and diastolic dysfunction, and we recommend treatment of these lesions according to current guidelines (Nishimura et al., 2017, 2014).

If underlying ischemia and valvular disease are excluded, diagnoses such as cardiac amyloidosis, hemochromatosis, sarcoidosis, thyroid abnormalities, and human immunodeficiency virus-associated cardiomyopathy may be considered based on risk factors. The clinical diagnosis of uremic cardiomyopathy, a condition which results from systemic hypertension and elevated intracardiac filling pressures, hinges in part on the timing of development of LV dysfunction with respect to decline in kidney function. High-output HF may occur in patients with arteriovenous fistulas created for HD access, and in other high-output states such as chronic, severe anemia. While routine right heart catheterization is not recommended, it may be valuable in certain patients who fail to improve or are unable to tolerate medical therapy due to hypotension or worsening kidney function, in order to clarify volume status and cardiac output (Yancy et al., 2013).

3. Pharmacotherapy

The major goals of medical therapy are to improve patient symptomatology, minimize hospitalizations, and improve survival. The presence of CKD in HF patients increases rates of complications and readmissions and tends to limit the use of GDMT. Despite the high prevalence of CKD in the HF population, the use of GDMT for HF worsens as CKD severity progresses. A large, prospective, longitudinal cohort study (IMPROVE HF) of 13,164 patients with chronic heart failure or recent MI with a left ventricular ejection fraction of $\leq$ 35% and CKD demonstrated that as CKD progressed, treatment with angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs) decreased (87.4% in stage 1 CKD vs. 57.9% in stage 4 CKD, $P < 0.001$). Patients with advanced CKD are also prescribed beta-blocker therapy less frequently than others (90.4% in stage 1 CKD vs. 86.2% in stage 4 CKD, $P < 0.001$) (Heywood et al., 2010).

3.1 Renin-angiotensin system (RAS) inhibitors

Large, randomized controlled trials have demonstrated that the use of renin-angiotensin system (RAS) inhibitors (ACE inhibitors and ARBs) is associated with decreased cardiovascular events, HF hospitalizations, and mortality among patients with HFrEF. Many of these studies excluded patients with advanced CKD, and providers are often concerned about risks of hyperkalemia, hypotension, and acute kidney injury in the setting of tenuous kidney function in this population. Importantly, there are no randomized controlled trials evaluating the benefit of RAS inhibitors in patients with HF and ESKD. However, subgroup analyses have shown similar cardiovascular benefits in patients with advanced CKD as compared to patients with normal kidney function (Hillege et al., 2006; Swedberg et al., 1990). Consequently, Kidney Disease: Improving Global Outcomes guidelines recommend specialist collaboration and close monitoring of potassium levels when using RAS inhibitors in patients with advanced CKD and advise against routine discontinuation of RAS inhibitors in patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2 (Herzog et al., 2011). In patients with progressive decline in kidney function and newly diagnosed HFrEF, we recommend initiating a discussion among cardiologist, nephrologist, and patient regarding risks and benefits of RAS blockade, with the caveat that drugs should be started at minimum dosages with close monitoring of eGFR and serum potassium. Once dialysis is initiated in such patients, initiation of RAS blockade is usually feasible if it has been deferred prior to that, though hyperkalemia may limit upward dosage titration. With the exception of fosinopril and ramipril, most ACE inhibitors are dialyzable, so it may be best to dose them after dialysis to maximize patient exposure.

Angiotensin receptor-neprilysin inhibitors (ARNIs) have recently become a standard component of treatment for patients with HFrEF. The PARADIGM-HF trial demonstrated that in patients with HFrEF, the use of sacubitril/valsartan was associated with significantly decreased mortality (17.0% vs. 19.8%, $P < 0.01$), hospitalizations for HFrEF, and symptoms and physical limitations of HF when compared with enalapril. It is important to note that hypotension and kidney dysfunction were common reasons for discontinuation of sacubitril/valsartan therapy, and exclusion criteria for the trial included an eGFR of less than 30 mL/min/1.73 m^2 or a serum potassium level of more than 5.2 mmol/L. Among patients with ESKD, the safety profile and efficacy of sacubitril/valsartan remains unclear (McMurray et al., 2014). A post hoc analysis of PARADIGM-HF was performed to evaluate outcomes in patient with and without CKD. CKD patients comprised 33% of the total cohort and had average eGFR 49 ml/min/1.73 m2. The benefit of sacubitril/valsartan over enalapril was similar in patients with and without CKD, including those with stage 3b CKD. Furthermore, the annual rate of decline in eGFR was significantly less with sacubitril/valsartan in both groups (Damman et al., 2018). These data suggest that initiation of sacubitril/valsartan in patients with advanced CKD is reasonable, provided that blood pressure and electrolytes can be monitored carefully.

3.2 Mineralocorticoid receptor antagonists (MRAs)

The use of mineralocorticoid receptor antagonists (MRAs) is associated with improved mortality and decreased hospitalizations in patients with HFrEF. In healthy patients, serum aldosterone is inversely related to extracellular volume (ECV). Typically, renin, angiotensin II, and aldosterone levels rise in response to low ECV and vice versa. However, aldosterone levels increase as eGFR decreases, so patients with CKD and ESKD have inappropriately high levels of aldosterone despite increased ECV, contributing to left ventricular hypertrophy and inflammatory effects. Small randomized controlled trials have shown that in patients with ESKD, the addition of MRAs is associated with decreased left ventricular mass (Bomback, 2016).

Despite the well-established benefits of MRAs in HFrEF, just as with RAS inhibitors and ARNIs, there is concern for hyperkalemia in patients with advanced CKD (Hein et al., 2019). The SPin-D trial randomized 129 patients on maintenance HD to placebo or spironolactone 12.5 mg, 25 mg, or 50 mg daily. After 36 weeks, similar rates of hyperkalemia and hypotension were observed with placebo and spironolactone 25 mg daily, though there was increasing hyperkalemia and hypotension with spironolactone 50 mg daily (Charytan et al., 2019). In further efforts to define the efficacy and safety of MRAs in this population, two randomized controlled trials are currently ongoing. The ACHIEVE trial (NCT03020303) is examining whether spironolactone reduces cardiovascular death and HF in dialysis patients. The ALCHEMIST trial (NCT01848639) is evaluating whether spironolactone reduces the composite endpoint of nonfatal myocardial infarction, acute coronary syndrome, HF hospitalization, nonfatal stroke, and cardiovascular death in dialysis patients with known cardiovascular disease or increased cardiovascular risk. In our opinion, use of an MRA is reasonable in a patient with ESKD, provided that hyperkalemia has not occurred recently and that the patient's nephrologist is in agreement.

3.3 Beta-blockers

Multiple trials have shown that use of beta-blockers in patients with HFrEF is associated with decreased morbidity and mortality, and some of these studies included patients with advanced CKD, confirming their benefit in this population. One randomized controlled trial evaluated the efficacy of carvedilol specifically in dialysis patients with HFrEF. One hundred fourteen patients were randomized to receive either carvedilol or placebo. Carvedilol use was associated with decreased all-cause mortality (51.7% vs. 73.2%, $P < 0.01$), cardiovascular deaths (29.3% vs. 67.9%, $P < 0.00001$), and hospitalizations (34.5% vs. 58.9%, textitP <0.005) (Cice et al., 2003). Though no prospective studies have compared different beta-blockers in the dialysis population, one retrospective study evaluated clinical outcomes among maintenance hemodialysis patients initiating carvedilol versus metoprolol. Treatment with carvedilol was associated with increased all-cause mortality and cardiovascular mortality. Post hoc analyses suggest that the mortality difference could have been driven by intradialytic hypotension, which was more common with carvedilol (Assimon et al., 2018). It is important to note that carvedilol is not dialyzable, whereas metoprolol is dialyzable (Table 1). Carvedilol was found to be superior to metoprolol tartrate in a HFrEF population in the COMET trial (all-cause mortality 34% vs. 40%, $P = 0.0017$) (Poole-Wilson et al., 2003). Therefore, if a twice-daily beta-blocker is to be used in a HFrEF patient with ESKD, we recommend carvedilol rather than metoprolol tartrate. If intradialytic hypotension is an issue, the first carvedilol dose of the day may be given following hemodialysis. Metoprolol succinate has a strong evidence base for use in HFrEF and may be used in ESKD, but at least in theory, it may be best to dose this drug after dialysis in order to maximize exposure for greatest cardiovascular benefit (MERIT-HF Study Group, 1999). While labetalol is often used as an antihypertensive in dialysis patients, it has not been shown to provide mortality benefit in HFrEF.

3.4 Other medications

Hydralazine and isosorbide dinitrate are often used in the ESKD population for afterload reduction and blood pressure control, since they are easily titratable and do not cause hyperkalemia. The A-HeFT trial demonstrated the mortality benefit of hydralazine plus isosorbide dinitrate in African-American patients with HFrEF (10.2% mortality in the placebo group vs. 6.2% in the active drug group, $P = 0.02$). Hydralazine-isosorbide was also associated with a decreased rate of first hospitalization for HF and an improvement in quality of life. It is important to note that while this trial had no kidney exclusion criteria, the rate of kidney insufficiency was low at 17.2% (Taylor et al., 2004).

In the pre-beta-blocker era, digoxin was shown to decrease hospitalizations in a HFrEF population, though no mortality benefit was observed (Digitalis Investigation Group, 1997). Since digoxin is renally cleared and has a narrow therapeutic index, the risks and benefits must be weighed carefully in the ESKD population, as digoxin can cause a variety of brady- and tachyarrhythmias (Chan et al., 2010). Finally, ivabradine may be considered in patients in sinus rhythm with HFrEF who are on maximally tolerated doses of beta-blockers, with resting heart rates of $\geq$ 70 beats per minute. This recommendation is based on the SHIFT trial, which found that ivabradine use was associated with decreased HF hospitalizations. However, patients with severe kidney disease were excluded from the study, and current HF guidelines specifically caution against using ivabradine in place of beta-blocker therapy (McCullough et al., 2016a; Rangaswami and McCullough, 2018; Swedberg et al., 2010; Yancy et al., 2016).

3.5 General principles of medical therapy for HFrEF in ESKD

Attention to detail and close follow up are essential to ensure safe and adequate dosing of cardiac medications in the dialysis population. Medication adjustments should be made carefully, and medication timing and dosages should take into consideration a patient's blood pressure response during dialysis and whether the medications are removed with dialysis. If a patient's volume status fluctuates over time, medication tolerance will likely be affected. For instance, in a patient who is volume overloaded when initially presenting with HFrEF, venous hypertension may be very difficult to control. As ultrafiltration is intensified, the blood pressure will fall, and tolerance for GDMT may decline, so medication dosages will likely need to be reduced. In patients with LV systolic dysfunction, GDMT should be favored over adjunctive anti-hypertensives, such as calcium-channel blockers or clonidine. It is common for the LV ejection fraction to fluctuate depending on pharmacotherapy, blood pressure control, and volume status.

Table 1. Heart failure medications in end-stage kidney disease.

Medication class	Medications	Dialyzability	Minimum Dose*
ACE inhibitors	Captopril	Dialyzable	1 mg TID (liquid)
	Enalapril	Dialyzable	2.5 mg daily
	Fosinopril	Not dialyzable	5 mg daily
	Lisinopril	Dialyzable	2.5 mg daily
	Quinapril	Dialyzable	2.5 mg daily
	Ramipril	Not dialyzable	1.25 mg BID
Angiotensin II receptor blockers	Candesartan	Not dialyzable	4 mg daily
	Losartan	Not dialyzable	12.5 mg daily
	Valsartan	Not dialyzable	20 mg BID
Angiotensin receptor-neprilysin inhibitors	Sacubitril/valsartan	Unknown	24/26 mg twice daily
Beta-blockers	Bisoprolol	Not dialyzable	2.5 mg daily
	Carvedilol	Not dialyzable	3.125 mg BID
	Metoprolol succinate	Dialyzable	12.5 mg daily
	Nebivolol	Not dialyzable	2.5 mg daily
Cardiac glycosides	Digoxin	Not dialyzable	62.5 mcg every 48 hours (recommended dosing in dialysis)
HCN blockers	Ivabradine	Unknown	2.5 mg BID
Mineralocorticoid receptor antagonists	Eplerenone	Poorly dialyzed	12.5 mg daily
	Spironolactone	Not dialyzable	12.5 mg daily
Vasodilators	Hydralazine	Not dialyzable	10 mg BID or TID
	Isosorbide dinitrate	Not dialyzable	10 mg TID

*This table provides the minimum possible dosages, based on dosage forms available in the U.S. For quinapril, eplerenone, and spironolactone, no dosage adjustments are provided in the manufacturer's labeling for ESKD.

ACE, angiotensin-converting enzyme; BID, twice daily; HCN, hyperpolarization-activated cyclic nucleotide-gate channel; BID, twice daily; TID, three times daily

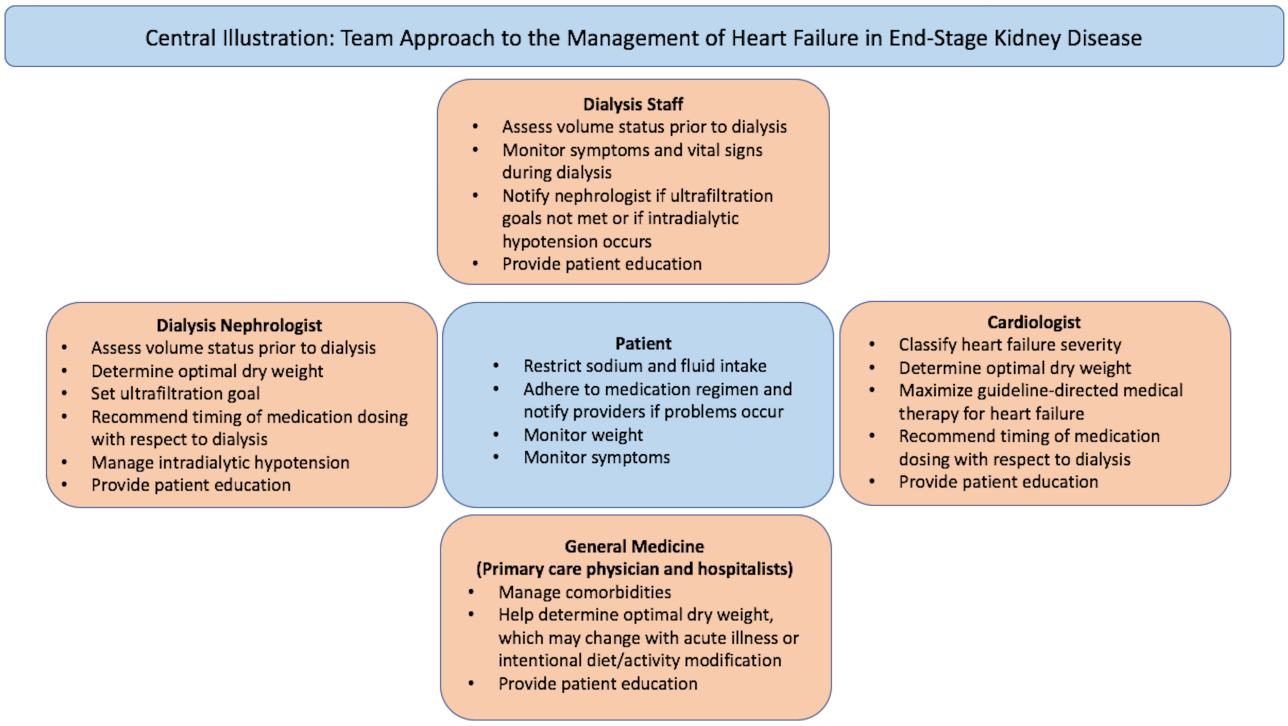

Figure 1. Central Illustration: Team approach to the management of heart failure in end-stage kidney disease. Multidisciplinary collaboration is critical when treating patients with such complicated physiology, as a combination of lifestyle modifications, medications, and dialysis is required.

Cases illustrating common challenges encountered in the care of ESKD patients with cardiovascular disease are presented in the Box .

4. Management of volume status with dialysis

Managing volume status in the context of HF and ESKD presents a unique set of challenges. Most patients with ESKD will develop HF symptoms if dialysis is not provided, and an individual's symptoms may fluctuate based on timing within the interdialytic period. As such, the traditional NYHA functional classification system is not an adequate rubric for describing disease severity in this population. As part of the Acute Dialysis Quality Initiative Workgroup, Chawla and colleagues proposed an alternative classification scheme for HF in ESKD, which considers whether an individual's symptoms are relieved by dialysis (Table 2). This patient-centered approach allows providers to identify HF that requires closer monitoring and potentially merits evaluation for advanced therapies. (Chawla et al., 2014).

Volume management in patients with ESKD and HF should be a multidisciplinary effort, as a combination of dietary modifications, diuretics, and dialysis is required (Central Illustration). Furthermore, acute HF exacerbation incrementally affects mortality in this population. Identifying and achieving an optimal dry weight is often challenging. A patient's pre-dialysis volume status should be determined based on a comprehensive clinical assessment, including the physical exam, weight gain between dialysis sessions, blood pressure, and symptoms. Dialysis staff typically look for peripheral edema and lung rales as signs of volume overload, but the subtler exam findings of jugular venous distension and a third heart sound can be helpful markers as well (Wang et al., 2005). Pre-dialysis hypertension may also be a sign of a volume-overloaded state. Finally, symptoms of dyspnea, bendopnea, poor appetite, early satiety, orthopnea, and abdominal distension, as well as interdialytic weight gain, can help guide fluid removal goals. During dialysis, patients should be monitored for signs that too much fluid has been removed, or that ultrafiltration has been done too rapidly. These signs include not only hypotension, but also tachycardia, lightheadedness, muscle cramps, and loss of appetite (Chou and Kalantar-Zadeh, 2017; Kalantar-Zadeh et al., 2009). When changes to the ultrafiltration goal are made, the patient's symptoms should be reassessed to determine whether an adequate dry weight has been achieved. Patient education regarding a low-sodium, fluid-restricted diet is also important, as greater interdialytic weight gain has been associated with increased all-cause and cardiovascular death risk (hazard ratio for all-cause death 0.67 for weight gain $<$ 1.0 kg vs. 1.25 for weight gain $\geq$ 4.0 kg) (Kalantar-Zadeh et al., 2009).

Volume removal with dialysis is often limited by intradialytic hypotension and cramping. Strategies to reduce hypotension include longer hemodialysis runs, lower dialysate temperature, and the use of medications such as midodrine and fludrocortisone (Table 3). Use of midodrine should be judicious, however, as it has been associated with significantly higher rates of mortality and hospitalization (Brunelli et al., 2018). Furthermore, use of midodrine prior to kidney transplantation has been associated with delayed graft function and graft failure in observational studies (Alhamad et al., 2016; Pottebaum et al., 2018).

In-center maintenance hemodialysis is typically performed

Box . Clinical vignettes highlighting diagnostic and therapeutic challenges encountered when managing patients with HF, HTN, and ESKD.

Case 1	Mr. X is a 39-year-old man with ESKD secondary to hypertension, on HD via arteriovenous (AV) fistula for 5 years. He was referred to cardiology clinic after a TTE, which was obtained as part of his evaluation for a kidney transplant, showed left ventricular (LV) dilation and LV ejection fraction (LVEF) 40-45%. TTE was also notable for prominent apical trabeculations. Because of his TTE findings and risk factors, the differential diagnosis for his cardiomyopathy included non-compaction cardiomyopathy, ischemic heart disease, and hypertensive cardiomyopathy. The first therapeutic intervention made was that his HD regimen was adjusted to target a lower dry weight. He subsequently underwent cardiovascular magnetic resonance (CMR), which revealed LVEF 61%, hypertrabeculation of the LV apex not meeting criteria for non-compaction cardiomyopathy, and no late gadolinium enhancement of the myocardium. His coronary angiogram was normal. Ultimately, he was felt to have a non-ischemic cardiomyopathy attributable to hypertension and ESKD, with recovered LVEF in the setting of improved loading conditions. He subsequently underwent kidney transplant without complications. Though his antihypertensive regimen was de-escalated post-transplant, he continued on carvedilol and low-dose lisinopril, given his history of LV dysfunction. Commentary: The improvement in this patient's LVEF was attributed to better volume management, highlighting the dynamic nature of LV dysfunction depending on volume status in ESKD. GDMT, including beta-blocker and angiotensin converting enzyme inhibitor, should be continued even after the LVEF has recovered. Finally, if his kidney function remains stable for at least 6-12 months after transplant, he may benefit from ligation of his AV fistula, as ligation has been associated with significant reduction in LV mass index by CMR and decrease in NT pro-B-type natriuretic peptide levels (Rao et al., 2019).
Case 2	Mr. Y is a 48-year-old man patient with a history of a bicuspid aortic valve with associated ascending aortic aneurysm and ESKD secondary to an unknown autoimmune disease who underwent a kidney transplant but subsequently developed graft failure and adult-onset type I diabetes mellitus. He was referred to cardiology clinic for management of resistant hypertension while on HD. Given his ascending aortic aneurysm, blood pressure control was felt to be critically important. He was initially maintained on clonidine 0.1 mg/24 hour transdermally, metoprolol succinate 100 mg daily, and extended-release nifedipine 60 mg daily. In an effort to improve blood pressure control, his antihypertensive regimen was adjusted to include carvedilol 25 mg twice daily, hydralazine 100 mg three times daily, losartan 25 mg daily, amlodipine 5 mg daily, and clonidine 0.2 mg/24 hour transdermally. Despite these changes, his blood pressure remained elevated, often as high as 180/100 mmHg. The cardiologist contacted his nephrologist, who felt that the patient was volume overloaded and suggested increased ultrafiltration. However, ultrafiltration was limited by cramping during HD, so no significant progress was possible. The patient elected to switch to PD, as he had done well on PD prior to his first transplant. Several weeks after the transition, his dry weight was decreased by approximately 5 kg, and home blood pressures were averaging 120/80 mmHg. Finally, as part of his kidney transplant workup, an evaluation for myocardial ischemia was recommended, given his history of diabetes mellitus and relatively sedentary lifestyle. A vasodilator nuclear stress test was ordered rather than a dobutamine stress echocardiogram, given his history of ascending aortic aneurysm; no evidence of ischemia was present. Commentary: If a patient's optimal dry weight is not identified and achieved, venous hypertension can be extremely challenging, if not impossible, to control. Modality for myocardial ischemia evaluation must be chosen based on an individual's risk factors and comorbidities.

Table 2. Acute Dialysis Quality Initiative XI Workgroup's proposed functional classification system of heart failure in patients with end-stage kidney disease (Chawla et al., 2014).

Heart Failure Class	Symptoms
1	Asymptomatic, with echocardiographic evidence of heart disease
2R	Dyspnea on exertion that is relieved with RRT/UF to a NYHA Class I level
2NR	Dyspnea on exertion that cannot be relieved with RRT/UF to a NYHA Class I level
3R	Dyspnea with ADLs that is relieved by RRT/UF to a NYHA Class II level
3NR	Dyspnea with ADLs that cannot be relieved by RRT/UF to a NYHA Class II level
4R	Dyspnea at rest that is relieved by RRT/UF to a NYHA Class III level
4NR	Dyspnea at rest that cannot be relieved by RRT/UF to a NYHA Class III level

RRT, renal replacement therapy; UF, ultrafiltration; NYHA, New York Heart Association; ADLs, activities of daily living

Table 3. Strategies to mitigate intradialytic hypotension.

Lengthen hemodialysis runs
Increase frequency of hemodialysis from 3 times weekly to 4-6 times weekly (may schedule one or more ultrafiltration-only runs per week)
Lower dialysate temperature (patient tolerability may be limited)
Hold anti-hypertensives the morning before dialysis (GDMT drugs may be given post-dialysis if tolerated)
Discontinuation of anti-hypertensives that have not been shown to provide mortality benefit in patients with heart failure (e.g., clonidine, minoxidil, calcium-channel blockers)
Use of midodrine or fludrocortisone (note that midodrine is associated with worse outcomes following kidney transplantation)
Switch from hemodialysis to peritoneal dialysis

GDMT, guideline-directed medical therapy for heart failure with reduced ejection fraction

three times per week, resulting in interdialytic intervals of 1 or 2 days. Some practitioners have advocated for more frequent hemodialysis, arguing that shorter interdialytic intervals are more hemodynamically favorable. In a retrospective review of 32,056 patients receiving hemodialysis three times per week, there was significantly higher all-cause mortality (22.1% vs. 18.0%, $P < 0.001$), mortality from cardiac causes (10.2% vs. 7.5%, $P < 0.001$), hospitalization for HF (29.9% vs. 16.9%, $P < 0.001$), and hospitalization for arrhythmia (20.9% vs. 11.0%, $P < 0.001$) on the day after the longer interdialytic interval of two days (Foley et al., 2011). The Frequent Hemodialysis Network Trial randomized 245 patients to receive frequent hemodialysis (six sessions per week) or conventional hemodialysis (three sessions per week). At the end of 12 months, more frequent dialysis was associated with lower mortality (16% vs. 28%, relative mortality hazard 0.54, 95% confidence interval 0.32-0.99) (Chertow et al., 2016). While more frequent hemodialysis may result in better cardiovascular outcomes, this approach is not always practical due to increased cost, constrained dialysis center resources, and limited patient adherence and enthusiasm (McCullough et al., 2016b).

Peritoneal dialysis (PD) is often preferred in patients with refractory heart failure, especially those with tenuous hemodynamics and moderate to severe LV systolic dysfunction, as it allows more gradual fluid shifts and therefore induces less hypotension. However, in the United States, PD is used by less than 10% of patients with ESKD on renal replacement therapy (Saran et al., 2019). Though there are no randomized trials examining different modalities of dialysis in patients with HF, observational data shows that initiation of PD is associated with significantly decreased body weight, reduced risk of HF hospitalization, and improved HF symptoms (Grossekettler et al., 2019). Additionally, loop diuretics can be used adjunctively in non-anuric patients. If euvolemia and adequate solute clearance cannot be achieved through PD, however, switching to hemodialysis may be necessary.

5. Conclusion

In summary, a collaborative approach is best when caring for patients with both ESKD and HF. Providers are often hesitant to prescribe GDMT in this population, particularly RAS inhibitors and MRAs, because of concerns about hypotension, hyperkalemia, and worsening kidney function. However, observational data suggest that with close monitoring these medications can be used safely and are associated with improved cardiovascular outcomes. Ideally, cardiologist, nephrologist, and patient should reach a consensus regarding medical regimen, dialysis modality, ultrafiltration goals, and optimal dry weight.

Abbreviations

ESKD: end-stage kidney disease; HF: heart failure; VHD: valvular heart disease; GDMT: guideline-directed medical therapy; CKD: chronic kidney disease; HFpEF: heart failure with preserved ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction; LV: left ventricular; TTE: transthoracic echocardiogram; CAD: coronary artery disease; PET: positron emission tomography; SPECT: single photon emission computed tomography; CMR: cardiovascular magnetic resonance; HD: hemodialysis; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; USRDS: United States Renal Data System; RAS: renin-angiotensin system; eGFR: estimated glomerular filtration rate; ARNI: angiotensin receptor-neprilysin inhibitor; MRA: mineralocorticoid receptor antagonist; ECV: extracellular volume.

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Conflict of Interest

The authors declare no conflicts of interest.

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