



Curbside Consults

Managing Heart Failure With Reduced Ejection Fraction in Patients With Chronic Kidney Disease: A Case-Based Approach and Contemporary Review

Arden R. Barry, BSc, BSc(Pharm), PharmD, ACPR

Associate Professor (Partner), Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada

Clinical Pharmacy and Research Specialist (Cardiology), Jim Pattison Outpatient Care and Surgery Centre, Lower Mainland Pharmacy Services, Surrey, British Columbia, Canada

ABSTRACT

Patients with heart failure with reduced ejection fraction (HFrEF) often have concurrent chronic kidney disease (CKD), which can make initiating and titrating the 4 standard pharmacologic therapies a challenge. Drug dosing is often based on a calculation of the patient's creatine clearance or estimated glomerular filtration rate (eGFR), but it should also incorporate the trend in their renal function over time and the risk of toxicity of the drug. The presence of CKD in a patient should not preclude the use of a renin-angiotensin system inhibitor, although patients should be monitored frequently for worsening renal function and hyperkalemia. Sacubitril/valsartan is not recommended in patients with an eGFR < 30 mL/min per 1.73 m². Of the 3 β -blockers recommended in the management of HFrEF, only bisoprolol may accumulate in patients with renal impairment; however, patients should still be titrated to the target dose (10 mg daily) or the maximally tolerated dose, depending on their clinical response. The sodium-glucose cotransporter 2 inhibitors are effective at reducing adverse cardiovascular and renal outcomes in patients with HFrEF and CKD (eGFR \geq 25 mL/min per 1.73 m² with dapagliflozin or \geq 20 mL/min per 1.73 m² with empagliflozin), although declining kidney func-

RÉSUMÉ

Les patients atteints d'insuffisance cardiaque avec fraction d'éjection réduite (ICFER) présentent souvent une néphropathie chronique (NC) concomitante, ce qui peut compliquer l'instauration et l'ajustement du traitement par les quatre types de médicaments principaux. La posologie repose souvent sur le calcul de la clairance de la créatine ou du débit de filtration glomérulaire estimé (DFGe), mais l'évolution de la fonction rénale du patient et le risque de toxicité du médicament devraient également être pris en compte. Une NC chez un patient ne devrait pas empêcher l'utilisation d'un inhibiteur du système rénine-angiotensine, mais il convient alors d'effectuer un suivi fréquent de ces patients pour détecter un éventuel déclin de la fonction rénale ou une hyperkaliémie. L'association sacubitril-valsartan n'est pas recommandée chez les patients ayant un DFGe < 30 ml/min/1,73 m². Parmi les trois β -bloqueurs recommandés pour la prise en charge de l'ICFER, seul le bisoprolol pourrait se bioaccumuler chez les patients souffrant d'une dysfonction rénale; il convient toutefois d'ajuster progressivement la posologie jusqu'à l'atteinte de la dose cible (10 mg par jour) ou de la dose maximale tolérée, selon la réponse clinique. Les inhibiteurs du cotransporteur sodium-glucose de type 2 permettent de

The pharmacologic management of heart failure with reduced ejection fraction (HFrEF) is well established. Contemporary foundational treatment of HFrEF includes the following 4 standard therapies: (i) a renin-angiotensin system (RAS) inhibitor (eg, an angiotensin-converting enzyme inhibitor [ACEI], angiotensin receptor blocker [ARB], or angiotensin receptor-neprilysin inhibitor); (ii) a β -blocker; (iii) a mineralocorticoid receptor antagonist (MRA); and (iv) a sodium-

glucose cotransporter 2 (SGLT2) inhibitor.¹ Many patients with HFrEF also have concurrent chronic kidney disease (CKD) as a consequence of multiple overlapping risk factors (eg, hypertension, diabetes mellitus, cardiovascular disease). CKD is defined as abnormal renal structure or function, or an estimated glomerular filtration rate (eGFR) of < 60 mL/min per 1.73 m², for 3 or more months, regardless of the cause.² Initiation and optimization of guideline-directed medical therapy is often influenced by the presence of CKD, as many of the 4 standard therapies can either negatively impact renal function or serum electrolytes, or require renal dose adjustment. The 2021 Canadian Cardiovascular Society (CCS) heart failure guidelines do not provide explicit guidance regarding the use of standard therapy in patients with HFrEF and CKD.¹ Thus, the objective of this review is to provide clinicians with a practical and nuanced overview of the use of guideline-directed medical therapy, by utilizing an example case of a patient with both HFrEF and impaired renal function.

Received for publication April 29, 2022. Accepted June 21, 2022.

Ethics Statement: This article was exempt from institutional ethics approval, as it involved the identification and analysis of previously published clinical studies.

Corresponding author: Dr Arden R. Barry, Faculty of Pharmaceutical Sciences, 2405 Wesbrook Mall, Vancouver, British Columbia V6T 1Z3, Canada. Tel.: +1-604-897-2439.

E-mail: arden.barry@ubc.ca

See page 808 for disclosure information.

tion is a risk, due to the osmotic diuretic effect. Finally, mineralocorticoid receptor antagonist therapy should be considered in all patients with HFREF and an eGFR ≥ 30 mL/min per 1.73 m². The starting dose should be low (eg, 6.25-12.5 mg daily or 12.5 mg every other day) and can be uptitrated based on the patient's renal function and serum potassium.

Case Vignette

An 83-year-old man of Asian descent (186 cm, 68 kg) is being discharged today after a 1-week hospitalization for a first episode of heart failure. His past medical history includes CKD, hypertension, dyslipidemia, type 2 diabetes mellitus (diet-controlled), coronary artery disease (CAD), and benign prostatic hypertrophy. He has no known medication allergies or intolerances. He initially presented with a 3-day history of progressive dyspnea on exertion and orthopnea. His high-sensitivity troponin I level was elevated at 64 ng/L (normal: < 18 ng/L), and his electrocardiogram demonstrated diffuse ST-segment depression. Coronary angiography demonstrated an 80% lesion in his proximal left circumflex artery, and he received percutaneous coronary intervention with 1 drug-eluting stent. He also had a chronic total occlusion of his right coronary artery and diffuse nonobstructive disease. His left ventriculogram showed diffuse hypokinesis with a left ventricular ejection fraction (LVEF) estimated at 25%, which was deemed to be disproportionate to his CAD. An echocardiogram the next day demonstrated an LVEF of 25%-30%, with moderate functional mitral regurgitation.

His baseline serum creatinine level prior to admission was 187 μ mol/L (eGFR of 34 mL/min per 1.73 m² based on the CKD-Epidemiology Collaboration [EPI] equation). However, he experienced an acute kidney injury while in the hospital, and his eGFR decreased to a nadir of 18 mL/min per 1.73 m² (though he did not require dialysis). Blood work on the day of discharge demonstrated a serum sodium level of 136 mmol/L, a serum potassium level of 4.6 mmol/L, and a serum creatinine level of 223 μ mol/L (eGFR: 27 mL/min per 1.73 m²). His creatinine clearance was calculated to be 23 mL/min normalized to 72 kg. His urine albumin-to-creatinine ratio was elevated, at 22 mg/mmol. The etiology of his heart failure was determined to be mixed ischemic/nonischemic, and he was referred to a heart function clinic for further assessment and medication optimization. His discharge medications were as follows: hydralazine 25 mg 3 times daily, isosorbide dinitrate 10 mg 3 times daily, furosemide 40 mg daily, bisoprolol 2.5 mg daily, acetylsalicylic acid 81 mg daily, clopidogrel 75 mg daily, atorvastatin 80 mg daily, and tamsulosin extended-release 0.4 mg daily. He was referred to your heart function clinic for follow-up in 2 weeks.

Estimation of Renal Function

Most drug-dosing recommendations in patients with impaired renal function are based on creatinine clearance (CrCl), which is calculated using the Cockcroft-Gault

réduire l'incidence des manifestations cliniques cardiovasculaires et rénales indésirables chez les patients atteints d'ICFER et de NC (DFGe ≥ 25 ml/min/ $1,73$ m² pour le traitement par la dapagliflozine ou ≥ 20 ml/min/ $1,73$ m² pour le traitement par l'empagliflozine), mais leur effet diurétique osmotique peut entraîner un risque de déclin de la fonction rénale. Enfin, le traitement par les antagonistes des récepteurs mi-nérocorticoïdes devrait être envisagé pour tous les patients atteints d'ICEFR ayant un DFGe ≥ 30 ml/min/ $1,73$ m². Il convient d'instaurer le traitement avec une dose faible (p. ex., de 6,25 à 12,5 mg par jour ou 12,5 mg tous les deux jours) et d'ajuster la dose à la hausse selon la fonction rénale du patient et son taux de potassium sérique.

formula, an antiquated equation published in 1976 using data from 249 white male patients.³ Despite this issue, the Cockcroft-Gault equation still is utilized often in practice, based on its ease of use and clinician familiarity. The Cockcroft-Gault equation incorporates body weight, although this is often standardized to 72 kg to avoid discrepancies due to extremes in body weight. However, most laboratories now report an eGFR based on more-contemporary equations that are adjusted for body surface area. The American National Kidney Foundation now recommends using the CKD-EPI or the Modification of Diet in Renal Disease (MDRD) Study equations to estimate GFR and modify drug dosing.⁴ The CKD-EPI formula can also use serum cystatin C level, as opposed to serum creatinine level, to estimate eGFR. Cystatin C is a protein biomarker that is found at elevated levels in patients with CKD, but it is less variable based on muscle mass, compared with serum creatinine level. The CKD-EPI and MDRD equations are considered to be superior to the Cockcroft-Gault equation for staging of CKD, but drug dosing is an area of controversy. Many references and drug monographs continue to use the Cockcroft-Gault formula for renal dose adjustments, despite its inaccuracy, as the CKD-EPI and MDRD equations have not been validated for adjusting drug dosages. One study found a discordance rate of 15%-25% for renal dose adjustments of antimicrobials as determined by the Cockcroft-Gault vs the CKD-EPI equation, although the clinical significance of this difference is unknown.⁵ One approach is to use the CKD-EPI equation as an initial screening tool to estimate renal function, and then confirm the estimate with the weight-standardized Cockcroft-Gault formula. Many pharmacists are well equipped to calculate CrCl and provide context as to how it compares to the eGFR reported by the laboratory. Regardless, drug dosing in patients with CKD should never be based solely on the estimated CrCl or eGFR, but rather should take into consideration the clinical status of the patient and the risk of toxicity associated with the drug. For most heart failure medications, a range of renal function is provided for a specific dose (eg, eGFR 30-50 mL/min per 1.73 m²), and relatively few have a narrow therapeutic index (with the exception of digoxin). Additionally, as renal function tends to fluctuate over time, clinician consideration of the *trend*, not the latest value, is imperative. When dosing heart failure medications in patients with CKD, clinicians should incorporate as much data as possible when making renal dose adjustments, and not simply use the eGFR value from the most recent blood work.

Table 1. Summary of select landmark randomized controlled trials in heart failure with reduced ejection fraction

Trial	Patient population	Intervention and comparator	Duration	Primary outcome	
				Overall	CKD subgroup (eGFR < 60 mL/min per 1.73 m ²)
ARNIs					
PARADIGM-HF ^{5,6}	N = 8442 patients with HFrEF and NYHA class II–IV symptoms 33% had eGFR < 60 mL/min per 1.73 m ² at baseline Excluded eGFR < 30 mL/min per 1.73 m ²	Sacubitril/valsartan 97/103 mg twice daily vs enalapril 10 mg twice daily	27 mo	CV death and HF hospitalization: 21.8% vs 26.5%, HR 0.80, 95% CI 0.73–0.87	CV death and HF hospitalization: 26.8% vs 32.9%, HR 0.79, 95% CI 0.69–0.90
PIONEER-HF ⁷	N = 881 patients with HFrEF admitted with ADHF Excluded eGFR < 30 mL/min per 1.73 m ²	Sacubitril/valsartan 97/103 mg twice daily vs enalapril 10 mg twice daily	8 wk	Proportional change in NT-proBNP: 0.53 vs 0.75, ratio of change 0.71, 95% CI 0.63–0.81	Proportional change in NT-proBNP: 0.55 vs 0.76, ratio of change 0.73, 95% CI 0.61–0.87
SGLT2 inhibitors					
DAPA-HF ^{11,12}	N = 4744 patients with HFrEF and NYHA class II–IV symptoms 41% had eGFR < 60 mL/min per 1.73 m ² at baseline Excluded eGFR < 30 mL/min per 1.73 m ² (or rapidly declining renal function)	Dapagliflozin 10 mg daily vs placebo	18 mo	CV death and HF hospitalization: 16.3% vs 21.1%, HR 0.74, 95% CI 0.65–0.85	CV death and HF hospitalization: 19.9% vs 26.4%, HR 0.72, 95% CI 0.59–0.86
EMPEROR-Reduced ¹⁴	N = 3730 patients with HFrEF and NYHA class II–IV symptoms 48% had eGFR < 60 mL/min per 1.73 m ² at baseline Excluded eGFR < 20 mL/min per 1.73 m ²	Empagliflozin 10 mg daily vs placebo	16 mo	CV death and HF hospitalization: 19.4% vs 24.7%, HR 0.75, 95% CI 0.65–0.86	CV death and HF hospitalization: 22.6% vs 26.2%, HR 0.83, 95% CI 0.69–1.00
MRAs					
RALES ^{19,20}	N = 1663 patients with HFrEF and NYHA class III–IV symptoms 48% had eGFR < 60 mL/min per 1.73 m ² at baseline Excluded SCr > 221 µmol/L	Spirolonactone 25–50 mg daily vs placebo	24 mo	All-cause death: 34.5% vs 45.9%, RR 0.70, 95% CI 0.60–0.82	All-cause death: HR 0.68, 95% CI 0.56–0.84
EMPHASIS-HF ^{21,22}	N = 2737 patients with HFrEF and NYHA class II symptoms 33% had eGFR < 60 mL/min per 1.73 m ² at baseline Excluded eGFR < 30 mL/min per 1.73 m ²	Eplerenone up to 50 mg daily vs placebo	21 mo	CV death or HF hospitalization: 18.3% vs 25.9%, HR 0.63, 95% CI 0.54–0.74	CV death or HF hospitalization: 24.4% vs 34.5%, HR 0.62, 95% CI 0.49–0.79

ADHF, acute decompensated heart failure; ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular disease; DAPA-HF, **D**apagliflozin and **P**revention of **A**dverse **O**utcomes in **H**eart **F**ailure; eGFR, estimated glomerular filtration rate; EMPEROR-Reduced, **E**mpagliflozin **O**utcome **T**rial in **P**atients **W**ith **C**hronic **H**eart **F**ailure **W**ith a **R**educed **E**jection **F**raction; EMPHASIS-HF, **E**plerenone in **M**ild **P**atients **H**ospitalization and **S**urvival **S**tudy in **H**eart **F**ailure; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; NR, not reported; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; NYHA, New York Heart Association; PARADIGM-HF, **P**rospective **C**omparison of **AR**Ni **W**ith **ACE**i to **D**etermine **I**mpact on **G**lobal **M**ortality and **M**orbidity in **H**eart **F**ailure trial; PIONEER-HF, **C**omparison of **S**acubitril/**V**alsartan **V**ersus **E**nalapril on **E**ffect on **N**t-**P**ro-**B**np in **P**atients **S**tabilized **F**rom an **A**cute **H**eart **F**ailure **E**pisode; RALES, **R**andomized **A**ldactone **E**valuation **S**tudy; RR, relative risk; SCr, serum creatinine; SGLT2, sodium-glucose cotransporter 2.

Standard Therapies for HFrEF

A summary of select landmark randomized controlled trials for the treatment of HFrEF in the context of patients with CKD is included in [Table 1](#).

Renin-angiotensin system inhibitors

Many landmark trials of RAS inhibitors, specifically ACEIs and ARBs, in patients with HFrEF excluded patients with CKD; however, post hoc subgroup analyses and observational

studies have shown a benefit of using ACEIs/ARBs in patients with both HFrEF and CKD, although data are lacking for patients with advanced CKD.⁶ Some clinicians consider ACEIs/ARBs to be contraindicated in patients with CKD, owing to the risk of worsening renal function. Rather, RAS inhibitors are indicated in most patients with CKD to delay the progression and severity of renal dysfunction and proteinuria. For this reason, some patients with CKD are inappropriately precluded from using an ACEI/ARB, due to a perceived risk of nephrotoxicity. The exception is patients with bilateral renal artery stenosis, as ACEIs/ARBs are contraindicated in these patients. In many cases, even patients with stage 4-5 CKD (eGFR \leq 29 mL/min per 1.73 m²) can be safely initiated on an ACEI/ARB, although they should be started on the lowest recommended dose, with frequent monitoring after initiation and dose titration. This approach may facilitate prompt identification of adverse effects, lower the risk of acute kidney injury, and improve overall tolerance. The general recommendation is to monitor a patient's serum creatinine and serum electrolytes levels approximately 1-2 weeks after either starting an ACEI/ARB or increasing the dose. Ideally, a patient's fluid status should be evaluated before every medication initiation or titration, and their loop diuretic dose should be reassessed at each visit to ensure they are on the minimum effective dose to minimize the risk of worsening renal function. Furthermore, an increase in serum creatinine of up to 30% after initiating an RAS inhibitor is generally considered to be acceptable in patients with CKD. Dose titration can often be done every 4 weeks in patients with CKD. The target doses of ACEIs/ARBs are the same in patients with vs without CKD, but achievement of target doses may be limited due to the risk of worsening renal function, hyperkalemia, and hypotension in patients with CKD.

Sacubitril/valsartan is not recommended in patients with an eGFR $<$ 30 mL/min per 1.73 m², as these patients were excluded from the landmark Prospective Comparison of ARNi With ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.⁷ This trial demonstrated that use of sacubitril/valsartan (target dose: 97/103 mg twice daily) reduced the rate of cardiovascular death and heart failure hospitalizations, compared to use of enalapril (target dose: 10 mg twice daily), in patients with symptomatic HFrEF. At baseline, the mean eGFR was 70 mL/min per 1.73 m² (based on the CKD-EPI equation), and 33% had an eGFR $<$ 60 mL/min per 1.73 m².⁸ The active metabolite of sacubitril (sacubitrilat) increases in patients with an eGFR of 30-60 mL/min per 1.73 m², but no dose adjustment was recommended in the PARADIGM-HF trial.⁷ In the prespecified subgroup analysis of patients with vs without CKD (eGFR $<$ 60 or \geq 60 mL/min per 1.73 m², respectively), the primary composite outcome of heart failure hospitalization and cardiovascular death was lower with use of sacubitril-valsartan, in both groups (interaction $P = 0.91$). A point to note is that the results of a subgroup analysis have inherent limitations, even if they are prespecified, due to the loss of randomization between groups that accounts for known and unknown confounders. In addition, the composite rate of heart failure hospitalization and cardiovascular death was significantly lower with use of sacubitril/valsartan vs enalapril in patients with an eGFR $<$ 60 mL/min per 1.73 m² (26.8% vs 32.9%, hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.69-0.90).⁸ In the overall analysis, the risk of an elevated serum creatinine level

or hyperkalemia was significantly lower with use of sacubitril/valsartan, compared to enalapril.⁷ Additionally, the post hoc composite renal outcome (development of end-stage renal disease or \geq 50% decrease in eGFR from baseline) was significantly lower with use of sacubitril/valsartan vs enalapril (0.9% vs 1.4%, HR 0.63, 95% CI 0.42-0.95) in the entire study population.⁸ The point estimate was similar in the subgroup of patients with CKD, although the difference did not reach statistical significance (HR 0.64, 95% CI 0.34-1.19). Although only one-third of patients in the PARADIGM-HF trial had CKD, these data indicate that sacubitril/valsartan is more effective at reducing heart failure hospitalizations and cardiovascular death in patients with stage 3 CKD (eGFR 30-59 mL/min per 1.73 m²), with a lower risk of adverse renal events, compared to an ACEI.

The **Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on Nt-Pro-Bnp in Patients Stabilized From an Acute Heart Failure Episode (PIONEER-HF)** trial enrolled patients with HFrEF who were admitted to the hospital for acute decompensated heart failure and compared use of sacubitril/valsartan (target dose: 97/103 mg twice daily) to use of enalapril (target dose: 10 mg twice daily).⁹ The median eGFR was 59 mL/min per 1.73 m² at baseline, and patients with an eGFR $<$ 30 mL/min per 1.73 m² were excluded. Use of sacubitril/valsartan showed a significantly greater reduction in the primary outcome of N-terminal pro-B-type natriuretic peptide over 8 weeks (ratio of change 0.71, 95% confidence interval 0.63-0.81). The primary outcome was also significantly lower in the subgroup of patients with an eGFR $<$ 60 mL/min per 1.73 m², with a similar point estimate (ratio of change 0.73, 95% confidence interval 0.61-0.87, interaction $P = 0.81$). These results show that use of an angiotensin receptor-neprilysin inhibitor may also be effective in patients with HFrEF and CKD who are admitted with acute decompensated heart failure, although the trial excluded patients with more severe renal dysfunction.

Case vignette (continued)

He presents to your heart function clinic today 2 weeks after being discharged from the hospital. He currently has New York Heart Association (NYHA) class III symptoms. In the clinic, he is euvolemic on examination. His blood pressure is 115/72 mm Hg with a heart rate of 60 beats per minute. He has not had any medication changes since his discharge from the hospital. Blood work from 2 days ago revealed that his serum electrolyte level was within normal limits, and his serum creatinine level was 213 μ mol/L (eGFR 29 mL/min per 1.73 m² based on the CKD-EPI equation; CrCl 24 mL/min normalized to 72 kg based on the Cockcroft-Gault equation).

This patient's acute kidney injury has now resolved, but his renal function appears to have decreased to a new baseline of approximately 29 mL/min per 1.73 m². However, this decrease should not preclude the use of an RAS inhibitor, because he has several other indications for therapy, including hypertension, CAD, and proteinuria. The combination of hydralazine and isosorbide dinitrate was a reasonable choice on discharge, as his renal function was low and still recovering from his acute kidney injury. However, he is now more stable from a renal perspective, is euvolemic on examination, and is not taking any other nephrotoxic medications (eg, nonsteroidal anti-inflammatory drugs). In this case, a reasonable approach is to discontinue hydralazine and isosorbide dinitrate, and initiate an

ACEI at the lowest possible starting dose (eg, ramipril 1.25 mg twice daily) and repeat measurement of his serum creatinine and electrolyte levels in approximately 2 weeks.

β-Blockers

The use of standard β-blockers for the treatment of HFrEF is relatively straightforward in patients with CKD. Neither carvedilol nor metoprolol requires renal dose adjustment in patients with impaired renal function, as these are predominantly metabolized by cytochrome P450 enzymes. However, approximately 50% of the dose of bisoprolol is excreted as unchanged drug in the urine, and thus is at risk of accumulating in patients with CKD.¹⁰ Although this risk does not often necessitate a reduction in bisoprolol dose in patients with CKD, clinicians should be aware that the clearance of bisoprolol may be reduced in patients with renal dysfunction. Therefore, the recommended approach is that patients with HFrEF and CKD be initiated on the lowest possible dose of bisoprolol (eg, 1.25 mg daily), with a gradual titration based on patient tolerance and clinical response. The 2021 CCS heart failure guidelines do not recommend a different target dose of bisoprolol in patients with CKD (ie, it is still 10 mg daily), but achievement of this dose may be impacted by actual or potential adverse effects, such as bradycardia or hypotension. As a result, patients with CKD may be able to achieve only a maximally tolerated dose of bisoprolol.

Case vignette (continued)

You perform an in-person follow-up with him 2 weeks after his initial heart function clinic visit. His current heart failure medications include ramipril 1.25 mg twice daily, furosemide 40 mg daily, and bisoprolol 2.5 mg daily. He had his serum creatinine and electrolyte levels measured yesterday. His serum creatinine level has increased to 223 μmol/L (eGFR 27 mL/min per 1.73 m² based on the CKD-EPI equation; CrCl 23 mL/min normalized to 72 kg based on the Cockcroft-Gault equation). His serum sodium level is 143 mmol/L, and his serum potassium level is 5.1 mmol/L. His home weight has been stable at 68 kg, and his home blood pressure over the past week has been an average of 114/71 mm Hg, with a pulse of 52 beats per minute. He still has symptoms consistent with NYHA class III. On examination, his blood pressure was 121/74 mm Hg, with a pulse of 51 beats per minute. His jugular venous pressure was 1 cm above the sternal angle, and his lungs were clear to auscultation with no adventitious sounds. He had normal S1 and S2 heart sounds, with no S3. His weight was 69 kg in the clinic. He did not have any peripheral edema.

Although his eGFR has decreased slightly, his serum creatinine level increased by only 5% from baseline, which is within the generally accepted range of < 30%. Although he has mild hyperkalemia, it should not necessitate a change to his ramipril dose, and he is referred to the dietician to discuss reducing his dietary intake of potassium. His bradycardia is of concern, as it may be indicative of renal accumulation of bisoprolol. Thus, you recommend he discontinue bisoprolol and initiate metoprolol at a therapeutically equivalent dose (eg, 25 mg twice daily). The addition of an MRA would not be appropriate at this time, based on his hyperkalemia. However, initiation of an SGLT2 inhibitor is a reasonable

consideration. Hence, you recommend empagliflozin 10 mg daily. Given that he appears euvolemic on examination, and to minimize the risk of worsening renal function due to hypovolemia, you recommend that he decrease his furosemide to 20 mg daily. Finally, you ask that he repeat measurement of his serum creatinine and electrolyte levels in another 2 weeks.

SGLT2 inhibitors

SGLT2 inhibitors are recommended in most patients with HFrEF and CKD, although initiating an SGLT2 inhibitor may increase the risk of worsening renal function secondary to volume depletion. Prior to initiation, all patients should undergo a fluid assessment, as hypovolemia may increase the risk of an acute kidney injury. However, chronic use of SGLT2 inhibitors has been shown to reduce the risk of adverse renal outcomes in patients with CKD.¹¹ As with other standard HFrEF therapies, patients with an eGFR < 60 mL/min per 1.73 m² on an SGLT2 inhibitor should have their renal function assessed frequently. Dapagliflozin is not recommended in patients with an eGFR < 25 mL/min per 1.73 m², whereas empagliflozin is not recommended in patients with an eGFR < 20 mL/min per 1.73 m².^{12,13} Both dapagliflozin and empagliflozin are contraindicated in patients on dialysis. As with non-CKD patients, the target dose for both dapagliflozin and empagliflozin is 10 mg daily. As SGLT2 inhibitors have a mild osmotic diuretic effect, a pragmatic approach is to empirically reduce the dose of a loop diuretic by 50% in patients who are euvolemic.

In the **Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF)** trial, 41% of patients had CKD (eGFR < 60 mL/min per 1.73 m² based on the CKD-EPI equation), and patients with an eGFR < 30 mL/min per 1.73 m², or rapidly declining renal function, were excluded.¹⁴ The dose of dapagliflozin could be temporarily reduced to 5 mg daily (from 10 mg daily) in patients with an acute, unexpected decline in renal function. In a prespecified subgroup analysis, the primary composite endpoint of worsening heart failure or cardiovascular death was significantly reduced with dapagliflozin vs placebo (19.9% vs 26.4%, HR 0.72, 95% CI 0.59-0.86) in patients with an eGFR < 60 mL/min per 1.73 m².¹⁵ The primary outcome of cardiovascular death or worsening heart failure did not differ significantly between subgroups of patients with vs without CKD (interaction *P* = 0.54).¹⁴ Furthermore, the reduction of cardiovascular and all-cause death did not differ significantly between groups (interaction *P* = 0.44 and *P* = 0.80, respectively).

The **Dapagliflozin and Prevention of Adverse Outcomes in CKD (DAPA-CKD)** trial evaluated dapagliflozin 10 mg daily vs placebo in patients with CKD (eGFR 25-75 mL/min per 1.73 m²; mean eGFR 43 mL/min per 1.73 m² at baseline) and albuminuria.¹¹ The trial was not specifically evaluating heart failure—only 11% had a history of heart failure (unknown type) at baseline, and patients with NYHA class IV symptoms were excluded. Overall, use of dapagliflozin reduced the primary composite renal outcome (50% decline in eGFR, end-stage renal disease, or death from renal or cardiovascular causes) vs placebo (9.2% vs 14.5%, HR 0.61, 95% CI 0.51-0.72). Use of dapagliflozin also reduced the secondary outcome of death from cardiovascular causes or hospitalization for heart failure (HR 0.71, 95% CI 0.55-0.92). However, the authors did not

report outcomes for the subgroup of patients with heart failure at baseline.

In the **Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With a Reduced Ejection Fraction (EMPEROR-Reduced)** trial, 48% of patients had an eGFR < 60 mL/min per 1.73 m² (based on the CKD-EPI equation) at baseline.¹⁶ Patients with an eGFR < 20 mL/min per 1.73 m² were excluded, although the authors did not report how many patients with severe CKD (ie, eGFR 20-29 mL/min per 1.73 m²) were included. The overall mean eGFR was 62 mL/min per 1.73 m². Use of empagliflozin 10 mg daily reduced the primary outcome of cardiovascular death or heart failure hospitalization, compared to placebo. However, in a subgroup of patients with an eGFR < 60 mL/min per 1.73 m², the point estimate favoured empagliflozin, but it did not reach statistical significance (22.6% vs 26.2%, HR 0.83, 95% CI 0.69-1.00). The secondary renal composite outcome (dialysis, transplantation, or sustained decline in eGFR based on baseline eGFR) for the overall population was significantly lower with empagliflozin (HR 0.50, 95% CI 0.32-0.77), although the rate was not reported for the subgroup of patients with CKD.

Case vignette (continued)

He has another in-person follow-up clinic visit 2 weeks after initiating metoprolol and empagliflozin. His average home blood pressure has stayed consistent at about 118/75 mm Hg, and his average home pulse has improved to 65 beats per minute. His symptoms have improved since his previous clinic visit. He reports less dyspnea and more stamina, consistent with NYHA class II. He had his repeat blood work done 2 days ago, which showed a serum sodium level of 138 mmol/L, a serum potassium level of 4.8 mmol/L, and a serum creatinine level of 243 μmol/L (eGFR 24 mL/min per 1.73 m² based on the CKD-EPI equation; CrCl 21 mL/min normalized to 72 kg based on the Cockcroft-Gault equation), which represents a 10% increase from his previous measurement (14% increase from baseline). On examination, his jugular venous pressure was below the sternal angle, and he did not have any peripheral edema. His weight is down 2 kg (to 67 kg) from that at his previous clinic visit.

You determine on examination that he is likely hypovolemic. Thus, you recommend changing his furosemide to 20 mg daily as needed, and educate him to monitor his home weight and symptoms. Although his eGFR has decreased to < 25 mL/min per 1.73 m², continuation of his empagliflozin is acceptable, whereas dapagliflozin would technically be contraindicated if his eGFR is consistently < 25 mL/min per 1.73 m². One week later, repeat blood work demonstrates his serum creatinine level has decreased to 219 μmol/L (eGFR 29 mL/min per 1.73 m² based on the CKD-EPI equation; CrCl 24 mL/min normalized to 72 kg based on the Cockcroft-Gault equation) and his serum electrolyte levels are within normal limits. At this point, you recommend initiating spironolactone 6.25 mg daily to complete his 4 standard heart failure therapies, and you recommend blood work again in about 1-2 weeks.

Mineralocorticoid receptor antagonists

MRAs are recommended to be used cautiously in patients with HFrEF and CKD secondary to the risk of worsening renal function and hyperkalemia. All patients with HFrEF and CKD

should have baseline serum creatinine and serum potassium levels measured prior to MRA initiation, and patients should be educated to limit their dietary intake of potassium. For eplerenone and spironolactone, no dose adjustment is required in patients with an eGFR > 50 mL/min per 1.73 m². In patients with an eGFR 30-50 mL/min per 1.73 m², the recommended approach is to use a low starting dose (eg, 6.25-12.5 mg daily or 12.5 mg every other day) and titrate up every 4 weeks if the patient's renal function is stable and serum potassium level is < 5 mmol/L.^{17,18} The CCS heart failure guidelines advocate that mild hyperkalemia is acceptable (serum potassium level 5.1-5.5 mmol/L) and should not necessitate a dose reduction.¹⁹ In most cases, the target dose should not exceed 25 mg daily. Avoiding MRA therapy is recommended in patients with an eGFR < 30 mL/min per 1.73 m².^{17,18}

Post hoc analyses of landmark trials have demonstrated a benefit with MRA therapy in patients with HFrEF and CKD.²⁰ In the **Randomized Aldactone Evaluation Study (RALES)** trial, patients with a serum creatinine level > 221 μmol/L were excluded.²¹ In the subgroups of patients with a serum creatinine level < 106 μmol/L or ≥ 106 μmol/L, all-cause death was significantly lower in both groups, with a higher relative risk reduction in patients with worse renal function. A subsequent post hoc analysis of the RALES trial demonstrated that patients with an eGFR < 60 mL/min per 1.73 m² (based on the MDRD equation) had a similar relative risk reduction in all-cause death (32%), compared to that of patients with an eGFR > 60 mL/min per 1.73 m² (29%).²² A similar relative risk reduction occurred in the composite of death or heart failure hospitalization in both groups, but hyperkalemia was more common with spironolactone in patients with an eGFR < 60 mL/min per 1.73 m². Worsening renal function (defined as a 30% decrease in eGFR from baseline to 12 weeks) with spironolactone was not associated with an increased adjusted risk of death. In the **Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)** trial, patients with an eGFR < 30 mL/min per 1.73 m² (based on the MDRD equation) were excluded, and roughly one-third (33%) had an eGFR < 60 mL/min per 1.73 m².²³ The prespecified subgroup of patients with an eGFR of 30-59 mL/min per 1.73 m² demonstrated that eplerenone, as compared to placebo, significantly reduced the incidence of the composite of heart failure hospitalization and cardiovascular death (24.4% vs 34.5%, HR 0.62, 95% CI 0.49-0.79), which was similar to that in the overall trial population.^{23,24} However, the risk of hyperkalemia was higher with eplerenone vs placebo in patients with an eGFR 30-59 mL/min per 1.73 m² (16.6% vs 9.3%, *P* = 0.002). Hence, patients with HFrEF and CKD may derive a similar or increased benefit with eplerenone or spironolactone than patients with higher renal function, though the risk of hyperkalemia appears to also be increased.

Contrary to these subgroup analyses, a prospective observational study conducted in Alabama using Medicare data (the Alabama Heart Failure Project) investigated spironolactone use and the risk of hospital readmission.²⁵ A total of 1140 patients hospitalized for heart failure with an LVEF < 45% and an eGFR < 45 mL/min per 1.73 m² were included in the analysis. The mean LVEF was 28%, and the mean eGFR was 31 mL/min per 1.73 m². A propensity-score-adjusted hazard ratio indicated that no significant difference occurred in 30-day all-cause or

heart failure-related readmission, or in all-cause mortality, among patients discharged on spironolactone vs not on spironolactone. At 1 year, an increase occurred in all-cause—but not heart failure-related—hospital readmission among spironolactone users vs nonusers. The authors concluded that patients discharged on spironolactone after a heart failure hospitalization had a higher risk of 1-year hospital readmission. Despite the propensity score-matched design, this study was at risk of bias and confounding due to the observational design and the small, highly selective population. As well, the authors utilized data from 1998–2001, prior to the advent of use of eplerenone, sacubitril-valsartan, and SGLT2 inhibitors.

Case vignette (continued)

You conduct a telephone follow-up 2 weeks after initiating spironolactone. His symptoms continue to be consistent with NYHA class II. His repeat blood work demonstrates a serum sodium level of 140 mmol/L, a serum potassium level of 5.2 mmol/L, and a serum creatinine level of 214 μ mol/L (eGFR 29 mL/min per 1.73 m² based on the CKD-EPI equation; CrCl 24 mL/min normalized to 72 kg based on the Cockcroft-Gault equation). He has been adhering to a low-potassium diet. His blood pressure at home has been an average of 110/68 mm Hg, with a pulse of 62 beats per minute. His current heart failure therapies are as follows: ramipril 1.25 mg twice daily, metoprolol 25 mg twice daily, spironolactone 6.25 mg daily, empagliflozin 10 mg daily, and furosemide 20 mg daily as needed (no recent use).

His renal function has improved back to his baseline on discharge from the hospital. However, his mild hyperkalemia should rule out titration of his ramipril and spironolactone. Based on his stage 4 CKD, his ACEI and MRA are unlikely to be titrated to the target doses. If his eGFR improves to be consistently > 30 mL/min per 1.73 m², a reasonable approach may be to discontinue his ramipril and initiate sacubitril/valsartan 24/26 mg twice daily, although he will need to monitor his home blood pressure frequently and monitor for symptoms of lightheadedness. His empagliflozin is at the target dose. At this time, the most reasonable option would be to cautiously uptitrate his metoprolol (eg, 37.5 mg twice daily), which should have a minimal impact on his blood pressure and does not require renal dose adjustment.

Potassium binders

Ongoing trials are evaluating the use of novel, non-absorbed potassium binders (patiromer and sodium zirconium cyclosilicate) to facilitate the initiation and uptitration of MRAs and RAS inhibitors in patients with HFrEF.^{26,27} Preliminary trials have demonstrated that patiromer and sodium zirconium cyclosilicate lower serum potassium levels and maintain normokalemia among patients with heart failure, with a history of hyperkalemia, who are receiving RAS inhibitor therapy.^{28–30} However, cost, polypharmacy, and adverse effects (eg, hypokalemia, edema with sodium zirconium cyclosilicate, gastrointestinal disorders with patiromer) may be barriers to uptake in practice.

Conclusion

Many patients with HFrEF also have concurrent CKD (eGFR < 60 mL/min per 1.73 m²), which presents a

challenge when initiating and titrating the 4 standard therapies for treatment. Drug dosing based on renal function is controversial, depending on the equation utilized. Clinicians should be aware of the limitations of each formula and should incorporate the clinical status of the patient, the trend in their renal function over time, and the risk of toxicity of the drug when making renal dose adjustments. The presence of CKD in a patient should not preclude the use of an RAS inhibitor, though patients should be monitored frequently for worsening renal function and hyperkalemia. However, sacubitril/valsartan is not recommended in patients with an eGFR < 30 mL/min per 1.73 m². Of the 3 β -blockers recommended in the management of HFrEF, only bisoprolol may accumulate in patients with renal impairment; however, patients should be titrated to either the target dose (10 mg daily) or their maximally tolerated dose, depending on their clinical response. The SGLT2 inhibitors appear to be effective at reducing adverse cardiovascular and renal outcomes in patients with CKD (eGFR \geq 25 mL/min per 1.73 m² with dapagliflozin or \geq 20 mL/min per 1.73 m² with empagliflozin), although declining kidney function is a risk, due to the osmotic diuretic effect. Finally, MRA therapy should be considered in all patients with HFrEF and an eGFR \geq 30 mL/min per 1.73 m². The starting dose should be low (eg, 6.25–12.5 mg daily or 12.5 mg every other day), and can be uptitrated every 4 weeks, based on the patient's renal function, in the absence of hyperkalemia.

Acknowledgements

Thank you to Ms Katherine Bishop, who was an entry-to-practice Doctor of Pharmacy student at the Faculty of Pharmaceutical Sciences, University of British Columbia, for her assistance with the literature search and data extraction. She is now a registered pharmacist in British Columbia.

Funding Sources

This review was unfunded. Funding for the publication fee was supported by the Shoppers Drug Mart Professorship in Clinical Pharmacy at the Faculty of Pharmaceutical Sciences at the University of British Columbia in Vancouver, Canada.

Disclosures

The author has no conflicts of interest to disclose.

References

1. McDonald M, Virani S, Chan M, et al. CCS/CHFS heart failure guidelines update: defining a new pharmacologic standard of care for heart failure with reduced ejection fraction. *Can J Cardiol* 2021;37:531–46.
2. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005;67:2089–100.
3. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.
4. Delgado C, Baweja M, Crews DC, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN Task Force on

- Reassessing the Inclusion of Race in Diagnosing Kidney Disease. *Am J Kidney Dis* 2022;79:268:88.e1.
- Wargo KA, English TM. Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for dosing antimicrobials. *Ann Pharmacother* 2010;44:439-46.
 - Hein AM, Scialla JJ, Edmonston D, et al. Medical management of heart failure with reduced ejection fraction in patients with advanced renal disease. *JACC Heart Fail* 2019;7:371-82.
 - McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.
 - Damman K, Gori M, Claggett B, et al. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. *JACC Heart Fail* 2018;6:489-98.
 - Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2019;380:539-48.
 - Lexi-Comp. Bisoprolol monograph, https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6461?cesid=2uMY0FFpczq&searchUrl=%2F%2F%2F%2Fsearch%3Fq%3Dbisoprolol%26t%3Dname%26acs%3Dfalse%26acq%3Dbisoprolol. Accessed April 8, 2022.
 - Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;383:1436-46.
 - AstraZeneca Canada. Forxiga product monograph, <https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=91978>. Accessed April 8, 2022.
 - Boehringer Ingelheim (Canada). Jardiance product monograph, <https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=92871>. Accessed April 8, 2022.
 - McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;381:1995-2008.
 - Jhund PS, Solomon SD, Docherty KF, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. *Circulation* 2021;143:298-309.
 - Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;383:1413-24.
 - Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure. *Can J Cardiol* 2017;33:1342-433.
 - Lexi-Comp. Spironolactone monograph, https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7699?cesid=83oBWBDLXTP&searchUrl=%2F%2F%2F%2Fsearch%3Fq%3Dspironolactone%26t%3Dname%26acs%3Dtrue%26acq%3Dspiron. Accessed April 8, 2022.
 - Upjohn Canada. Inspra product monograph, <https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=80855>. Accessed April 8, 2022.
 - Khan MS, Khan MS, Moustafa A, et al. Efficacy and safety of mineralocorticoid receptor antagonists in patients with heart failure and chronic kidney disease. *Am J Cardiol* 2020;125:643-50.
 - Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709-17.
 - Vardeny O, Wu DH, Desai A, et al. Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). *J Am Coll Cardiol* 2012;60:2082-9.
 - Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;364:11-21.
 - Eschaliel R, McMurray JJV, Swedberg K, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure). *J Am Coll Cardiol* 2013;62:1585-93.
 - Inampudi C, Parvataneni S, Morgan CJ, et al. Spironolactone use and higher hospital readmission for Medicare beneficiaries with heart failure, left ventricular ejection fraction < 45%, and estimated glomerular filtration rate < 45 ml/min/1.73 m². *Am J Cardiol* 2014;114:79-82.
 - Butler J, Anker SD, Siddiqi TJ, et al. Patiromer for the management of hyperkalaemia in patients receiving renin-angiotensin-aldosterone system inhibitors for heart failure: design and rationale of the DIAMOND trial. *Eur J Heart Fail* 2022;24:230-8.
 - Murphy D, Ster IC, Kaski JC, Anderson L, Banerjee D. The LIFT trial: study protocol for a double-blind, randomised, placebo-controlled trial of K⁺-binder Lokelma for maximisation of RAAS inhibition in CKD patients with heart failure. *BMC Nephrol* 2021;22:254.
 - Pitt B, Anker SD, Bushinsky DA, et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J* 2011;32:820-8.
 - Anker SD, Kosiborod M, Zannad F, et al. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial. *Eur J Heart Fail* 2015;17:1050-6.
 - Pitt B, Bakris GL, Bushinsky DA, et al. Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. *Eur J Heart Fail* 2015;17:1057-65.