Medication management for heart failure with reduced ejection fraction

Clinical pearls for optimizing evidenced-informed therapy

Arden R. Barry PharmD ACPR Lynette Kosar MSc(Pharm) Sheri L. Koshman PharmD ACPR Ricky D. Turgeon PharmD ACPR

There have been numerous developments in the management of heart failure (HF) over the past several years. Terminology has evolved, with systolic dysfunction now referred to as *HF with reduced ejection fraction (HFrEF)* (ie, a left ventricular ejection fraction [LVEF] of ≤40%) (**Table 1**).[1,2] Medications, such as sacubitril-valsartan and sodium-glucose cotransporter-2 inhibitors (SGLT2Is), have been added to the list of agents that provide mortality and morbidity benefits in this patient population.[3] Recommended pharmacotherapy for individuals with HFrEF has subsequently expanded to include 4 types of foundational medications, also referred to as *HFrEF quadruple therapy* (**Table 2**).[3,4] Furthermore, the 2021 Canadian Cardiovascular Society (CCS) HF guidelines suggest initiating HFrEF quadruple therapy and completing titration to maximally tolerated doses within 3 to 6 months of diagnosis.[3] This may seem ambitious but, despite the evidence for and advances in medication management, the mortality and morbidity rates in HF remain high. The mortality rate of individuals with HF is approximately 50% within 5 years of diagnosis.[5] These patients also have a high risk of being hospitalized for HF, which is associated with a subsequent increased risk of death.[6] Underuse and underdosing of HFrEF medications are thought to be key contributors to the continued high rates of mortality and HF hospitalizations.[7] Notably, loop diuretics (eg, furosemide) are crucial to managing fluid retention, but do not reduce the risk of mortality and may even limit the titration of other mortality-reducing HF medications. Thus, diuretics should be reassessed at every visit and tapered to the minimum effective dose to maintain euvolemia.[3]

This article reviews the evidence for the newer HFrEF medications, illustrates how HFrEF quadruple therapy

Table 1. Classification of HF according to A) NYHA functional classification and B) ejection fraction

A) HF ACCORDING TO NYHA CLASS		
NYHA CLASS	**DESCRIPTION**	**EXAMPLES OF ACTIVITIES THAT CAN BE PERFORMED WITHOUT PRODUCING SYMPTOMS**
I	Asymptomatic: ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations	• Carry objects >36.5 kg (80 lb) or carry objects >11.5 kg (25 lb) up 8 steps • Shovel snow, spade soil • Ski, play basketball • Jog or walk 8 km/h
II	Mild symptoms: comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations	• Sexual intercourse without stopping • Garden, rake, weed • Play golf, dance the fox trot • Walk 6 km/h on level ground
III	Moderate symptoms: comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations	• Mop floors, make bed • Push lawn mower • Shower and dress without stopping • Walk 4 km/h
IV	Severe symptoms or symptoms at rest: unable to carry on any physical activity without discomfort	• Cannot perform any of the above without symptoms

B) HF ACCORDING TO EJECTION FRACTION	
CLASSIFICATION	**LVEF**
HF with reduced ejection fraction	≤40%
HF with mildly reduced or mid-range ejection fraction	41%-49%
HF with preserved ejection fraction	≥50%
HF with improved ejection fraction	Baseline ≤40% with a later measurement that increased by ≥10% from baseline to >40%

HF—heart failure, LVEF—left ventricular ejection fraction, NYHA—New York Heart Association.
Data from Goldman et al[1] and Bozkurt et al.[2]

Table 2. Heart failure with reduced ejection fraction quadruple therapy dosing and monitoring: ***Table includes agents that have evidence for reducing mortality and morbidity in individuals with HFrEF.***

MEDICATION	INITIAL DOSE	TARGET DOSE	SELECT MONITORING PARAMETERS	COMMENTS
ACEIs				
• Captopril	6.25-12.5 mg 3 times daily	50 mg 3 times daily	BP, serum creatinine level, urea level, serum potassium level, cough, angioedema	There is no compelling evidence to suggest one ACEI is better than another
• Enalapril	1.25-2.5 mg twice daily	10-20 mg twice daily		
• Lisinopril	2.5-5 mg/d	20-35 mg/d		
• Ramipril	1.25-2.5 mg twice daily	5 mg twice daily		
• Trandolapril	1-2 mg/d	4 mg/d		
ARBs				
• Candesartan	4-8 mg/d	32 mg/d	BP, serum creatinine level, urea level, serum potassium level	Reserve for patients who are intolerant to ACEIs. Lower risk of cough and angioedema vs ACEIs, but inconsistent mortality benefit
• Valsartan	40 mg twice daily	160 mg twice daily		
Angiotensin receptor–neprilysin inhibitor				
• Sacubitril-valsartan	24 mg–26 mg twice daily or 49 mg–51 mg twice daily	97 mg–103 mg twice daily	BP, serum creatinine level, urea level, serum potassium level	When switching to or from an ACEI, a minimum 36-h washout period is required to reduce the risk of angioedema. No washout period is required when switching from an ARB
β-blockers				
• Bisoprolol	1.25-2.5 mg/d	10 mg/d	BP, heart rate, fatigue	Carvedilol has more potent BP-lowering effects owing to α-blocking activity
• Carvedilol	3.125 mg twice daily	25 mg twice daily (patient weighs ≤ 85 kg) or 50 mg twice daily (patient weighs > 85 kg)		
• Metoprolol tartrate	6.25-25 mg twice daily	100 mg twice daily		
MRAs				
• Eplerenone	12.5-25 mg/d	50 mg/d	BP, serum creatinine level, urea level, serum potassium level, gynecomastia, menstrual irregularities	There are no head-to-head trials of eplerenone vs spironolactone. Eplerenone is not associated with gynecomastia, but is more costly
• Spironolactone	12.5-25 mg/d	25-50 mg/d		
SGLT2Is				
• Dapagliflozin	10 mg/d	10 mg/d	BP, serum creatinine level, hypovolemia. In patients with T2DM: mycotic genital infection, hypoglycemia, or euglycemic DKA	Effective in those with and without T2DM. Contraindicated in T1DM. All patients should be counseled on personal hygiene to help prevent mycotic genital infections
• Empagliflozin	10 mg/d	10 mg/d		

ACEI—angiotensin-converting enzyme inhibitor, ARB—angiotensin receptor blocker, BP—blood pressure, DKA—diabetic ketoacidosis, HFrEF—heart failure with reduced ejection fraction, MRA—mineralocorticoid receptor antagonist, SGLT2I—sodium-glucose cotransporter-2 inhibitor, T1DM—type 1 diabetes mellitus, T2DM—type 2 diabetes mellitus.
Data from Ezekowitz et al.[4]

can be achieved within the suggested time frame, and provides practice pearls on how to optimize therapy (The Art of Optimizing HFrEF Medications: Practical Tips For Common Clinical Concerns is available from **CFPlus***).

Case description

Mr R.F., a 71-year-old man who is known to you, was admitted to hospital approximately 1 month ago for an ST-segment elevation myocardial infarction that was treated with primary percutaneous coronary intervention. On discharge, he was instructed to make a follow-up appointment with you. His discharge summary notes show that he had pulmonary edema while in hospital and echocardiography findings revealed an LVEF of 25% to 30%, resulting in the diagnosis of HFrEF.

Mr R.F.'s past medical history includes hypertension, dyslipidemia, atrial fibrillation, and osteoarthritis. He is a non-smoker and rarely drinks alcohol. Before admission, he was taking 25 mg of hydrochlorothiazide daily, 10 mg of atorvastatin daily, 5 mg of apixaban twice daily, and 400 mg of ibuprofen once or twice daily as needed (approximately 5 to 6 doses per week). During his hospitalization hydrochlorothiazide was discontinued; 5 mg of ramipril twice daily and 10 mg of bisoprolol daily were started to treat HFrEF. A daily furosemide dose of 40 mg was added for HF symptom management secondary to fluid retention. Atorvastatin was increased to 80 mg daily, 75 mg of clopidogrel daily was initiated for 1 year, and he continued to take apixaban. Ibuprofen was discontinued and replaced with 1300 mg of extended-release acetaminophen twice daily. (**Table 3** lists medications that should be avoided in HF.[8-10]) The discharge summary indicated the cardiologist will see Mr R.F. 3 months after his admission, and the cardiologist requested your assistance in optimizing HFrEF medications by starting a mineralocorticoid receptor antagonist (MRA) before this follow-up appointment. Laboratory test results on discharge showed a serum sodium level of 141 mmol/L, serum potassium level of 4.8 mmol/L, serum creatinine level of 137 µmol/L (estimated glomerular filtration rate [eGFR] of 43 mL/min/1.73 m^2), urea level of 6.8 mmol/L, N-terminal pro–brain natriuretic peptide level of 1260 ng/L, and hemoglobin level of 134 g/L.

In the clinic today he denies any shortness of breath at rest or on exertion, cough, orthopnea, and paroxysmal nocturnal dyspnea. He goes for daily walks but is unable to go as far as he did before this admission owing to fatigue. He can walk up 1 flight of stairs without stopping, but needs to rest at the top. You classify his functional status as New York Heart Association (NYHA) class II (**Table 1**).[1,2] His weight today is 85 kg (approximately his dry weight). On examination, his jugular venous pressure is not elevated and there are no pulmonary crackles or extra heart sounds on auscultation. He has bilateral grade +1 pitting edema (on a scale from +1 to +4) to both ankles, but no ascites. He has reduced his fluid intake to roughly 2 L per day and is attempting to adhere to a low-salt diet. Mr R.F.'s blood pressure (BP) is 117/72 mm Hg sitting and 112/70 mm Hg standing, without postural lightheadedness. His heart rate is 65 beats/min.

Based on your assessment, you recommend initiating 25 mg of spironolactone daily and provide Mr R.F. with a laboratory requisition to assess his serum electrolyte and serum creatinine levels in approximately 2 weeks.

Bringing evidence to practice: MRA therapy

The CCS HF guidelines recommend MRA therapy in all patients with HFrEF (LVEF ≤40%) and symptoms consistent with NYHA classes II to IV.[3] Both spironolactone and eplerenone have been studied in HFrEF, although in slightly different patient populations (spironolactone in NYHA classes III and IV HFrEF and eplerenone in NYHA class II HFrEF).[11,12] There are no head-to-head trials comparing the 2 agents, but each has shown a reduction in mortality and HF hospitalizations when compared with placebo.[11,12] For example, the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trial[12] demonstrated that eplerenone, compared with placebo, statistically significantly reduced cardiovascular mortality and HF hospitalization (absolute risk reduction [ARR] = 7.6%) and all-cause death (ARR = 3%) over approximately 2 years (**Table 4**).[12-15] Most clinicians recommend spironolactone over eplerenone, regardless of NYHA class, owing to lower cost and better provincial drug plan coverage. However, spironolactone has a higher risk of breast tenderness and gynecomastia (10% vs 1% with placebo in the RALES [Randomized Aldactone Evaluation Study] trial).[11] The target dose of eplerenone or spironolactone is typically 25 to 50 mg daily. Patients should be monitored for hyperkalemia (particularly in combination with a renin-angiotensin inhibitor or in patients with diabetes, although this should not preclude them from receiving an MRA); hypotension, although these agents usually do not worsen hypotension in patients with asymptomatic "low" BP; and renal dysfunction (these agents should be avoided in patients with eGFRs < 30 mL/min/1.73 m^2).[4,16] Typically, potassium supplements and potassium-sparing agents should be discontinued in patients taking an MRA and a renin-angiotensin inhibitor.

Back to Mr R.F.

During a telephone call 2 weeks after starting spironolactone, you review Mr R.F.'s laboratory test

***The Art of Optimizing HFrEF Medications: Practical Tips For Common Clinical Concerns** is available at **www.cfp.ca**. Go to the full text of the article online and click on the **CFPlus** tab.

Table 3. Medications that can cause or worsen HF

TYPE	MEDICATIONS
Medications that can cause fluid retention	• Corticosteroids • COX-2 inhibitors (eg, celecoxib) • Gabapentinoids (gabapentin and pregabalin) • Thiazolidinediones (eg, pioglitazone) • NSAIDs (including ASA at doses ≥ 325 mg/d, but excluding topical products) • Black licorice • Kelp
Medications that decrease cardiac output	• Certain antiarrhythmic drugs (eg, dronedarone, flecainide, propafenone) • Certain calcium-channel blockers (eg, diltiazem, verapamil) • β-blocker eye drops (rare, but usually associated with incorrect use) • Carbamazepine (overdose) • Itraconazole • Tricyclic antidepressants (overdose)
Oral medications with high sodium content	• Sodium polystyrene sulfonate (1500 mg of sodium per 15-g dose) • Sodium zirconium cyclosilicate (800 mg of sodium per 10-g dose) • Polyethylene glycol–electrolyte solution (1500 mg of sodium per 1 L)
Medications with a miscellaneous mechanism of cardiotoxicity	Central nervous system • Bromocriptine (heart valve thickening) • Clozapine (myocarditis) • Lithium • Sympathomimetics drugs (eg, amphetamines, methylphenidate, cocaine) Diabetes • Saxagliptin (other DPP4 inhibitors have not been associated with an increased risk of HF) Rheumatology • Hydroxychloroquine (acquired lysosomal storage disorder) • Tumour necrosis factor inhibitors (eg, infliximab)
Oncology drugs	• Anthracyclines (eg, doxorubicin) • Antimetabolites (eg, 5-fluorouracil) • Alkylating agents (eg, cyclophosphamide) • Anti-HER2 agents (eg, trastuzumab, pertuzumab) • Interferons • Interleukin 2 • Taxanes (eg, paclitaxel)

ASA—acetylsalicylic acid, COX-2—cyclooxygenase 2, DPP4—dipeptidyl peptidase 4, HER2—human epidermal growth factor receptor 2, HF—heart failure, NSAID—nonsteroidal anti-inflammatory drug.
Data from Page et al,[8] Al Hamarneh et al,[9] and Yogasundaram et al.[10]

results. His renal function is stable; however, his serum potassium level has increased from 4.8 mmol/L to 5.2 mmol/L. During your discussion, Mr R.F. denies using nonsteroidal anti-inflammatory drugs and salt substitutes that contain potassium. He has no signs or symptoms of hypovolemia. You encourage him to continue taking his 25 mg of spironolactone daily and avoid foods high in potassium (eg, bananas, potatoes, tomatoes), and confirm he will have repeat blood tests done before his upcoming cardiologist appointment.

Bringing evidence to practice: hyperkalemia

The CCS HF guidelines recommend that mild hyperkalemia (serum potassium level of 5.1 to 5.5 mmol/L) is generally acceptable and does not require any reduction or interruption of MRA therapy.[4] Assessing trends and absolute changes in serum potassium level is also important. Patients should be encouraged to maintain a low-potassium diet, as this can have a measurable effect on their serum potassium level. A dietitian consultation may be warranted. Certain drug-drug interactions can also result in an elevated serum potassium level (eg, nonsteroidal anti-inflammatory drugs, trimethoprim, potassium-sparing diuretics).

Back to Mr R.F.

It is now approximately 4 months after Mr R.F.'s initial HFrEF diagnosis. He saw his cardiologist 1 month ago (3 months after discharge); ramipril was discontinued and 49 mg–51 mg of sacubitril-valsartan twice daily was initiated after a 48-hour washout period (often more practical than the manufacturer-recommended 36-hour washout period). At an in-person visit, you review the results of his blood tests done 2 weeks after this change. His renal function is unchanged and his serum potassium level is normal (4.9 mmol/L), as he has been avoiding foods high in potassium. His sitting

Table 4. Summary of newer HFrEF landmark randomized controlled trials

STUDY	POPULATION	INTERVENTION AND COMPARATOR	OUTCOMES		
			PRIMARY	SECONDARY	SAFETY
EMPHASIS-HF (2011)[12]	N = 2737 Key inclusion criteria • Mild HFrEF (NYHA class II) and LVEF ≤ 30% • Taking ACEI or ARB and β-blocker Key exclusion criteria • eGFR < 30 mL/min/1.73 m^2 • Serum potassium level > 5.2 mmol/L	50 mg/d of eplerenone vs placebo	CV death or HFH: 18.3% vs 25.9%, HR = 0.63 (95% CI 0.54 to 0.74), NNT = 14 over 1.8 y	• CV death: 10.8% vs 13.5%, HR = 0.76 (95% CI 0.61 to 0.94), NNT = 38 over 1.8 y • HFH: 12% vs 18.4%, HR = 0.58 (95% CI 0.47 to 0.70), NNT = 16 over 1.8 y • All-cause death: 12.5% vs 15.5%, HR = 0.76 (95% CI 0.62 to 0.93), NNT = 14 over 1.8 y	Hyperkalemia: 8% vs 3.7% (*P* < .001), NNH = 24 over 1.8 y
PARADIGM-HF (2014)[13]	N = 8399 Key inclusion criteria • Clinically stable HFrEF patients (70% NYHA class II) • Elevated natriuretic peptide level (eg, NT-proBNP ≥ 400 ng/L if HFH in the past 12 mo) • Taking a stable dose of ACEI or ARB (equivalent to enalapril ≥ 10 mg/d) and β-blocker • Use of an MRA was encouraged (56%) Key exclusion criteria • Symptomatic hypotension or SBP < 100 mm Hg at screening • eGFR < 30 mL/min/1.73 m^2 • Serum potassium level > 5.2 mmol/L • History of angioedema	97 mg–103 mg of sacubitril-valsartan twice daily vs 10 mg of enalapril twice daily	CV death or HFH: 21.8% vs 26.5%, HR = 0.8 (95% CI 0.73 to 0.87), NNT = 22 over 2.3 y	• CV death: 13.3% vs 16.5%, HR = 0.8 (95% CI 0.71 to 0.89), NNT = 32 over 2.3 y • HFH: 12.8% vs 15.6%, HR = 0.79 (95% CI 0.71 to 0.89), NNT = 36 over 2.3 y • All-cause death: 17% vs 19.8%, HR = 0.84 (95% CI 0.76 to 0.93), NNT = 36 over 2.3 y	Symptomatic hypotension: 14% vs 9.2% (*P* < .001), NNH = 21 over 2.3 y
DAPA-HF (2019)[14]	N = 4744 Key inclusion criteria • Clinically stable HFrEF (68% NYHA class II) • Elevated natriuretic peptide level (eg, NT-proBNP ≥ 400 ng/L if HFH in the past 12 mo) • Taking standard HFrEF therapy (94.4% ACEI, ARB or ARNI; 96% β-blocker; 71% MRA) • 45% had type 2 diabetes at baseline Key exclusion criteria • eGFR < 30 mL/min/1.73 m^2	10 mg/d of dapagliflozin vs placebo	CV death or worsening HF (HFH or an urgent visit resulting in intravenous HF therapy): 16.3% vs 21.2%, HR = 0.74 (95% CI 0.65 to 0.85), NNT = 21 over 1.5 y	• CV death: 9.6% vs 11.5%, HR = 0.82 (95% CI 0.69 to 0.98), NNT = 53 over 1.5 y • HFH: 9.7% vs 13.4%, HR = 0.7 (95% CI 0.59 to 0.83), NNT = 28 over 1.5 y	NS
EMPEROR-Reduced (2020)[15]	N = 3730 Key inclusion criteria • Clinically stable HFrEF (75% NYHA class II) • Elevated natriuretic peptide level • Taking standard HFrEF therapy (89% ACEI, ARB, or ARNI; 95% β-blocker; 71% MRA) • 50% had type 2 diabetes at baseline Key exclusion criteria • eGFR < 20 mL/min/1.73 m^2	10 mg/d of empagliflozin vs placebo	CV death or HFH: 19.4% vs 24.7%, HR = 0.75 (95% CI 0.65 to 0.86), NNT = 19 over 1.3 y	• CV death: 10.0% vs 10.8%, HR = 0.92 (95% CI 0.75 to 1.12), NS • HFH: 13.2% vs 18.3%, HR = 0.69 (95% CI 0.59 to 0.81), NNT = 20 over 1.3 y	Genital infections: 1.7% vs 0.6% (*P* = .005), NNH = 91 over 1.3 y

ACEI—angiotensin-converting enzyme inhibitor, ARB—angiotensin receptor blocker, ARNI—angiotensin receptor–neprilysin inhibitor, CV—cardiovascular, DAPA-HF—Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure, eGFR—estimated glomerular filtration rate, EMPHASIS-HF—Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure, EMPEROR-Reduced—Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction, HF—heart failure, HFH—heart failure hospitalization, HFrEF—heart failure with reduced ejection fraction, HR—hazard ratio, LVEF—left ventricular ejection fraction, MRA—mineralocorticoid receptor antagonist, NNH—number needed to harm, NNT—number needed to treat, NS—not significant, NT-proBNP—N-terminal pro–brain natriuretic peptide, NYHA—New York Heart Association, PARADIGM-HF—Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure, SBP—systolic blood pressure.

BP is 108/68 mm Hg and standing BP is 102/70 mm Hg. Mr R.F. denies any lightheadedness in the clinic, but notes he occasionally feels "woozy" when getting out of his chair. His heart rate today is 62 beats/min. His weight at home has been stable. His mild peripheral edema has resolved and there are no other signs of decompensated HF. His HF remains at NYHA class II.

Mr R.F. states he has been feeling better overall, but he wonders if his BP is too low since starting sacubitril-valsartan. He denies presyncope or syncope, confusion, and blurred vision. You recommend that he continue sacubitril-valsartan at the current dose. However, since he is euvolemic on examination today, you recommend reducing his furosemide from 40 mg daily to 20 mg daily.

Bringing evidence to practice: sacubitril-valsartan

Sacubitril-valsartan is recommended by the CCS HF guidelines for patients who remain symptomatic (NYHA classes II to IV) despite appropriate doses of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker, β-blocker, and MRA.[3] In the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial,[13] sacubitril-valsartan significantly reduced the risk of cardiovascular death or HF hospitalization (ARR = 4.7%) versus an ACEI (enalapril) over 2.3 years (**Table 4**).[12-15] Sacubitril-valsartan also decreased all-cause death (ARR = 2.8%).[13] However, symptomatic hypotension (absolute risk increase = 4.8%) and symptomatic hypotension with a systolic BP of less than 90 mm Hg (absolute risk increase = 1.3%) were statistically significantly increased with sacubitril-valsartan.[13] There is no specific BP target in patients taking sacubitril-valsartan, but a dose reduction or discontinuation should be considered in patients who have persistent symptomatic hypotension. Mild postural lightheadedness usually improves within 2 to 3 weeks of initiating sacubitril-valsartan without a dose adjustment. As such, patients should be encouraged to rise slowly from bed or a seated position, and reassured that these symptoms tend to improve over time. Of note, patients with symptomatic hypotension or systolic BP of less than 100 mm Hg at screening were excluded from the PARADIGM-HF trial.[13] Sacubitril has a natriuretic effect and, therefore, a patient's fluid status and diuretic regimen should be reassessed before and after initiating therapy.

Back to Mr R.F.

It has now been 2 months since Mr R.F. initiated sacubitril-valsartan. His postural lightheadedness resolved after furosemide was reduced to 20 mg daily. He denies peripheral edema and his weight at home has been consistent. He was able to increase his sacubitril-valsartan to the target dose of 97 mg–103 mg twice daily. His home BP has been steady at approximately 110/70 mm Hg. He reports more energy since starting sacubitril-valsartan, but his symptoms remain at NYHA class II. Recent laboratory test results indicate his renal function remains stable (serum creatinine level of 146 μmol/L and eGFR of 41 mL/min/1.73 m^2) and serum electrolyte levels are within normal limits. At a recent follow-up appointment, his cardiologist recommended initiating an SGLT2I to complete his HFrEF quadruple therapy. You discuss this with Mr R.F. by telephone, specifically initiating 10 mg of dapagliflozin daily. He does not have diabetes but he does have insurance that will cover the cost of the medication. He agrees to try dapagliflozin and you provide him with a laboratory requisition to reassess his renal function in 2 weeks.

Bringing evidence to practice

Sodium-glucose cotransporter-2 inhibitors were added to HFrEF foundational therapy in the latest iteration of the CCS HF guidelines and are recommended in individuals with symptomatic HFrEF (ie, NYHA classes II to IV), with or without concomitant type 2 diabetes.[3] Specifically, both dapagliflozin and empagliflozin have been studied in HFrEF (**Table 4**).[12-15] In the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, dapagliflozin statistically significantly reduced the risk of cardiovascular death or worsening HF compared with placebo over 1.5 years (ARR = 4.9%).[14] There was no statistically significant difference in adverse events between the 2 treatment groups. Patients should be counseled on personal hygiene to reduce the risk of mycotic genital infections, although this is more common in individuals with diabetes.[14,17,18] Similar to renin-angiotensin inhibitors, an initial decline in eGFR of 15% to 20% is expected after initiating SGLT2Is, but this tends to improve over time.[14] Volume depletion was more common in the dapagliflozin group (7.5% vs 6.8%), although this difference was not statistically significant.[14] As such, diuretic therapy should be reassessed when initiating SGLT2Is, and the furosemide dose should be reduced if volume depletion occurs. Patients should also be counseled on holding SGLT2Is during acute illness or if at risk of dehydration (patient handout: **https://www.rxfiles.ca/rxfiles/uploads/documents/Heart-Failure-Sick-Days.pdf**). Rates of hypoglycemia were low overall. Further, in a subgroup analysis of the DAPA-HF trial, there was no difference in hemoglobin A_{1c} between dapagliflozin and placebo in individuals without diabetes.[19]

Case resolution

Three weeks later, Mr R.F. has a clinic visit with you to assess his HFrEF quadruple therapy. His eGFR is now 33 mL/min/1.73 m^2, which reflects a 20%

reduction since starting dapagliflozin, and his urea level is 16.2 mmol/L. His weight at home decreased by 2 kg since starting dapagliflozin. He has no peripheral edema, his jugular venous pressure is below the sternal angle, and his lungs are clear on auscultation. His HF remains at NYHA class II. As his serum creatinine and urea levels have increased, and he has examination findings consistent with hypovolemia, you reduce his furosemide from 20 mg daily to as needed and counsel him about how to self-manage his diuretic. You arrange for repeat bloodwork in 2 weeks; the results of this bloodwork indicate improved renal function (serum creatinine level of 150 µmol/L and eGFR of 40 mL/min/1.73 m^2).

This patient case illustrates how HFrEF quadruple therapy can be achieved within a 6-month time frame using collaborative care between a cardiologist and a primary care provider. Another strategy to facilitate this goal is to include a pharmacist or a nurse to help educate and monitor patients and to optimize medications.[20,21] This example also included a mix of in-person and telephone patient encounters. Virtual or telephone visits can be a suitable format for initiating medications (eg, MRAs, SGLT2Is), titrating medications, and following up with patients whose HF is stable, who have demonstrated the ability to assess their HF symptoms, and who have tools at home to facilitate this (eg, weigh scale, BP monitor).[22] Finally, medication adherence should be regularly assessed by all members of the patient's health care team and efforts should be made to address any barriers to implementing therapy.

It is important to note that there is no evidence-based sequence for initiating or titrating HFrEF quadruple therapy and that the order can be tailored to individuals (eg, an SGLT2I may be prescribed before sacubitril-valsartan). There are also additional medications (eg, ivabradine, digoxin) that may be added in select patients as needed.

Conclusion

The management of HFrEF is complex, and current guidelines recommend implementation of HFrEF quadruple therapy within 6 months of diagnosis. Primary care providers can play an important role in managing therapy, promoting adherence, and reducing the risk of de-escalating therapy by addressing concerns related to HF medications. This article highlights practical approaches to some of these concerns, including mild hyperkalemia after starting an MRA, asymptomatic hypotension with sacubitril-valsartan, reduced renal function after starting an SGLT2I, and reassessing diuretics at every visit to maintain euvolemia. Strategies such as collaborative care, in-person and telephone visits, and shared decision-making tools may also facilitate optimization of HFrEF quadruple therapy.

Dr Arden R. Barry is a clinical pharmacist in the Primary Care Clinic at Chilliwack General Hospital in British Columbia and Assistant Professor (Partner) in the Faculty of Pharmaceutical Sciences at the University of British Columbia in Vancouver. **Lynette Kosar** is Clinical Assistant Professor and Information Support Pharmacist in the RxFiles Academic Detailing Program in the College of Pharmacy and Nutrition at the University of Saskatchewan in Saskatoon, and Clinical Pharmacist in the Heart Function Clinic in Chronic Disease Management at the Saskatchewan Health Authority. **Dr Sheri L. Koshman** is Associate Professor in the Mazankowski Alberta Heart Institute and the Division of Cardiology at the University of Alberta in Edmonton. **Dr Ricky D. Turgeon** is Assistant Professor in the Faculty of Pharmaceutical Sciences at the University of British Columbia and Clinical Pharmacy Specialist in the PHARM-HF Clinic at St Paul's Hospital in Vancouver.

Acknowledgment

We thank **Dr Tessa Laubscher** for her review of the manuscript.

Competing interests

RxFiles and contributing authors do not have any commercial competing interests. The RxFiles Academic Detailing Program is funded through a grant from Saskatchewan Health; additional "not for profit; not for loss" revenue is obtained from sales of books and online subscriptions. No financial assistance was obtained for this publication.

Correspondence

Lynette Kosar; e-mail **lynette@rxfiles.ca**

References

1. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation* 1981;64(6):1227-34.
2. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J Card Fail* 2021 Mar 1. Online ahead of print.
3. McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz JA, Giannetti N, 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(4):531-46.
4. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, et al. 2017 Comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure. *Can J Cardiol* 2017;33(11):1342-433. Epub 2017 Sep 6.
5. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. *Eur J Heart Fail* 2019;21(11):1306-25. Epub 2019 Sep 16.
6. Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J* 2007;154(2):260-6.
7. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. *J Am Coll Cardiol* 2018;72(4):351-66.
8. Page RL 2nd, O'Bryant CL, Cheng D, Dow TJ, Ky B, Stein CM, et al. Drugs that may cause or exacerbate heart failure. A scientific statement from the American Heart Association. *Circulation* 2016;134(6):e32-69. Epub 2016 Jul 11. Erratum in: *Circulation* 2016;134(12):e261.
9. Al Hamarneh YN, Tsuyuki RT. Heart failure. In: Tisdale JE, Miller DA, editors. *Drug-induced diseases: prevention, detection, and management.* 3rd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2018.
10. Yogasundaram H, Putko BN, Tien J, Paterson DI, Cujec B, Ringrose J, et al. Hydroxychloroquine-induced cardiomyopathy: case report, pathophysiology, diagnosis, and treatment. *Can J Cardiol* 2014;30(12):1706-15. Epub 2014 Aug 23.
11. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341(10):709-17.
12. Zannad F, McMurray JJV, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;364(1):11-21. Epub 2010 Nov 14.
13. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371(11):993-1004. Epub 2014 Aug 30.
14. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;381(21):1995-2008. Epub 2019 Sep 19.
15. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;383(15):1413-24. Epub 2020 Aug 28.
16. Serenelli M, Jackson A, Dewan P, Jhund PS, Petrie MC, Rossignol P, et al. Mineralocorticoid receptor antagonists, blood pressure, and outcomes in heart failure with reduced ejection fraction. *JACC Heart Fail* 2020;8(3):188-98. Epub 2020 Jan 8.
17. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380(4):347-57. Epub 2018 Nov 10.
18. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373(22):2117-28. Epub 2015 Sep 17.
19. Petrie MC, Verma S, Docherty KF, Inzucchi SE, Anand I, Belohlávek J, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. *JAMA* 2020;323(14):1353-68. Erratum in: *JAMA* 2021;325(13):1335.

20. Cao VFS, Cowley E, Koshman SL, MacGillivray J, Sidsworth M, Turgeon RD. Pharmacist-led optimization of heart failure medications: a systematic review. *J Am Coll Clin Pharm* 2021;4(7):862-70. Epub 2021 Apr 30.
21. Koshman SL, Charrois TL, Simpson SH, McAlister FA, Tsuyuki RT. Pharmacist care of patients with heart failure: a systematic review of randomized trials. *Arch Intern Med* 2008;168(7):687-94.
22. Miller RJH, Howlett JG, Fine NM. A novel approach to medical management of heart failure with reduced ejection fraction. *Can J Cardiol* 2021;37(4):632-43. Epub 2021 Jan 14.

This article is eligible for Mainpro+ certified Self-Learning credits. To earn credits, go to **www.cfp.ca** and click on the Mainpro+ link.
Can Fam Physician 2021;67:915-22. DOI: 10.46747/cfp.6712915
La traduction en français de cet article se trouve à **www.cfp.ca** dans la table des matières du numéro **de décembre 2021** à la **page e329**.