"MORTAR & PESTLE" CONCORDIA UNIVERSITY WISCONSIN SCHOOL OF PHARMACY STUDENT WRITING CLUB:

The Use of Sodium Glucose Co-transporter-2 Inhibitors in the Treatment of Heart Failure

by Dragana Vlaski, 2024 PharmD Candidate, Timothy H. Vogt, 2024 PharmD Candidate

Heart failure (HF) is a clinical manifestation showing functional impairment and anatomical changes of the heart resulting in inadequate filling or ejection of blood from the heart.[1] Symptoms arise over time as cardiac output declines, making it difficult for the heart to support the body's blood and oxygen needs. Congestive HF is a highly prevalent, chronic condition that affects a little more than 6 million patients in the United States. The number of people diagnosed with heart failure is increasing and projected to rise 46 percent by 2030.[2] As this condition can get worse if left untreated, it is imperative that patients remain adherent to medications and make any needed changes in diet, physical activity, and lifestyle to have the best quality of life possible.

Patients with HF are initially classified as having HF with reduced ejection fraction (HFrEF; EF ≤40%) or preserved ejection fraction (HFpEF; EF ≥50%).[3] Ejection fraction is a measurement of the percentage of blood the left ventricle pumps out with each contraction.[4] HFrEF is a type of heart failure where the heart muscle is weakened and is unable to pump enough blood to the rest of the body, while HFpEF is caused by the lowered filling of the ventricle and/or impaired relaxation of the ventricle.[5] The aim of treatment is to improve quality of life, lessen symptoms, and decrease the likelihood of disease progression.[6] Herein, we explain the classification and pathophysiology of HF, describe the beneficial role of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in heart failure, and lastly, inform healthcare professionals about how to effectively educate patients on SGLT2i therapy when they are prescribed for HF.

TABLE 1. Stages of Heart Failure[6]

Stage	Structural Damage	Patient Factors	Recommended use of SGLT2i
A	At risk for HF No structural damage	Has HTN, CVD, DM, obesity, family history or genetic predisposition for cardiomyopathy	Add-on for primary prevention for patients with T2DM only
B	Pre-HF Evidence of structural damage	May not be symptomatic May have 1 of: evidence of increased filling pressures, structural disease, risk factors and increased BNP or troponin levels	Add-on to reduce the risk of exacerbation regardless of T2DM diagnosis and EF (only if the patient is symptomatic).
C	Symptomatic HF Structural damage with ongoing symptoms	Ongoing or previous symptoms. Ex: fatigue, pain, dyspnea	Start dapagliflozin or empagliflozin regardless of T2DM diagnosis and EF.
D	Advanced HF	Symptoms that impede daily life with repeated hospitalizations despite drug therapy management	Start dapagliflozin or empagliflozin regardless of T2DM diagnosis and EF.

CVD = cardiovascular disease; BNP = b-type natriuretic peptide; DM = diabetes mellitus HF = heart failure; HTN = hypertension; EF = ejection fraction; T2DM = type 2 diabetes mellitus;

Classification, Etiology, Risk Factors, & Primary Prevention

According to the 2022 AHA/ACC/HFSA Guideline, HF is defined by four stages (A–D) of varying development and worsening of the disease.[6] See Table 1 for details on staging criteria. Heart failure is further characterized using the New York Heart Association (NYHA) classification system for stages C (symptomatic HF) and D (advanced HF). This is a subjective assessment that may change over time, whereas the stage of heart failure a patient is in (A–D) can only progressively get worse. The NYHA classification is described by class (I-IV) in Table 2.[6]

To prevent progression of the disease, clinicians should focus on primary prevention and optimization of medication therapy. For instance, patients with hypertension and/or cardiovascular disease (CVD) should have antihypertensive medications, a healthy lifestyle maintaining adequate diet and exercise, and cholesterol management. Furthermore, if these patients have type 2 diabetes mellitus (T2DM) and have or are at risk of CVD, they should be started on SGLT2i therapy. Lastly, those with genetic cardiomyopathies or family history of an abnormality should receive genetic screening and counselling, while those who have been exposed to cardiotoxic agents should receive interdisciplinary assessment.[6]

The most common causes of HF include ischemic heart disease and myocardial infarction (MI), hypertension (HTN), and valvular heart disease.[6] In the United States, approximately 115 million people have hypertension, 100 million have obesity, 92 million have prediabetes, 26 million have diabetes, and 125 million have atherosclerotic cardiovascular disease, which are all known risk factors for developing HF.[6] Coronary artery disease is one of the major risk factors for HF because it damages the myocardium and may cause remodeling and scar formation, resulting in decreased cardiac output and contractility.[3] Furthermore, previous myocardial infarction

raises HF risk 10 times higher than in the normal population during the first year after the infarction and up to 20 times in following years.[7]

Pathophysiology

Heart failure is a complex condition that results in a lowered cardiac output unable to adequately profuse or fulfill the body's metabolic demands.[5,8] Cardiac output, generated primarily by heart rate and stroke volume (SV), is defined as the quantity of blood pumped by the heart over a given time. Stroke volume, which is the volume of blood ejected from the ventricle during each heartbeat, is influenced by preload, contractility, and afterload. Typically, all these factors work together to produce an efficient cardiac output, which results in a higher mean arterial pressure (MAP) and adequate perfusion of blood throughout the body. HF primarily results from dysfunction of the left or right ventricle. Dysfunction of the left ventricle can be further classified as diastolic or systolic dysfunction. Diastolic dysfunction is insufficient relaxation and filling of the ventricle, which results in an ejection fraction (EF) >40%, while systolic dysfunction is the impaired contraction of the ventricle, which has an EF <40%. Common symptoms of left ventricular dysfunction include symptoms of pulmonary congestion, like dyspnea and sputum-producing cough. Often, as the left ventricle fails, the right ventricle is also impaired, leading to increased pressure in the vena cava and right atrium due to increased amounts of blood in the right ventricle. This results in higher blood volume throughout the body and lower extremities, causing peripheral edema, jugular venous distention, hepatomegaly, and other symptoms.[8]

Following the loss of or injury to cardiac tissue induced by the aforementioned risk factors, HF manifests itself as structural, cellular, and neurohormonal changes to compensate for the anatomical dysfunction. These changes work synchronously, primarily through the Renin-angiotensin-aldosterone-system (RAAS) and sympatho-adrenergic systems, to maintain the functioning of the heart by retaining sodium and water to increase SV.[8] However, these compensatory mechanisms lead to ongoing deterioration of the cardio-renal system and increased peripheral vasoconstriction and volume overload.[5] For instance, the sympathetic nervous system releases catecholamines, activating β-1, β-2, and α-1 receptors, and increasing heart rate, contractility, and peripheral vasoconstriction. This continuous activation induces cardiac toxicity through high oxygen demand, prompting arrhythmias and lowered EF. In response to this activation and lowered EF, the kidneys secrete renin to further trigger the RAAS, which leads to additional dysfunction. This system causes sodium and water retention

TABLE 2. NYHA Functional Classification for Heart Failure[6]

NYHA Class I	No limitations in physical activity resulting from their HF
NYHA Class II	Comfortable at rest but have slight symptoms resulting from HF (dyspnea, fatigue, lightheadedness) with ordinary activity
NYHA Class III	Comfortable at rest but have symptoms of HF with less than ordinary activity
NYHA Class IV	Unable to carry out any physical activity without symptoms and have symptoms at rest

TABLE 3. Heart Failure with Reduced Ejection Fraction (HFrEF) Medication Education

HF Medication Class	*Benefit in HF*	*How Medication Works*	*Teaching Points*
Angiotensin receptor-Neprilysin Inhibitors (ARNi) **Sacubitril/valsartan (Entresto)** **Angiotensin-Converting Enzyme Inhibitors (ACEi)** Lisinopril Enalapril Captopril **Angiotensin Receptor Blockers (ARBs)** Candesartan Valsartan Losartan	↓ mortality ↓ hospitalizations ↑ quality of life	• ARNi specific: blocks neprilysin (protein) which breaks down important hormones known as natriuretic peptides. Natriuretic peptides regulate blood volume and vascular tone. ARNis also block angiotensin II type 1 receptor, preventing vasoconstriction and aldosterone release. • Reduces how hard the heart works. • Delay or slow progression of HF.	• ARNi specific: there should be at least 36 hours between ACEi and ARNi doses. • Will cause potassium levels to increase, avoid additional potassium in foods and salt substitutes. Kidney function and potassium levels will be checked regularly. • Will lower blood pressure, use caution when making rapid changes in posture. • ACEi specific: May cause a persistent, dry cough. • Rare adverse effects include angioedema (swelling around mouth or face).
Beta Blockers (BB) Metoprolol Succinate Carvedilol Bisoprolol	↓ mortality ↓ hospitalizations	• Decrease heart rate and workload of the heart. • Reverse remodeling process. • Improve strength and contractility of heart.	• Monitor for worsening symptoms of HF: fluid retention, fatigue, shortness of breath. • Will lower blood pressure, use caution when making rapid changes in posture. • May worsen wheezing in patients with reactive airway diseases. Monitor use of rescue therapies (ex: albuterol). • Fatigue may occur, but it is dose related and transient (4-6 weeks). • Patients with Diabetes should monitor blood glucose levels more closely, and the s/s of hypoglycemia may be masked.

TABLE 3. Heart Failure with Reduced Ejection Fraction (HFrEF) Medication Education (Cont.)

HF Medication Class	*Benefit in HF*	*How Medication Works*	*Teaching Points*
Aldosterone Antagonists Spironolactone Eplerenone	↓ mortality ↓ hospitalizations ↑ quality of life	• Blocks aldosterone stress hormone, leading to NaCl/ water excretion, while maintaining potassium levels.	• Will cause potassium levels to increase, avoid additional potassium in foods and salt substitutes. Kidney function and potassium levels will be checked regularly. • May cause some fluid loss; monitor for dehydration. • Spironolactone specific: May cause breast tissue swelling or breast tenderness in males.
Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i) Dapagliflozin Empagliflozin	↓ mortality ↓ hospitalizations ↑ quality of life	• Protects the heart and kidneys by decreasing excess fluid, improving BP. • May help with symptoms of HF, such as SOB or swollen ankles, feet and legs.	• Renal function, volume status, BP, and electrolytes (Mg, K, Phos) will be monitored periodically throughout treatment. • Will lower blood pressure, use caution when making rapid changes in posture – especially elderly and renal impairment. • Monitor for dehydration and dizziness. • Use proper hygiene and monitor for mycotic/UTI infections. • Rare but life threatening: too much acid in the blood/urine in T2D (DKA). Monitor for signs/symptoms of nausea/ vomiting, abdominal pain, SOB, malaise. Fournier's Gangrene - necrotizing fasciitis of the genitalia. **Other warnings/precautions:** • SGLT2i should be held at least 3 days prior to surgical procedures to avoid risk of ketoacidosis. • Use of SGLT2i is contraindicated in patients with diabetic ketoacidosis or patients with type 1 DM. • Not recommended for dialysis patients; do not use if eGFR<20 mL/min for Empagliflozin and <30 for dapagliflozin.
Loop Diuretics Furosemide Bumetanide Torsemide	↑ quality of life NO impact on mortality	• Reduce fluid in the lungs, abdomen, lower extremities, and other parts of the body. • Decrease in excess fluid decreases workload of the heart.	• Take medication early in the day, avoid taking at bedtime • Check weight daily and contact provider with significant weight gain. • Monitor for dehydration and dizziness. • Renal function, potassium, and magnesium levels will be checked regularly. • Limit salt intake to avoid additional fluid retention.
Hydralazine/Nitrates	↓ mortality* ↓ hospitalizations ↑ quality of life **Benefit in mortality is seen in African American patients and those intolerant to an ACEI or ARB*	• Relax blood vessels. • Increase supply of blood and oxygen to the heart. • Reduce the workload of the heart.	• Nitrates may initially cause a headache which is transient. Acetaminophen may be used to treat headaches. • Will lower blood pressure, use caution when making rapid changes in posture. • Avoid use of phosphodiesterase type 5 inhibitors with nitrates.
The following may be used as add-on therapy after other goal directed medical therapy (GDMT) has been optimized			
Ivabradine	↓ hospitalizations ↑ quality of life ↓ mortality	• Slows the heart rate by inhibiting the electrical current made by the heart's natural pacemaker (SA node).	• Heart rhythm will be monitored prior to initiation and with any dose adjustment as use increases the risk of Afib. • Take with food around the same time of day; avoid grapefruit/grapefruit juice. • Monitor for signs of high blood pressure like very bad headache or dizziness, passing out, or change in eyesight. • Monitor signs for slow or abnormal heartbeat, shortness of breath, vision changes, feeling dizzy, tired, or weak. • Contraindicated in patients with: acute decompensated HF; clinically significant hypotension (BP <90/50 mmHg) or bradycardia (HR <50 bpm); pacemaker dependence, severe hepatic impairment; concomitant use with strong CYP3A4 inhibitors.
Vericiguat	↓ hospitalizations ↑ quality of life ↓ mortality	• Increases levels of cyclic guanosine monophosphate (cGMP) leading to smooth muscle relaxation and vasodilation.	• Take this medication with food. • Common side effects include dizziness or passing out, feeling tired or weak. • Avoid use of phosphodiesterase type 5 inhibitors (ex: erectile dysfunction medications) while on vericiguat.
Digoxin	↓ hospitalizations ↑ quality of life NO impact on mortality	• Improves heart contractility. • Blocks stressful hormones.	• Digoxin levels will be monitored. • Signs of toxicity include: nausea, vomiting, blurred or colored vision, and abnormal heart rhythms. • Several drug interactions, ask the pharmacist to assess interactions.

and vasoconstriction. The continued activation of both neurohormonal systems eventually causes ventricle remodeling.[5,8]

Due to the constant failure and compensation stress, the ventricles' shape, size, and structure are altered. These changes manifest as chamber dilatation, the disarray of cardiac muscle, hypertrophy, and overall shape. This remodeling continues until it becomes antagonistic to heart function while furthering compensation processes and less effective pumping.[5,8]

As this cycle of poor pumping and compensation continues, cardiomyocytes alter intracellular calcium for positive inotropic effects and release natriuretic peptides ANP and BNP, along with other components, to counteract vasoconstriction and inhibit vasopressin release and the RAAS. The changes in intracellular calcium increase energy demand, impair relaxation, and cause pro-arrhythmic effects.[5,8]

Treatment for Heart Failure

In the last five years, leading changes have been made regarding heart failure treatment. The 2022 ACC/AHA guidelines for the diagnosis and treatment of HFrEF established 4 classes of medications as goal-directed medical therapy (GDMT): an angiotensin system blocker (ACE-inhibitor [ACEi] or angiotensin receptor blocker [ARB], or angiotensin receptor-neprilysin inhibitor [ARNI]); beta-blockers; mineralocorticoid receptor antagonists (MRA); and the new addition of SGLT2i drugs, specifically, dapagliflozin or empagliflozin.[6] The benefits of use and mechanisms of action of each of these classes along with additional therapy for HFrEF for symptom management are listed in Table 3. The 2022 ACC/AHA guidelines recommend the use of diuretics (as needed) and SGLT2i for the treatment of symptomatic HFpEF and HFmEF with an ejection fraction of 41-49% and ≥50%, respectively. These agents provide the same mechanistic benefits as mentioned for HFrEF. Weaker recommendations with moderate-quality evidence support the use of an ARNI, MRA, ACEi, and ARB as additional pharmacologic treatment options for these patients.

Use of SGLT2i in Heart Failure

Sodium glucose co-transporter-2 inhibitors were added as a class of heart failure medications that historically were only used for the treatment of T2DM. They function by inhibiting glucose reabsorption in the proximal tubule of the nephron and, thus, reducing plasma glucose levels.[9] However, cardiorenal benefits that have been observed from SGLT2i mechanisms that are independent of lowering glucose levels. For example, beneficial hemodynamic effects of an SGLT2i in heart failure patients result from reduced preload and plasma volume. In addition, newer SGLT2i mechanisms target pathways that focus on controlling inflammation, as current evidence suggests that chronic inflammation plays a key role in the development of HF.[10] Within this class of medications, empagliflozin and dapagliflozin are the only two agents approved for use in heart failure at this time.[6] A few large-scale, groundbreaking clinical trials have shown that SGLT2is have a positive impact on cardiovascular outcomes in heart failure patients, irrespective of diabetes presence. In November of 2020, the New England Journal of Medicine (NEJM) published a double-blind randomized placebo-controlled trial, titled Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), which studied the effects of dapagliflozin in patients with heart failure

TABLE 4. Comparison of the DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved Trials[9,11,12]

	DAPA-HF (n=4,744)	*EMPEROR-Reduced (n=3,730)*	*EMPEROR-Preserved (n=5,988)*
Clinical Outcomes	Dapagliflozin 10 mg vs placebo	Empagliflozin 10 mg once daily vs placebo	Empagliflozin 10 mg once daily vs placebo
Primary Outcome	Composite of death from CV causes or worsening HF	Composite of CV death or hospitalization for worsening HF.	Composite outcome event (death from CV causes or hospitalization for HF).
Primary Outcome Results	HR, 0.74; 95% CI (0.65–0.85) P<0.001	HR, 0.75; 95% CI (0.65–0.86) P<0.001	HR, 0.79; 95% CI (0.69 to 0.90) P<0.001)
Median follow-up (mo)	18	16	26
Number Needed to Treat (NNT)	21 (95% CI, 15 to 38)	19 (95% CI, 13 to 37).	31 (95% CI, 20 to 69)
Inclusion Criteria*	Age of at least 18 years, an ejection fraction of 40% or less, and NYHA class II, III, or IV symptoms.	Age of at least 18 years, an ejection fraction of 40% or less, and (NYHA) class II, III, or IV symptoms.	Age of at least 18 years, an ejection fraction of >40%, and (NYHA) class II, III, or IV symptoms.
Exclusion Criteria*	(eGFR) <30 mL/min/1.73m2, type 1 diabetes, or systolic blood pressure of <95 to 100 mmHg.	(eGFR) <20 mL/min/1.73m2, type 1 diabetes, or systolic blood pressure of <95 to 100 mmHg.	See full list of exclusion criteria within the trial data
Conclusion	Patients who received dapagliflozin had a lower risk of worsening HF or death from CV causes.	Patients who received Empagliflozin had a lower risk of CV death or hospitalization for HF.	Empagliflozin reduced the risk of CV death or hospitalization for HF in patients with HF and a preserved ejection fraction.

** See full list of inclusion and exclusion criteria within the DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved trials*
Abbreviations: HF = heart failure, CV = Cardiovascular

and reduced ejection fraction. Following the DAPA-HF trial, the empagliflozin trials that were also published in the NEJM included evidence in both HFrEF and HFpEF: the Empagliflozin Outcome trial in patients with chronic heart failure with reduced ejection fraction (EMPEROR-Reduced) and the Empagliflozin Outcome trial in patients with heart failure with a preserved ejection fraction (EMPEROR-Preserved). The results of DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved were consistent among patients with or without diabetes at baseline.[9,11,12] Table 4 summarizes key findings from each trial.

The 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure now supports using SGLT2i in patients with symptomatic chronic HFrEF to reduce hospitalization and cardiovascular mortality with or without comorbid T2DM. The use of an SGLT2i may also be beneficial in patients with heart failure with midrange ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF).[6]

As of now, further research is being conducted to provide more data on the use of SGLT2i for patients living with heart failure with a preserved ejection fraction. More evidence to support the use of SGLT2i, specifically the addition of dapagliflozin, in patients with HFpEF is underway. These findings have extended the therapeutic use of dapagliflozin and empagliflozin beyond agents used for glycemic control in patients with T2DM. For individuals with T2DM and cardiovascular disease or those who are at a high risk of cardiovascular disease, the guidelines now recommend using SGLT2i as an add-on therapy in stage A for primary prevention. Additionally, SGLT2i can be used to reduce the risk of HF exacerbation in stage B HF patients. Patients with stages C and D heart failure can begin taking an SGLT2i at any time during their HF treatment. In stages B, C, and D, an SGLT2i can be used independently regardless of whether the patient has T2DM. Table 1 includes these recommendations.

Pharmacist Patient Education

When educating a heart failure patient, pharmacists should focus on the benefits of and reasons for taking the SGLT2i; how the patient should take it; potential adverse drug reactions (ADRs) to be aware of; and when the patient should return to the clinic for evaluation of therapy (Table 5). In addition to these points, the pharmacist should address any concerns brought up by the patient during the education and following visits. In addition, pharmacists should implement teach-back methods to ensure adequate education and emphasize the importance of lifestyle modifications along with any education on new medications.[6]

TABLE 5. SGLT2-Inhibitor Patient Education[13,14,15]

Benefits in HF Treatment	• Lower risk of CV death • Lower risk of all-cause mortality • Lower risk of hospitalization due to HF • Lower body weight • Lower BP
Dosing	• 10mg by mouth daily (FDA approved dosing for HF treatment for Dapagliflozin and Empagliflozin) • Commonly taken in the AM • No regard to food intake
Monitoring Parameters	• Volume status • Blood pressure • Blood glucose levels • Serum electrolytes • Renal function • HbA1c (if patient has T2DM)
Return to Clinic	• 2 weeks post-initiation
Common ADRs	• Increased urination • Urinary tract infections • Genital mycotic infections
Serious/Rare ADRs	• Ketoacidosis » Nausea/vomiting, excessive thirst, frequent urination, sweet-smelling breath, fatigue, confusion » More likely with ketogenic diets and acutely ill • Acute Kidney Injury » Low urine output, dizziness, tachycardia, dry mucous membranes, thirst • Fournier's Gangrene » Pain in genital/perianal area, subcutaneous crepitus odor, scrotal swelling, tachycardia, exudate from region, fever • Allergic reaction » Peeling/blistering skin, rash, swelling of face, tongue, lips, or airway, difficulty breathing
Avoidance of ADRs	• Increase personal hygiene, especially before/following intercourse • Avoid restraining from urinating • Report discomfort when urinating • Report discharge from genitals • Report fever • Report pelvic/abdominal pain • Consider suspending use during acute illness
Drug-Drug Interactions	• Insulin (caution: increased risk of hypoglycemia) • Insulin Secretagogues (caution: increased risk of hypoglycemia) • NSAIDs (caution: increased risk of Acute Kidney Injury)
Contraindications	• Dialysis patients • Patients with Type 1 diabetes

Conclusion

Heart failure is a complex disease state necessitating complex management to lower a patient's risk of heart failure exacerbation. Through lifestyle modifications and proper medication use, the addition of SGLT2i drugs to GDMT gives clinicians and patients another avenue to achieve control of heart failure signs/symptoms and comorbidities. The recently updated national guidelines for heart failure, coordinated by AHA/ACC/HSFA, are excellent resources to educate clinicians on the best recommendations and evidence for patient treatment. It is vital for pharmacists to stay up to date on current treatments to inform and educate patients and clinicians on the best choices of therapy and to achieve the best patient care possible.

Dragana Vlaski and Timothy Vogt are 2024

Doctor of Pharmacy Candidates at Concordia University Wisconsin School of Pharmacy in Mequon, WI.

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