Management of Heart Failure in Advancing CKD: Core Curriculum 2018

Andrew A. House

Heart failure and chronic kidney disease have increasing incidence and prevalence owing in part to the aging population and increasing rates of hypertension, diabetes, and other cardiovascular and kidney disease risk factors. The presence of one condition also has a strong influence on the other, leading to greater risks for hospitalization, morbidity, and death, as well as very high health care costs. Despite the frequent coexistence of heart failure and chronic kidney disease, many of the pivotal randomized trials that guide the management of heart failure have excluded patients with more advanced stages of chronic kidney disease. In this Core Curriculum article, management of a challenging, yet not unusual, case of heart failure with reduced ejection fraction in a patient with stage 4 chronic kidney disease provides an opportunity to review the relevant literature and highlight gaps in our knowledge.

Complete author and article information provided before references.

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Case: *An 82-year-old man is referred for steadily worsening kidney function in the setting of chronic congestive heart failure (HF). His history is remarkable for long-standing hypertension and a myocardial infarction in his late 60s with Canadian Cardiovascular Society grade I stable angina. Coronary angiography shows no lesions believed to be amendable to percutaneous or surgical revascularization. He has been treated for HF with reduced ejection fraction (HFrEF) for approximately 5 years and has noted slowly increasing serum creatinine concentrations. His current medications include acetylsalicylic acid, 81 mg; bisoprolol, 2.5 mg; furosemide, 40 mg; candesartan, 8 mg; and atorvastatin, 40 mg, all once daily. He has no drug allergies, although treatment with an angiotensin-converting enzyme (ACE) inhibitor was discontinued due to cough. He still works 6 days per week running his own small business. He experiences at worst New York Heart Association (NYHA) class II symptoms and has edema to the shins, mostly by the end of the day and improved by morning.*

Physical examination reveals an elderly man with mild kyphoscoliosis, no distress, appearing his stated age. Blood pressure is 118/72 mm Hg with a heart rate of 64 beats/min, regular rhythm, and normal respiratory rate. He has no carotid bruits, and jugular venous pressure is ~4 cm above the sternal angle. Chest auscultation reveals some scattered crackles in the bases, and heart sounds are somewhat distant with a soft pansystolic murmur radiating to the left axilla and no extra heart sounds. Examination of the abdomen has unremarkable findings, and he has mild pitting edema to the lower shins with some chronic venous stasis changes to the skin. His extremities feel warm and are well perfused.

Laboratory tests reveal serum creatinine concentrations of 1.2 to 1.5 mg/dL for many years, but during the past 2 years, they have slowly increased to 2.0 to 2.2 mg/dL. Estimated glomerular filtration rates (eGFRs) are between 27 and 30 mL/min/1.73 m². Serum potassium concentrations are consistently <5.0 mEq/L, hemoglobin concentration is 12.0 g/dL, other chemistry results are normal, and urinary albumin-creatinine ratio (UACR) is 45 mg/g with no hematuria. An ultrasound of the kidneys shows poor corticomedullary differentiation, some cortical thinning, and no obstruction, consistent with chronic medical kidney disease. An echocardiogram reveals mild to moderate mitral regurgitation, mild aortic valve sclerosis with no gradient, and left ventricular ejection fraction (LVEF) of 38% with wall motion abnormalities consistent with ischemic heart disease.

Question 1: How common is it for a patient with HFrEF to have or develop concomitant chronic kidney disease (CKD) with eGFR < 60 mL/min/1.73 m²?

a) <5%
b) 5%-25%
c) 45%-65%
d) >90%

Question 2: Which one of the following statements is most correct?

a) With more severe stages of CKD, the risk for death in patients with HF increases significantly
b) Cardiac resynchronization therapy (CRT) is indicated in all patients with HFrEF, regardless of kidney function
c) CRT is indicated in all patients with CKD stages 1 to 3
d) Most studies of HFrEF included patients with CKD stages 1 to 4

For answers, see the following text.

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Epidemiology of Combined HF and CKD

The patient described in this scenario is unfortunately one of a growing number who live in the intersection of 2 increasingly prevalent diseases, HF and CKD. Both conditions have increasing incidence and prevalence owing in part to the aging population, but also due to increasing rates of hypertension, diabetes, or other cardiovascular and kidney disease risk factors. The presence of one condition also has a strong influence on the other, leading to greater risks for hospitalization, morbidity, and death, as well as very high health care costs. HF is very common, projected to affect more than 8 million Americans by 2030, and currently is implicated in 1 of every 9 deaths in the United States. There are approximately 1 million hospitalizations for HF each year in the United States, at a total cost of nearly $30.7 billion; this cost is projected to reach nearly $70 billion by 2030. CKD is also very common, with estimates suggesting that nearly 500 million people worldwide have CKD stage 3 or greater (eGFR < 60 mL/min/1.73 m^2). Due to declining death rates globally from such diseases as human immunodeficiency virus (HIV)/AIDS, malaria, and other infectious diseases, as well as cardiovascular diseases and many cancers, CKD has increased dramatically as a cause of both morbidity and mortality worldwide.

Individuals with heart disease as a primary disorder can experience reduced kidney function as a secondary disorder, and vice versa, or both can coexist based on shared risk factors or systemic disorders, so called cardiorenal syndromes (CRSs). CRSs are generally defined as disorders of the heart and kidneys in which acute or chronic dysfunction in one organ triggers acute or chronic dysfunction of the other. Box 1 presents the 5 phenotypes and their definition. Figure 1 shows a proposed schematic by which the heart and kidneys interact with one another, and disease of one organ can produce progressive dysfunction through hemodynamic, neurohormonal, and other modulating processes.

Box 1. Classification and Definitions of Cardiorenal Syndromes

General Definition of Cardiorenal Syndromes
Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other.

Acute Cardiorenal Syndrome (Type 1)
Acute worsening of cardiac function leading to decreased kidney function.

Chronic Cardiorenal Syndrome (Type 2)
Long-term abnormalities in cardiac function leading to decreased kidney function.

Acute Renocardiac Syndrome (Type 3)
Acute worsening of kidney function causing cardiac dysfunction.

Chronic Renocardiac Syndrome (Type 4)
Long-term abnormalities in kidney function leading to cardiac disease.

Secondary Cardiorenal Syndromes (Type 5)
Systemic conditions causing simultaneous dysfunction of the heart and kidney.

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Estimates of the prevalence of the coexistence of HF and CKD are challenging and subject to bias. For instance, observational studies typically collect a cohort of patients characterized by the presence of one of the diseases and then determine the prevalence of the other, leading to large variations in the estimates of coexisting CKD and HF. The Acute Decompensated Heart Failure National Registry (ADHERE) analyzed data from nearly 120,000

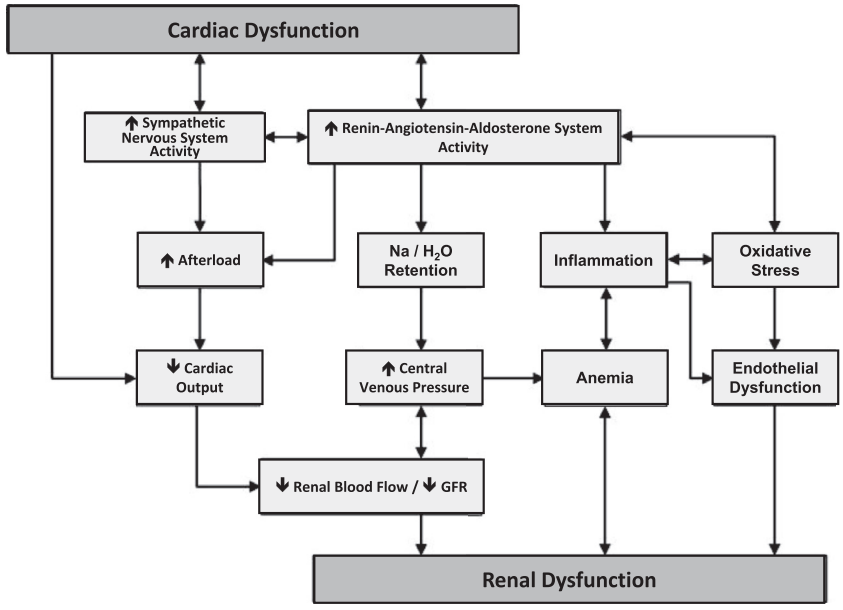

Figure 1. Postulated mechanisms underlying the interactions between the heart and kidneys. Arrows indicate pathways by which heart failure may lead to chronic kidney disease and vice versa. The relative importance of these and other mechanisms is not known, and many of these relationships are based on animal models. Abbreviation: GFR, glomerular filtration rate. Reproduced from Szymanski et al (*Heart Fail Rev.* 2012;17(3):411-420), which is copyright of the authors and was released under a CC BY-NC license by Springer Publishing.

hospitalizations for decompensated HF and found significant concurrent CKD on admission in more than half the cases. In a large meta-analysis of 25 prospective HF studies, patients with HFrEF and HF with preserved EF (HFpEF) were stratified into various levels of CKD using GFR estimates obtained from the CKD-EPI (CKD Epidemiology Collaboration) equation, and nearly 55% of both groups were found to have eGFRs < 60 mL/min/1.73 m^2 (hence the answer to Question 1 is [c]). There is a stepwise increase in mortality risk with each increasing CKD stage. For patients with better preserved eGFRs, the presence of albuminuria is also associated with adverse clinical outcomes and is present in nearly a third of patients with HFrEF or HFpEF. Looking at this the other way, determining the prevalence of HF in patients identified with CKD, the National Kidney Foundation–Kidney Early Evaluation Program (NKF-KEEP) examined more than 100,000 individuals screened for kidney disease. HF was reported by 1.6% of respondents with eGFRs > 120 mL/min/1.73 m^2, increasing with every increasing stage of CKD to an estimated prevalence of 14.9% for those with CKD stage 4 or higher (eGFRs < 30 mL/min/1.73 m^2). Using Medicare data and examining older enrollees with cardiovascular disease, the US Renal Data System (USRDS) estimates that >40% of patients with CKD have HF as a cardiac diagnosis, versus <20% of those without CKD, as shown in Figure 2.

CKD is also associated with the development of de novo HF. The Atherosclerosis Risk in Communities (ARIC) Study analyzed data from nearly 15,000 individuals free of HF at baseline whose kidney function was captured with serial estimates of GFR. Using individuals with GFRs ≥ 90 mL/min/1.73 m^2 as a referent group, the multivariable-adjusted relative hazard of incident HF was 1.10 (95% confidence interval [CI], 0.97-1.26) for those with eGFRs in the range of 60 to 89 mL/min/1.73 m^2 and 1.94 (95% CI, 1.49-2.53) for those with eGFRs < 60 mL/min/1.73 m^2. In other words, the presence of CKD at stage 3 or greater was independently associated with nearly a doubling in risk for incident HF.

ARIC investigators also estimated GFR using serum cystatin C concentrations ($eGFR_{cys}$) and measured UACR. At every level of eGFR, an increase in UACR was associated increased risk for de novo HF. The same was true when examining kidney function within each category of albuminuria, whereby decreasing eGFR was associated with increased risk for HF. The fully adjusted hazard ratios (HRs) ranged from 5.6 for those in the $eGFR_{cys}$ category of 45 to 59 mL/min/1.73 m^2 and UACR of 30 to 299 mg/g to as high as 14.0 for those with $eGFR_{cys}$ of 30 to 44 mL/min/1.73 m^2 and UACR ≥ 300 mg/g. This is demonstrated in Figure 3.

For many patients who present with both disorders, such as the patient in our example, it may be almost impossible to pinpoint which disease is primary and which is secondary or whether both are the result of shared pathophysiology or risk factors (eg, hypertension as in this case), and one could argue for inclusion into several of the different subtypes (CRS 2, 4, or 5). This illustrates an important limitation of the CRS classification and a likely reason why it has not been universally accepted or adopted.

Regardless of whether HF begat CKD or vice versa or both developed and progressed more or less simultaneously, the

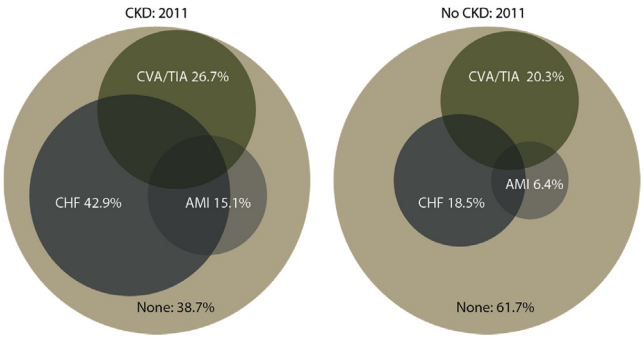

Figure 2. Cardiovascular disease in patients with or without chronic kidney disease (CKD) as of December 31, 2011. Point prevalent Medicare enrollees with cardiovascular disease, age 66 and older, with fee-for-service coverage for the entire calendar year. Abbreviations: AMI, acute myocardial infarction; CHF, congestive heart failure; CVA, cerebrovascular accident; TIA, transient ischemic attack. Reproduced from Figure 4.1.i of the US Renal Data System 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States (National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013).

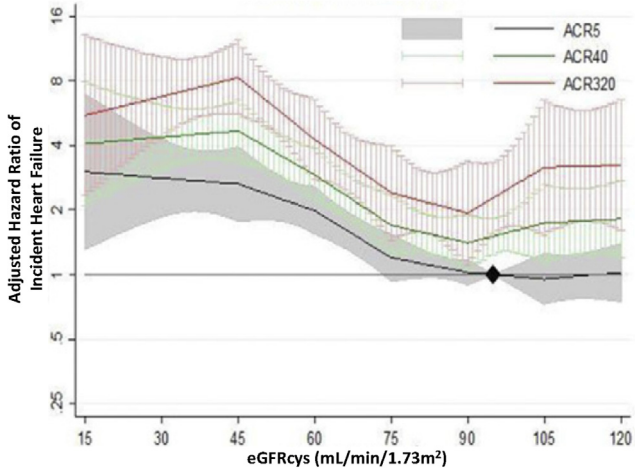

Figure 3. Adjusted hazard ratios with 95% confidence intervals of incident heart failure at varying degrees of albumin-creatinine ratio (ACR), along the continuum of estimated glomerular filtration rate based on cystatin C concentration ($eGFR_{cys}$). eGFR knots at 45, 60, 75, 90, and 105 mL/min/1.73 m^2. Reference group is $eGFR_{cys}$ of 95 mL/min/1.73 m^2 and ACR of 5 mg/g. Reproduced from Waheed et al (*Am J Kidney Dis.* 2012;60(2):207-216) with permission of the National Kidney Foundation, the copyright holder.

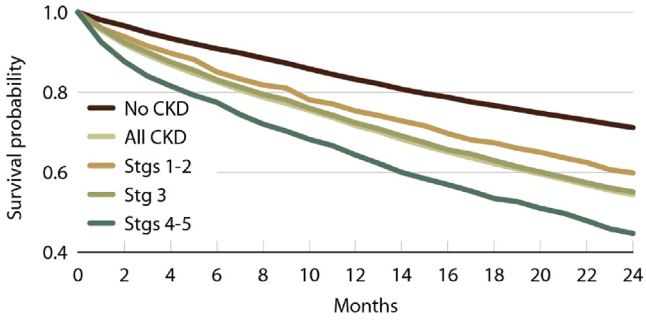

Figure 4. Unadjusted survival in patients with systolic heart failure, by chronic kidney disease (CKD) status, 2010 to 2011. Point prevalent Medicare patients identified with a heart failure diagnosis in 2009. Abbreviation: Stg, stage of CKD. Reproduced from Figure 4.7.i of the US Renal Data System 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States (National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013).

prognosis of our patient with HFrEF and CKD stage 4 is concerning. As illustrated by Figure 4, a strong graded relationship between HF mortality and CKD stage exists (meaning the answer to Question 2 is [a]). Furthermore, in a recent meta-analysis of 30 cohort studies comprising nearly 40,000 patients with HF, the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) investigators found that serum creatinine concentration was 1 of the 5 most powerful predictive variables associated with mortality, along with EF, age, NYHA class, and diabetes mellitus. In terms of creatinine, the association became evident at a serum concentration as low as 1.25 mg/dL.

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Management of HF and CKD

General Considerations

Returning to the case presented previously, how do we manage this patient with HFrEF and CKD? The goal of treatment for any patient with HF is to improve symptoms, function, and quality of life while reducing hospitalizations and mortality. Over the decades, the management of most patients with HFrEF has become clear and evidence based. The European Society of Cardiology (ESC) guidelines for patients with symptomatic HFrEF provide class I recommendations that include ACE inhibition and β-blockers in maximum-tolerated evidence-based doses as first-line therapy, with the addition of a mineralocorticoid receptor antagonist (MRA) for those who remain symptomatic. Substitution of an angiotensin receptor blocker (ARB) for an ACE inhibitor is acceptable for patients who cannot tolerate the latter, recognizing that ARBs do not have the consistent strength of evidence of ACE inhibitors. All this therapy is in conjunction with diuretics, which are used for symptoms or signs of volume overload and congestion. This may be followed by substitution of an angiotensin receptor neprilysin inhibitor (ARNI) for ACE inhibition in select patients and consideration of CRT in appropriate candidates. Beyond this is consideration for an implantable cardioverter defibrillator in those with persistently low EFs and the use of therapies for more select subgroups of patients that could include ivabradine, digoxin, hydralazine/isosorbide dinitrate, mechanical support, or a heart transplant. The patient in the previously presented case is complex and warrants multidisciplinary

care in a heart function clinic, if available. Increasingly, these clinics are integrating the decision making of cardiologists and nephrologists.

Evidence for Use of Angiotensin Blockade in CKD

Does the patient in this scenario, with eGFRs hovering around 30 mL/min/1.73 m^2, verging on stage 4 CKD, align with the patients for whom the guidelines are meant to apply? Unfortunately, many of the pivotal studies of HF management excluded patients with advanced CKD. Much of what we know from the literature is based on the experience of patients with moderate CKD (stage 3, representing eGFRs of 30-59 mL/min/1.73 m^2), who are reasonably well represented in randomized clinical trials. For instance, an analysis of SOLVD (Studies of Left Ventricular Dysfunction Treatment), which tested enalapril versus placebo in more than 2,500 patients with HFrEF and serum creatinine concentrations ≤ 2.0 mg/dL at baseline, found that enalapril significantly reduced hospitalizations for cardiovascular events and HF in patients with eGFRs < 60 mL/min/1.73 m^2, although the effect on all-cause, cardiovascular, and HF mortality was not improved to a statistically significant degree. The Survival and Ventricular Enlargement (SAVE) trial enrolled nearly 2,200 patients following myocardial infarction with HFrEF and serum creatinine concentrations ≤ 2.5 mg/dL at baseline and randomly assigned to treatment with captopril or placebo. Despite this exclusion, approximately a third of individuals had eGFRs < 60 mL/min/1.73 m^2, including approximately 200 with eGFRs < 45 mL/min/1.73 m^2. Study outcomes worsened with each incremental decline in kidney function, but the efficacy of captopril was maintained in the group with CKD stage 3 or greater. Other trials of ACE inhibitors (and ARBs) have yielded similar results, so the evidence for using ACE inhibition in patients with stage 3 CKD and HFrEF is compelling and consistent.

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) enrolled 253 patients with NHYA class IV HF to enalapril (ranging from 2.5 mg daily to 20 mg twice daily) or matching placebo, with dose reductions for hypotension, reduced kidney function, or other side effects. Enrollment in the trial was terminated early because of a compelling difference in the 180-day mortality rates of 44% for placebo and 26% for enalapril. There was also a significant improvement in symptoms, with more enalapril-treated patients improving NHYA class. Mean serum creatinine concentration at baseline was ~1.5 mg/dL and the study enrolled patients considered by the investigators to be at high risk for adverse effects because of serum creatinine concentrations in the range of 1.7 to 3.4 mg/dL. Given the age and other demographic characteristics of the study population, a significant number of participants had eGFRs in the severely reduced range (CKD stage 4, 15-29 mL/min/1.73 m^2). In a post hoc analysis of the data, serum creatinine concentrations of individuals in the enalapril group were found to increase to about 10% to 15% above baseline (commonly within the first several weeks), consistent with the recognized hemodynamic effects of ACE inhibition on GFRs. Following this increase, creatinine concentrations increased to a similar degree to the placebo group. Serum creatinine concentrations doubled in significantly more patients receiving enalapril, although comorbid conditions or hypotension explained most of these occurrences. In most individuals, creatinine concentrations returned to within 30% of baseline, including a number of patients who could continue on ACE inhibition at a lower dose.

The Valsartan in Heart Failure Trial (Val-HeFT) randomly assigned approximately 5,000 patients with NYHA classes II to IV HF to receive the ARB valsartan or placebo in addition to optimal HF therapy, which included ACE inhibition in >90% of patients. Like many other trials, patients with serum creatinine concentrations > 2.5 mg/dL were excluded from the trial. However, almost 60% of patients had eGFRs < 60 mL/min/1.73 m^2. Furthermore, 8% had proteinuria by dipstick assessment. This allowed for a secondary analysis of valsartan's efficacy for patients with CKD. Consistent with other studies, patients with both reduced eGFRs and proteinuria experienced the highest mortality and morbidity from HF, compared with patients with normal eGFRs and no proteinuria, and the remaining subgroups of patients faced intermediate risk. Adding valsartan to ACE inhibition did not affect overall mortality. However, the group with CKD randomly assigned to valsartan treatment experienced a rate of first morbid event (including death or HF hospitalization or intravenous vasoactive drug administration) that was statistically significantly lower.

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Evidence for Use of β-Blockers in CKD

In terms of β-blockers, one of the large early trials in HF was MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Chronic HF), a randomized study of nearly 4,000 patients with symptomatic HF and EF < 40%. There was no specific exclusion for kidney disease and in a post hoc analysis, the investigators categorized patients on the basis of eGFR and found that nearly 500 patients had baseline eGFRs < 45 mL/min/1.73 m^2. In this group, the HR for total mortality for metoprolol versus placebo was 0.41 (95% CI, 0.25-0.68), which compared favorably to those with eGFRs > 60 mL/min/1.73 m^2, for whom the HR was 0.71 (95% CI, 0.54-0.95). This demonstrated that metoprolol CR/XL was at least as effective in reducing death and hospitalization in the more advanced CKD group. A similar analysis was undertaken for participants of the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) of 2,600 patients with HFrEF and baseline serum creatinine concentrations < 300 μmol/L (<3.4 mg/dL), which likewise did not find a decrease in the efficacy of bisoprolol with decreased kidney function.

In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS), ~10% of study participants had normal kidney function (eGFRs ≥ 90 mL/min/1.73 m^2), ~48% had mildly reduced kidney function (eGFRs of 60-89 mL/min/1.73 m^2), and 39% had moderately reduced kidney function (GFRs of 30-59 mL/min/1.73 m^2). The primary outcome (composite of all-cause mortality or cardiovascular hospital admission) was significantly reduced in the nebivolol group with CKD, with an HR of 0.86 (95% CI, 0.74-0.99). There were similar point estimates in the groups with preserved kidney function and no evidence for interaction between kidney function and effect of nebivolol.

Not all β-blocker trials have been consistent in this regard. In a meta-analysis of randomized trials of carvedilol involving just over 4,200 patients, it was identified that ~60% of individuals had eGFRs < 60 mL/min/1.73 m^2 at baseline, and this group experienced a similar reduction in total mortality as the non-CKD group (HR, 0.76; 95% CI, 0.63-0.93), with comparable reductions in HF mortality and hospitalizations. This analysis also included 1,100 patients with eGFRs < 45 mL/min/1.73 m^2 (including ~200 patients with eGFRs < 30 mL/min/1.73 m^2), and unlike the mentioned studies, the HR for this group was 0.94 for total mortality (95% CI, 0.72-1.23), with similar results for cause-specific mortality and hospitalizations. It is also important to remember that some β-blockers have substantial renal excretion, such as atenolol, nadolol, or sotalol, and it may be wise to refrain from using these drugs in patients with advancing CKD, favoring agents with randomized controlled trial evidence instead.

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Evidence for Use of MRAs in CKD

Studies of MRAs have also excluded patients with more advanced CKD. The earliest large-scale trial of MRAs in more than 1,600 individuals with EFs < 35%, the Randomized Aldactone Evaluation Study (RALES), excluded patients with serum creatinine concentrations ≥ 2.5 mg/dL or hyperkalemia with potassium concentrations > 5.0 mEq/L. This led to the inclusion of significant numbers of patients with eGFRs < 60 mL/min/1.73 m^2, who experienced a similar significant reduction in all-cause death or hospitalizations for HF as those with higher baseline eGFRs. Similar results have been shown in HF trials with eplerenone. Patients with CKD randomly assigned to spironolactone in RALES were at greater risk for hyperkalemia and for experiencing an early reduction of eGFR ≥ 30%. This led to a greater likelihood of dose reduction or discontinuation but was offset by the reduction in mortality. Early after the publication of RALES, concerns were raised about the unsafe use of MRAs, especially because patients with HF generally receive ACE inhibition or ARB therapy in conjunction. Investigators found that prescriptions for spironolactone and rates of serious events related to hyperkalemia increased dramatically, and they estimated that its use may

be related to approximately 37,000 excess hospitalizations and 4,200 deaths annually in the United States. A very recent study using the Taiwanese National Health Insurance Research Database examined more than 27,000 patients with stage 5 CKD (eGFRs < 15 mL/min/1.73 m^2), of whom more than 1,300 were receiving spironolactone. This group experienced a significantly increased risk for death and hospitalization for HF after adjustment for multiple covariates, including underlying HF. Combined, these studies suggest that limiting patients to those with serum creatinine concentrations < 2.5 mg/dL (or eGFRs > 30 mL/min/1.73 m^2), normokalemia, and HFrEF should deliver the benefit of MRA therapy, but all patients, especially those with CKD, warrant very close monitoring to mitigate risk.

Finerenone is a newer nonsteroidal MRA with higher selectivity for the mineralocorticoid receptor than spironolactone and stronger binding affinity than eplerenone, with much more balanced distribution between heart and kidney tissue. It was studied in a trial entitled Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS) in just more than 1,000 patients with worsening HFrEF and type 2 diabetes mellitus and/or CKD (ie, eGFRs > 30 mL/min/1.73 m^2 in patients with diabetes and 30-60 mL/min/1.73 m^2 in patients without diabetes). Although the primary outcome of the study was a surrogate outcome, namely reduction in plasma N-terminal pro–brain natriuretic peptide (NT-proBNP) concentration, a secondary outcome was a composite of death, cardiovascular hospitalization, or emergency department visit for worsening HF. Patients were randomly assigned to 1 of 5 different finerenone dosing strategies or a control group receiving eplerenone. All groups achieved the primary surrogate outcome to a similar degree, and the highest finerenone dose showed a statistically significant decrease in the secondary composite end point. Except for the lowest dose group, there was a trend of reduction in the composite end point in the other finerenone groups over eplerenone. This did not come at the expense of risks for hyperkalemia or worsening kidney function, which were evenly distributed across the groups. Confirming the clinically important outcomes and safety in a larger trial will be a necessary next step and extending such a trial to include a subset with stage 4 CKD would better inform practice.

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Evidence for Use of ARNIs in CKD

The addition of a neprilysin inhibitor, sacubitril, to the ARB valsartan in a novel combination agent (LCZ696; referred to as an ARNI) is recommended in the ESC guidelines as a replacement for ACE inhibitor (or ARB) in patients who have symptomatic HFrEF with LVEF ≤ 35% and who remain symptomatic despite maximum-tolerated evidence-based doses of ACE inhibitors (or ARBs), β-blockers, and MRAs. PARADIGM-HF (Prospective Comparison of ARNI with ACE Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial) randomly assigned about 8,400 patients with HFrEF, half to enalapril and half to LCZ696. The trial was stopped early due to an overwhelming benefit of LCZ696 in terms of overall mortality, cardiovascular mortality, hospitalizations, and HF symptoms. Fewer LCZ696 patients experienced worsening kidney function or hyperkalemia. With respect to CKD, there are a number of noteworthy caveats. The study excluded patients with baseline eGFRs < 30 mL/min/1.73 m^2, and during the run-in period, any patient treated with enalapril or LCZ696 who had an eGFR that decreased to <30 mL/min/1.73 m^2 or had a >35% decrease in eGFR from baseline or potassium concentration ≥ 5.5 mEq/L were also excluded. Slightly more than half the patients were being treated with an MRA at baseline. Further research will be required to understand the role of this new agent in patients with HF with CKD stage 4 or higher, and given the ESC recommendations to add to patients receiving an MRA, it is likely that effects on serum potassium concentrations will require further scrutiny in postmarketing surveillance.

Additional Reading

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Safety Considerations and Hyperkalemia

The astute reader will by this time have noted that the patient in the case scenario has HFrEF and poses a challenge due to a lack of data in the more advanced CKD population. The management of patients with CKD with HFpEF is fraught with even greater uncertainty because there has yet to be a study to demonstrate important efficacy of any therapy for HFpEF in patients with normal kidney function or lesser stages of CKD, let alone the patient described in this case. The approach to balancing the

risks and benefits of applying evidence-based therapies to the advanced CKD population is therefore a different task when dealing with patients with HFrEF versus HFpEF, in which the latter would seemingly have very little to gain, at much greater risk for medication toxicities such as hyperkalemia.

CKD and HF, along with concomitant illnesses such as diabetes mellitus, blockade of the renin-angiotensin system with ACE inhibitors and/or ARBs, and use of MRAs (and now the addition of ARNIs) all heighten the risk for hyperkalemia, which has been associated with serious adverse outcomes in many studies. New agents have been developed to mitigate this risk. In the PEARL-HF (Evaluation of Patiromer in Heart Failure Patients) Study, patients with HF and high-normal potassium concentrations, many with eGFRs < 60 mL/min/1.73 m^2, were initiated on treatment with spironolactone and patiromer, an ion-exchange resin that increases fecal potassium excretion. Although this was a short-term study of 28 days, patiromer significantly lowered potassium and allowed a large number of patients with HF to tolerate a 50-mg spironolactone dose. The randomized open-label dose-ranging AMETHYST-DN (Patiromer in the Treatment of Hyperkalemia in Patients With Hypertension and Diabetic Nephropathy) Study examined patients with mostly stages 3 and 4 CKD (eGFRs, 15-60 mL/min/1.73 m^2) and diabetes, HF, or both for a longer period of 52 weeks. Patients were then treated with an ACE inhibitor, ARB, or both, with the addition of spironolactone if blood pressure was not reaching target. Approximately 35% of this group had a diagnosis of HF, tolerance of the study drug was good, and potassium was well controlled.

Sodium zirconium cyclosilicate (ZS-9) is another binding agent that traps potassium in the gastrointestinal tract. This too has been studied in a randomized open-label study, HARMONIZE (Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance), which included a subset of patients with HF with hyperkalemia, most receiving an ACE inhibitor, ARB, MRA, or some combination. ZS-9 demonstrated excellent management of hyperkalemia, though the exposure of 28 days was relatively short. In addition, ZS-9 has been associated with edema in some patients, and it exchanges sodium and hydrogen for potassium, leading to approximately 17, 34, and 50 mmol of additional sodium load for maintenance doses of 5, 10, or 15 g per day, respectively.

Further postmarket monitoring will be required to understand the long-term efficacy and safety of both these agents, including the possibility of interference of absorption of other medications, to understand fully their role in the management of patients with HF and CKD. The older agent, sodium polystyrene sulfonate, has had many decades of use for the management of hyperkalemia in a broad range of clinical situations despite a dearth of evidence and the potential delivery of an increased sodium load. A small clinical trial demonstrating short-term efficacy in the treatment of mild hyperkalemia of CKD does not provide adequate evidence for its long-term use in patients with CKD with HF. It has been speculated that some of the benefit of MRAs could be mediated through a high potassium concentration itself. Others have posited that a high potassium concentration leads to a further compensatory increase in aldosterone, which has been implicated in the progression of both heart and kidney disease. Hence lowering potassium concentrations through binding resins or other means should provide a further reduction in aldosterone concentrations and additional benefits beyond the safety of lowering potassium concentrations. Only long-term randomized trials will discern the benefits or harms of potassium reduction in this context.

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Complexities of Conventional HF Treatments in More Advanced CKD

Case, continued: *The patient in this scenario is currently being treated with bisoprolol, 2.5 mg, once daily; candesartan, 8 mg, once daily (he is intolerant of ACE inhibitors); and furosemide, 40 mg, once daily, with good control of congestive symptoms and edema. His blood pressure is not low, and his heart rate is well controlled. Most importantly, his symptoms are very well controlled with excellent functional capacity. As the nephrologist seeing this patient in consultation, you believe that given the lack of symptoms and borderline kidney function, the risk of MRA outweighs the benefits. You provide him with "Sick Day Medication List" instructions and advise a modest sodium restriction, strict avoidance of nonsteroidal anti-inflammatory drugs, and modest fluid restriction.*

Some months later, the patient is admitted to the hospital with severe community-acquired pneumonia and acute kidney

injury, with a serum creatinine concentration reaching ~5.0 mg/dL and serum potassium concentration of 6.3 mEq/L. His diuretic and ARB treatment are withheld, and he receives gentle fluid resuscitation and medical management of hyperkalemia. He improves, but his creatinine concentration on discharge is now 2.8 mg/dL. He returns to your clinic for review 7 days after discharge and the creatinine concentration is unchanged, with a potassium concentration of 5.5 mEq/L. He has NYHA class III symptoms, his weight has increased by 4 kg, and he has pitting edema to the knees with crackles in the lungs and an elevated jugular venous pulse. His blood pressure is 138/75 mm Hg with a pulse rate of 68 beats/min and regular. Extremities seem well perfused. Repeat echocardiography indicates that EF has declined to between 30% and 35%, with no other new findings.

Question 3: What effect(s) does withdrawal of ACE inhibition have for patients with HFrEF and CKD?

a) Immediate relative increase in eGFR
b) Immediate relative increase in cardiac function
c) Slow progressive decline in cardiac function
d) Immediate increase in serum potassium concentration
e) Both a and c
f) Both b and d

For answer, see the following text.

The management of this patient is now becoming more complex. Withdrawal of ACE inhibition and diuretics for patients who develop acute kidney injury and hyperkalemia is not evidence based, yet given their mode of action, conventional wisdom and national guidelines suggest that this is a reasonable course of action. Nonetheless, there is evidence from randomized controlled trials that withdrawal of ACE inhibition leads to a slow but significant deterioration in heart function in patients with HF. The approach taken in this patient in the hospital seems prudent in the short term; however, he is now presenting with symptoms of worsening congestion and fluid overload, with kidney function that has not returned to baseline. The ongoing management of this patient, given the lack of clear evidence base in this population, will require some interpretation and extrapolation from the existing literature.

Reintroduction of furosemide treatment to relieve the patient's symptoms of congestion would be a reasonable approach. Whether this warrants admission to the hospital or close outpatient follow-up is debatable, but his worsening kidney function may at this point be related to worsening heart function secondary to recent pneumonia and withdrawal of angiotensin blockade, but could also be exacerbated by high venous pressure and volume overload. Aggressive diuresis to improve congestive symptoms and decrease venous pressure needs to be counterbalanced by the potential to aggravate electrolyte imbalances, activate neurohormones, lower blood pressure, and worsen kidney function. Given the significant decline in kidney function, with an eGFR of ~20 mL/min/1.73 m^2 and recent significant hyperkalemia with an ongoing potassium concentration of 5.5 mEq/L, an MRA is not an optimal choice, and a loop diuretic will have greater efficacy than a thiazide, though combinations of agents may be required. The patient may require hospitalization or use of parenteral diuretics in a specialized HF clinic if he does not respond adequately to oral diuretics. Although high-quality randomized controlled data for the use of diuretics other than MRAs in HF are surprisingly limited, there are randomized controlled trial data from the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) indicating the utility of a stepped pharmacologic approach to patients with acute decompensated HF, for which therapy using parenteral diuretics and other medications in an organized fashion was reported to be superior to ultrafiltration for preserving kidney function, with a comparable degree of weight loss.

When the patient has stabilized in terms of congestive symptoms, the next decision will be whether to reintroduce angiotensin blockade. This would seem to be an appropriate choice given the evidence of benefit, admittedly weaker though in the setting of more advanced CKD. If this route is chosen, it is clear that very close clinical and laboratory monitoring will be required. The mechanism of action of an ARB in this patient is such that one should anticipate a decline in eGFR. This is particularly true in the presence of other risk factors such as age and diuretics and has been a significant finding in many studies of ACE inhibition and ARBs for HFrEF (thus the answer to Question 3 is [e]). It is important to remember that a decrease in GFR does not equate to kidney damage per se, and there are data from clinical trials examining the use of ACE inhibitors to prevent the progression of a variety of kidney diseases that demonstrate that serum creatinine concentration increases of up to 30% that stabilize within the first few months of therapy strongly associate with preservation of kidney function over the longer term. This supports the recommendation that a 30% increase in creatinine concentration (or decline in eGFR) that stabilizes be tolerated, otherwise the risks of therapy may start to outweigh benefits.

The other consideration for this patient is that his eGFR has now declined well into stage 4 CKD, and the evidence supports transition to a multidisciplinary clinic focusing on treating or avoiding CKD-related complications such as anemia and bone mineral disease and provision of tailored dietary advice, as well as education, planning, and shared decision making around renal replacement options, akin to the goals of the multidisciplinary heart function clinic. Although the Kidney Failure Risk Equation would indicate relatively low risk for progression to kidney failure in the next 2 years, data from the Initiating Dialysis Early and Late (IDEAL) Study indicate that volume overload is a very common reason for patients randomly assigned to delayed initiation to require an earlier start than planned.

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Options for Intolerance to Angiotensin Blockade in Advanced CKD

Case, continued: *Furosemide treatment is initiated at a dose of 40 mg twice daily as an outpatient, and the patient is provided instructions on a flexible diuretic regimen to achieve a target weight of 63 kg. His symptoms of volume overload have improved significantly and edema is limited to just above the ankles, though he remains easily fatigued and is unable to run his business. When he returns to the clinic, he has blood pressure of 136/84 mm Hg and heart rate of 64 beats/min; jugular venous pulse is no longer elevated and chest sounds are clear. His serum creatinine concentration is 3.0 mg/dL and potassium concentration is 4.9 mEq/L. Hemoglobin concentration is 11.0 g/dL, calcium and phosphate concentrations are within the reference ranges, and ferritin concentration is 150 µg/L with transferrin saturation of 18%.*

You decide to reinitiate candesartan therapy at a lower dose of 4 mg, arrange for weekly blood tests to monitor effects on kidney function and electrolytes, and arrange a return to a multidisciplinary CKD clinic. The patient is also reassessed by his cardiologist, who has concerns about the risks and benefits of an implantable cardioverter defibrillator and does not believe he meets electrocardiographic criteria for CRT.

Upon return to the clinic, you learn that the patient is feeling increasing fatigue, his blood pressure is 112/79 mm Hg with a heart rate of 58 beats/min, and the rest of his clinical examination findings are unchanged. However, serum creatinine concentration has increased abruptly to 3.9 mg/dL, eGFR is 13 mL/min/1.73 m², and potassium concentration is 5.6 mEq/L.

Question 4: What is the best option at this time?

a. Decrease furosemide to once daily
b. Decrease candesartan dose to 2 mg, as well as above
c. Discontinue candesartan and start isosorbide dinitrate and hydralazine combination therapy
d. Continue the present regimen and initiate treatment with dialysis

For answer, see the following text.

The patient's condition is becoming increasingly difficult to manage. Reintroduction of an ARB, although it was at a reduced dose to what he had received previously, has led to a significant increase in serum creatinine concentration and reemergence of hyperkalemia and at this point should be abandoned. Although the subgroup of patients with HF with true intolerance of ACE inhibitors and ARBs has not been the subject of specific studies, they remain a substantial challenge. As an alternative, the fixed-dose combination of isosorbide dinitrate and hydralazine has been investigated in populations in which CKD is not an exclusion criterion. For example, the African-American Heart Failure Trial (A-HeFT) found an early and persisting benefit of this combination, taken 3 times daily, when used to supplement standard therapy in a study of more than 1,000 African American patients with HFrEF and NYHA class III or IV symptoms. The A-HeFT investigators found a 37% improvement in event-free survival ($P < 0.001$) and a 39% reduction in risk for HF hospitalization ($P < 0.001$). Estimates of risk reduction were about the same in a variety of subgroups, including patients with CKD, who made up ~17% of the study group. Although in previous trials this drug combination was less effective than enalapril with respect to mortality and morbidity, the Vasodilator–Heart Failure trials (V-HeFT I and II) showed hydralazine and isosorbide dinitrate taken 4 times daily to be significantly better than placebo for mortality. Detailed information for kidney function is lacking in these older trials, so firm recommendations for their use in patients with significant CKD cannot be made. However, in practice, their use seems justifiable when faced with patients who cannot tolerate ACE inhibitor or ARB treatment of HF (thus, the answer to Question 4 is [c]).

The cardiologist's hesitancy about the appropriateness of CRT and an implantable cardioverter defibrillator is understandable given the dearth of good-quality evidence in patients who have moved beyond stage 3 CKD.

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Management of Anemia and/or Iron Deficiency in HF and CKD

Case, continued: *The patient discontinues candesartan treatment and is started on hydralazine and isosorbide dinitrate, starting at a dose of 100 mg of the former and 60 mg of the latter, in 4 divided doses daily. During the next few visits, you are able to titrate the hydralazine dosage to 200 mg daily and the isosorbide dinitrate dosage to 120 mg daily before the patient's blood pressure reaches a point at which he becomes symptomatic. When you see him in the clinic, blood pressure is 108/74 mm Hg with heart rate of 68 beats/min and regular. He has minimal pedal edema and his lungs sound clear. His fatigue has improved and he has improved back to NYHA class II symptoms. He has gradually been able to return to 6 half-days per week running his business. Serum creatinine concentration has stabilized at 3.1 mg/dL (eGFR, 18 mL/min/1.73 m^2), and electrolyte concentrations are maintained within the reference ranges. He continues on a flexible diuretic regimen.*

Question 5: As mentioned, hemoglobin concentration is 11 g/dL. At this point you would:

a) Initiate treatment with an erythropoiesis-stimulating agent (ESA) with a goal of increasing the hemoglobin concentration to 12 to 13 g/dL
b) In addition to above, treat with ferric carboxymaltose with a hemoglobin goal of 12 to 13 g/dL
c) Assess iron status and if iron deficient would treat with ferric carboxymaltose with no ESA
d) None of the above

For answer, see the following text.

To this point in the case scenario, we have managed our patient as best we can with the tools and evidence available to us. There are a few additional considerations. For instance, both CKD and HF are associated with anemia, and there is evidence to suggest that ESAs could have significant cardioprotective properties. However, a randomized trial of darbepoetin in patients with HFrEF, including those with creatinine concentrations up to 3.0 mg/dL, failed to show a significant improvement in symptoms, quality of life, exercise endurance, or other parameters. There have also been very significant concerns raised about treating patients with CKD with ESAs in attempts to target hemoglobin concentrations considered to be "normal," with well-documented increases in adverse outcomes. For the patient in this case scenario with a hemoglobin concentration of 11.0 mg/dL, there is clearly no role to introduce an ESA. However, there are several lines of evidence to suggest that parenteral iron may play a role in the improvement of symptoms and outcomes of HF, irrespective of hemoglobin concentration. In the Ferinject Assessment in Patients With Iron Deficiency and Chronic Heart Failure (FAIR-HF), more than 450 patients with both HF and iron deficiency (with or without anemia) received either ferric carboxymaltose or placebo. The parenteral-iron group had significant improvement in NYHA class, Patient Global Assessment score, 6-minute walk test, and quality of life during the 24-week study. The authors did not list a specific cutoff for kidney function, and a significant proportion had CKD. A recent meta-analysis that examined more than 800 patients with HF in 4 clinical trials of ferric carboxymaltose and found that HF hospitalizations and mortality were significantly decreased in the group receiving iron, and these studies included >40% of participants with eGFRs < 60 mL/min/1.73 m^2. Our patient fits within the criteria with respect to laboratory features of iron deficiency that were used in these HF trials (ferritin < 100 μg/L or between 100 and 300 μg/L if transferrin saturation is <20%) and should be considered for parenteral iron, which has a long track record in patients with advanced CKD (thus, the answer to Question 5 is [c]).

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Conclusions

In summary, with slow and steady improvements in prevention and treatment of infectious diseases, cancers, and cardiovascular diseases globally and with an aging population with high rates of hypertension and diabetes, the worldwide incidence of CKD is steadily increasing. Because of shared risk factors with cardiovascular disease and also the important contribution that ailing kidneys play in the pathophysiology of HF, the prevalence of patients with both CKD and HF is also increasing. Patients with both disorders face a heightened risk for disability, hospitalization, and death, and yet many of the pivotal randomized trials that guide the management of HF have excluded patients with more advanced stages of CKD. In this Core Curriculum, the management of a challenging, yet not unusual, case of HFrEF in a patient with significant CKD has afforded the opportunity to review the relevant literature and provide our patient with care that follows the best evidence available, pointing out obvious gaps that will hopefully lead to the development of randomized controlled trials of interventions and strategies to manage CRSs and better inform clinical care in the future.

Article Information

Author's Affiliation: Western University, London, Ontario, Canada.

Address for Correspondence: Andrew A. House, MD, FRCPC, MSc, Division of Nephrology, London Health Sciences Centre, Room A10-211 University Hospital, 339 Windermere Road, London, ON N6A 5A5 E-mail: Andrew.House@lhsc.on.ca

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