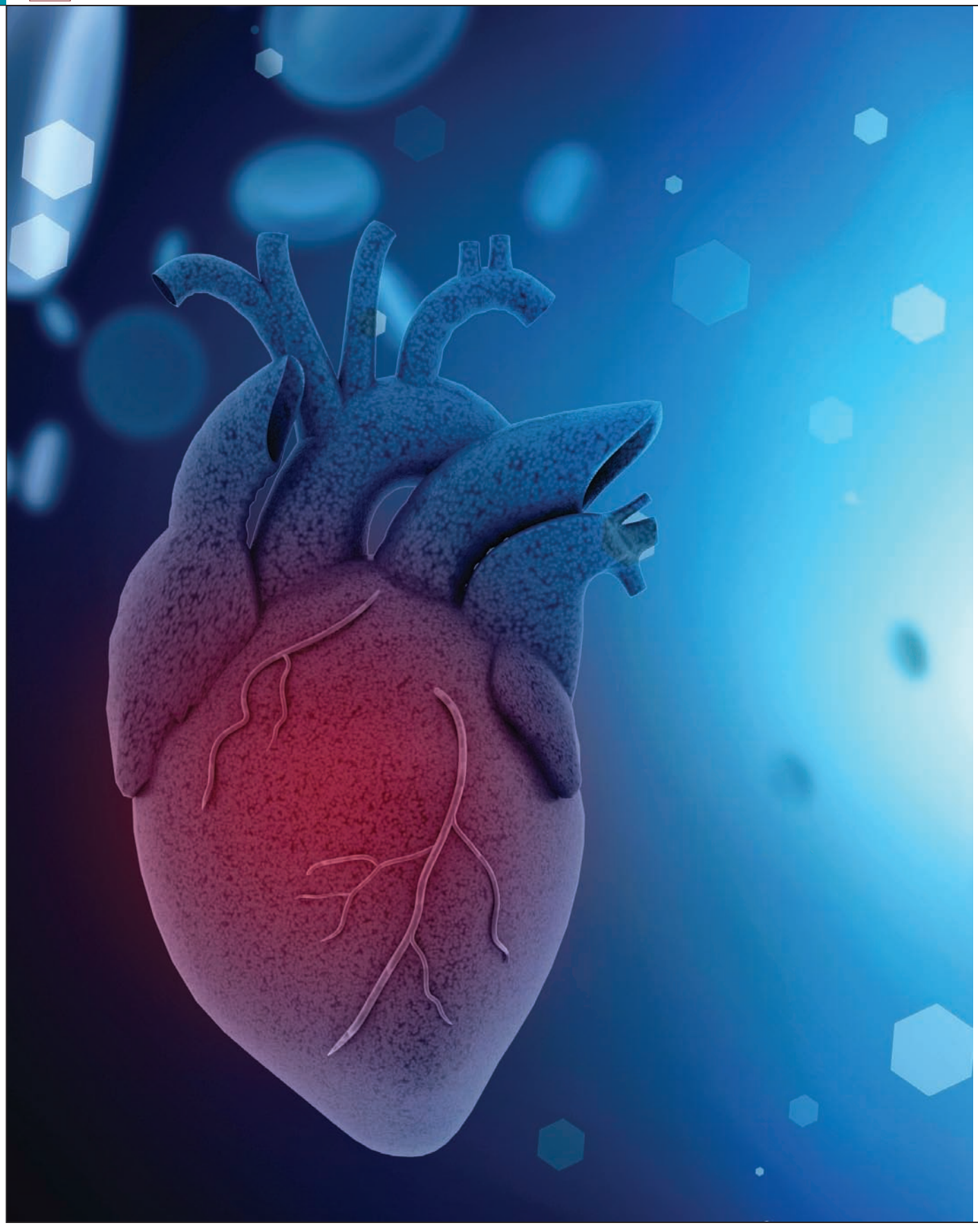
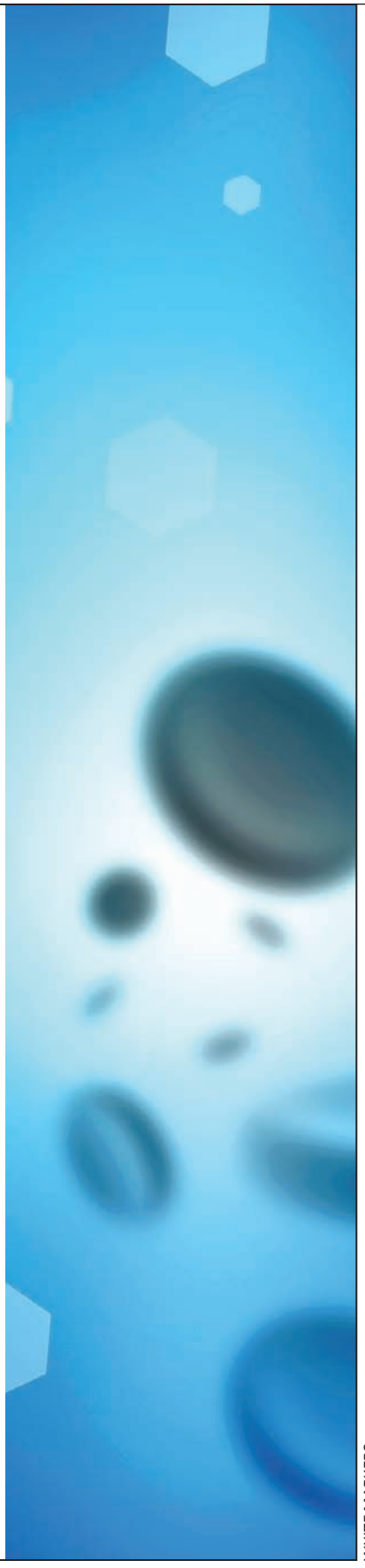
NCPD 2.0 CONTACT HOURS

℞ 1.5 CONTACT HOURS





SGLT2 inhibitors: What role do they play in heart failure with reduced ejection fraction?

Abstract: Sodium-glucose cotransporter-2 (SGLT2) inhibitors can decrease risk for heart failure in patients with type 2 diabetes and can decrease risk of major cardiovascular events in patients with heart failure (HF) and diabetes. Specific SGLT2 inhibitors can also decrease major cardiovascular events in patients with HF only.

By Christy McDonald Lenahan, DNP, FNP-BC, ENP-C, CNE; Deedra Harrington, DNP, MSN, ACNP-BC; and Frances Stueben, DNP, RN, CHSE

Lifetime risk of heart failure (HF) is estimated to be one in five in Americans age 40 or over and carries an annual cost burden of over $30 billion.[1,2] In patients with type 2 diabetes (T2D), there is a two- to four-fold increased risk for HF.[3] Reasons for the increased risk of HF include similar risk factors for both disease processes: obesity, hypertension, coronary artery disease, and/or history of myocardial infarction (MI) as well as macrovascular disease and fibrosis of the cardiac wall secondary to long-term effects of poor glycemic control.[3]

Risk for major adverse cardiovascular events (MACEs), which include cardiovascular (CV) death, nonfatal MI, and stroke, as well as hospitalization for HF, increases exponentially in patients who have concomitant T2D and HF.[4] Further, studies have demonstrated that in patients diagnosed with HF with reduced ejection fraction (HFrEF), risk for CV mortality and hospitalization for HF increase, and in some instances, is doubled when compared with patients with HF with preserved ejection fraction (HFpEF).[5,6]

Recent evidence has demonstrated that use of sodium-glucose cotransporter-2 (SGLT2) inhibitors, a class of medications already approved for use in T2D, can prevent HF in patients with T2D and decrease MACEs and hospitalization for HF in patients with concomitant HF and T2D.[2] Further discussion will detail diagnosis and staging of HF, efficacy of SGLT2 inhibitors in prevention and treatment of HF in patients with T2D, and the potential of SGLT2 inhibitor use in HF alone.

HF classification and suggested management

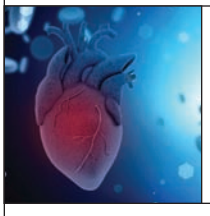
The American College of Cardiology (ACC) classifies HF into one of three categories. HFpEF is defined as HF with a preserved ejection fraction (EF) of greater than or equal to 50%.[2,7] HF with midrange EF (HFmrEF) typically has an EF of less

Keywords: canagliflozin, dapagliflozin, empagliflozin, heart failure, heart failure with reduced ejection fraction, major adverse cardiovascular events, SGLT2 inhibitors, type 2 diabetes

WHITE MARKERS

than 50% but greater than 40%.[8] HFrEF is defined as HF with a reduced EF of less than or equal to 40%.[7,8]

HFrEF is a complex clinical syndrome in which the body is not able to maintain adequate metabolic supply to organs and tissues due to structural and/or functional myocardial dysfunction.[9,10] Current recommendations and goals for HFrEF treatment focus on identification of correctable causes and prevention of disease progression. The mainstay of treatment for initial and chronic management of HFrEF is guideline-directed medical therapy (GDMT), which has been shown to improve the overall survival rate of patients living with HFrEF.[7] GDMT involves treatment of HF with evidence-based medication therapies to prevent and/or delay the need for more invasive treatment modalities such as implantable cardioverter-defibrillator (ICD), left ventricular assist device (LVAD), or heart transplant, and is based on the 2013 ACC/American Heart Association (AHA) Guideline for the Management of Heart Failure and the 2017 ACC/AHA/Heart Failure Society of America (HFSA) focused update.[7,11]



HFrEF is a complex clinical syndrome in which the body is not able to maintain adequate metabolic supply to organs and tissues due to structural and/or functional myocardial dysfunction.

The ACC/AHA stage heart failure as Stage A through D while the New York Heart Association (NYHA) classifies heart failure as class I-IV (see *HF ACC/AHA stage vs. NYHA class*).[7,10] Management recommendations are dependent on HF stage.

Stage A is classified as individuals at risk for developing HF with no clinical signs of HF. Treatment recommendations for Stage A include management of comorbidities: hypertension (HTN), diabetes mellitus, atherosclerotic disease, obesity, and metabolic syndrome as per current guidelines.[7,11] Pharmacologic therapy may include thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), and/or calcium channel blockers (CCBs) in non-Black patients with hypertension and T2D who do not have chronic kidney disease (CKD), and may include thiazide diuretics and/or CCBs in Black patients with hypertension and T2D who do not have CKD. In patients with hypertension and T2D with CKD, pharmacologic management should include an ACE inhibitor or ARB.[12] In all patients with T2D, agents for glycemic control and/or statins should be used for lipid control as needed in combination with lifestyle changes.[7,11]

Stage B (NYHA I) is classified as individuals with asymptomatic structural heart disease such as left ventricular hypertrophy.[7] Pharmacologic treatment recommendations include ACE inhibitors or ARBs, beta-blockers, BP control, and lipid management with statins in combination with lifestyle changes, to be individualized based on factors such as presence of reduced EF, history of MI or acute coronary syndrome, and structural cardiac abnormalities.[7,11]

Stage C (NYHA I-IV) is classified as individuals that present with symptomatic or previously symptomatic structural heart disease; left ventricular systolic dysfunction is present in those with HFrEF. Management is dependent on EF. In patients with HFpEF, management is focused on improved quality of life, prevention of hospitalization, and identification and treatment of comorbidities. In patients with HFrEF, management is focused on symptom control and prevention of hospitalization and death. In addition to guideline-directed treatment of comorbidities (for example, HTN, T2D, coronary artery

HF ACC/AHA stage vs. NYHA class[7,10]

ACC/AHA Heart Failure Stage	NYHA Class
A. at risk for developing HF, without signs and symptoms	
B. asymptomatic structural heart disease	I. asymptomatic
C. symptomatic or previously symptomatic structural heart disease	I. asymptomatic II. symptomatic with moderate exertion III. symptomatic with minimal exertion IV. symptomatic at rest
D. refractory heart failure requiring advanced interventions	IV. symptomatic at rest

SGLT2 inhibitors[27,34,35]

Drug	Brand names	Labeled indications*
Canagliflozin	Invokana	T2D–as adjunct to diet and exercise. Decrease MACEs in T2D + CVD
Dapagliflozin	Farxiga	T2D–as adjunct to diet and exercise. Decrease risk of HF hospitalization in T2D + CVD/CV risk factors Decrease risk of CV death and HF hospitalization in HFrEF
Empagliflozin	Jardiance	T2D–as adjunct to diet and exercise. Decrease CV death in T2D + CVD

Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; HFrEF, heart failure with reduced ejection fraction; MACE, major adverse cardiovascular events; T2D, type 2 diabetes.
*Not a complete list of all FDA-labeled indications.

disease), routine pharmacologic management typically includes diuretics for fluid retention, ACE inhibitors or ARBs, beta-blockers, and, for certain patients, aldosterone receptor antagonists and/or ivabradine. If the patient has adequate BP control and is on an ACE inhibitor or ARB, the patient can be transitioned to an angiotensin receptor-neprilysin inhibitor (ARNI). In patients who are Black, it is recommended to add a combination hydralazine-isosorbide dinitrate.[7,11] Another management strategy focuses on sudden cardiac death prevention with ICD placement for patients who are NYHA class II-III with an EF of less than or equal to 35% and who are 40 days or more post MI and have an expected survival of more than 1 year.[7,11]

Stage D (NYHA IV) is classified as refractory HF (severe symptoms that persist despite maximum GDMT). Management focuses on symptom control, improved quality of life, and reduced hospitalizations through advanced treatment strategies with the continuum ending at LVAD or cardiac transplantation.[7,11] Finally, for patients receiving maximum GDMT who do not wish to pursue advanced treatment strategies or who are not eligible for them, hospice may be a consideration if the patient has 6 months or less to live.[13]

When to refer

Timely referral to cardiology for patients who may require advanced intervention for HF including heart transplantation or LVAD is necessary to improve patient outcomes and decrease mortality.[14] Patients with advanced HF, NYHA class III or IV, and/or an EF of less than 25% should be referred to a cardiologist at an advanced HF center.[14] Other indications for referral to cardiology include, but are not limited to, patients with HF who exhibit early organ dysfunction, persistent hypotension (systolic BP < 90 to 100 mm Hg), maximally tolerated GDMT, at least one hospitalization for HF within the past 12 months, continuing edema despite increased diuretic use, and/or history of ventricular arrhythmias resulting in hemodynamic instability.[7,11]

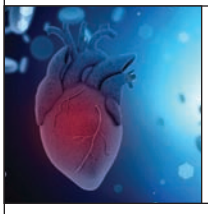
While the primary care provider and cardiology team can provide assistance with symptom management, support for emotional distress, and assistance with advanced care planning for patients with HF, referral to a palliative care specialist should be considered if these issues are complex or severe.[15] Among other things, palliative care can provide improved quality of life through symptom management, assistance with medical decision-making, and care that addresses emotional and spiritual needs.[13,15]

SGLT2 inhibitors and HF

SGLT2 inhibitors have been approved for use in T2D as an adjunct to diet and exercise. Recent studies have demonstrated reduced mortality and HF hospitalizations in T2D with use of SGLT2 inhibitors.[16-19] In 2020, the ACC released guidelines based on several clinical trials outlining a decision pathway for the use of novel therapies for CV risk reduction in patients with T2D that included SGLT2 inhibitors.[20] In patients 18 years or older with T2D and HF (or other CV risk factors), clinicians should optimize GDMT and consider starting an SGLT2 inhibitor.[20] In May 2020, the FDA approved the use of the SGLT2 inhibitor dapagliflozin for treatment of HFrEF even in patients without T2D.[21] Dapagliflozin was shown to prevent worsening HF and reduce risk of death from CV causes in patients with HF and T2D as well as in patients with HF alone.[19] Another SGLT2 inhibitor, empagliflozin, has been used off-label for HFrEF (see *SGLT2 inhibitors*).[22]

Pharmacodynamics of SGLT2 inhibitors

SGLT2 inhibitors block SGLT2, which are glucose transport proteins that facilitate reabsorption of glucose in the proximal tubules of the kidney, thus promoting excretion of glucose, resulting in modest reductions of glucose levels in patients with T2D.[22] SGLT2 receptors are overexpressed in patients with diabetes, which increases glucose reabsorption and glycemia.[23] In euglycemia, SGLT2 reabsorbs 80% or more of the filtered glucose.[22] SGLT2 inhibitors also exert a mild diuretic effect and promote calorie loss through glycosuria, which results in sustained weight reduction over time.[19,22]



In addition to pharmacodynamic effects that assist in excretion of glucose, SGLT2 inhibitors have multidimensional cardiovascular benefits in HF.

In addition to pharmacodynamic effects that assist in excretion of glucose, SGLT2 inhibitors have multidimensional CV benefits in HF. As discussed previously, SGLT2 inhibitors have a mild diuretic effect and decrease sodium, which results in sodium homeostasis and a decrease in plasma volume and BP.[23] The reduced circulating volume decreases preload. Afterload is decreased with the lower BP, improving cardiac blood flow.[23] SGLT2 inhibitors have also demonstrated an ability to improve arterial stiffness through smooth muscle relaxation.[23] Other CV benefits that are not clearly understood include protective effects on cardiac myocytes and promotion of ketone production, which can be used by the heart for energy generation and ultimately improve cardiac function.[23]

Adverse reactions

Because SGLT2 inhibitors only lower plasma glucose levels by blocking reabsorption of filtered glucose, they are not likely to cause hypoglycemia in the absence of other therapies that can cause hypoglycemia.[24] The most frequent and relevant adverse reaction is genital mycotic infection, such as vulvovaginal candidiasis. While it occurs in both men and women, it is four to five times more common in women.[24] The FDA has also received reports of rare but potentially fatal adverse reactions: serious urinary tract infections such as pyelonephritis and urosepsis and necrotizing fasciitis of the perineum (Fournier's gangrene).[24]

Because of the mild diuretic effect, there is a risk of intravascular volume contraction and hypotension, especially in older adults and patients taking other diuretic medications. There have been reports of acute kidney injury, with some requiring hospitalization and dialysis. Patients experiencing acute kidney injury may have been volume-depleted, hypotensive, or taking other medications affecting the kidney.[25]

Additionally, canagliflozin is associated with an increased risk of lower limb amputations. There may be an increased risk of bone fracture with some SGLT2 inhibitors.[26,27]

SGLT2 inhibitors are contraindicated in type 1 diabetes mellitus because they promote ketone production and may increase the risk of diabetic ketoacidosis. Ketoacidosis can also occur with SGLT2 inhibitors in patients with T2D. Serum ketones should be obtained in any patient with nausea, vomiting, shortness of breath, or malaise while taking SGLT2 inhibitors.[24,27]

SGLT2 inhibitors and HFrEF–Clinical trials

Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) Trial

The EMPA-REG OUTCOME trial was conducted to assess the CV safety of empagliflozin, an SGLT2 inhibitor, in patients with T2D with atherosclerotic CV disease.[16,28] The primary outcome of reduction in MACEs for the empagliflozin group yielded a 14% reduction in MACEs when compared with the placebo group. There was a relative risk reduction of 38% for CV deaths, 32% for all-cause deaths, and 35% for hospitalization for HF in the empagliflozin group when compared with the placebo group. All-cause mortality was also reduced in the empagliflozin group.

Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced)

In the EMPEROR-Reduced study, investigators evaluated the effects of empagliflozin on CV death and hospitalization for HF in patients with a NYHA classification of II-IV and an EF of 40% or less as compared with a placebo.[29] Some patients had T2D, while others did not. Overall, there was a 25% reduction in the combined risk of the primary outcomes of CV

death and hospitalization for HF regardless of T2D status. Unlike the EMPA-REG OUTCOME trial, there was no significant decrease in all-cause mortality noted in the EMPEROR-Reduced study.

Canagliflozin Cardiovascular Assessment Study (CANVAS) Program

Data from the CANVAS and CANVAS-Renal trials were combined for analysis in the CANVAS Program.[17] Investigators compared CV events in patients with T2D taking the SGLT2 inhibitor canagliflozin versus patients taking a placebo.[17,30] As with the EMPA-REG OUTCOME trial, MACEs were significantly reduced and occurred in 26.9 participants per 1000 patient years in the canagliflozin group as compared with 31.5 per 1,000 patient years in the placebo group. Benefits were equivalent in patients who had HFrEF and those who had HFpEF.[30] Moreover, reduction in CV death and hospitalization for HF was greater among participants who had a history of HF. Of note, lower extremity amputations were significantly increased in patients taking canagliflozin.[17,30]

Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) Trial

The DECLARE-TIMI 58 trial was designed to assess CV safety of the SGLT2 inhibitor dapagliflozin in patients with T2D with established CV disease (CVD) or who were at high risk for CVD.[18,31] Although patients in the dapagliflozin group did experience statistically significant improvement in glycemic control when compared with patients in the placebo group, there was no significant difference in MACEs. However, for patients with HFrEF, CV death and hospitalization were significantly reduced.[31]

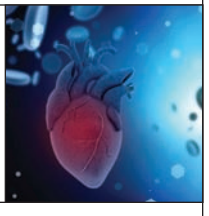
Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial

In the DAPA-HF trial, investigators evaluated the efficacy of the SGLT2 inhibitor dapagliflozin for HFrEF in patients with and without T2D.[19] Worsening HF occurred in 10% of the dapagliflozin group versus 13.7% of the placebo group. CV death occurred in 9.6% of the dapagliflozin group versus 11.5% in the placebo group. All-cause mortality was also reduced in the dapagliflozin group. Results were similar in patients with and without T2D. Adverse events were increased in the placebo group suggesting dapagliflozin is safe to administer in HFrEF in patients with and without T2D.

Summary of clinical trials

Use of SGLT2 inhibitors in patients with T2D and HF have been shown to improve overall patient outcomes; however, results vary based on the type of SGLT2 inhibitor used. A statistically significant decline in specific MACEs and HF hospitalization was seen in patients with HF and/or CVD with T2D who were taking the SGLT2 inhibitors empagliflozin or canagliflozin.[26,29] Use of the SGLT2 inhibitor dapagliflozin also showed promising results in patients with T2D and HF by decreasing CV death and hospitalizations for HF.[31] Further, the SGLT2 inhibitors empagliflozin and dapagliflozin significantly decreased CV death and hospitalizations for HF in patients with HFrEF regardless of presence or absence of T2D.[19,29] SGLT2 inhibitors improve outcomes in patients who have T2D with HF or HFrEF alone and should be considered as pharmaceutical therapy in these patients.

SGLT2 inhibitors improve outcomes in patients who have T2D with HF or HFrEF alone and should be considered as pharmaceutical therapy in these patients.



Discussion

HF carries a significantly increased risk for MACEs: CV death, nonfatal MI, and stroke. In patients with T2D and HF, this risk increases exponentially.[4] SGLT2 inhibitors, a class of medications already approved for the treatment of T2D, have shown efficacy in decreasing MACEs, hospitalizations for HF, and all-cause mortality for patients with concomitant T2D and HF.[16-19,28-31] Further, studies have shown that in patients with HFrEF, regardless of the presence of T2D, dapagliflozin can reduce worsening HF, CV death, and all-cause mortality and empagliflozin can decrease hospitalizations for HF.[19,29]

As with all medications, risk versus benefit should be evaluated for each patient. Clinicians should avoid use of SGLT2 inhibitors in patients with type 1 diabetes.[24] In patients who are predisposed to the need for lower extremity amputation (for example, neuropathy,

peripheral vascular disease, ulcers, infections, history of previous amputation), careful consideration should be given when prescribing canagliflozin.[26,27] Clinicians should strongly consider use of SGLT2 inhibitors in patients with HF and T2D and use of the SGLT2 inhibitors dapagliflozin or empagliflozin in patients with HFrEF alone to improve overall CV outcomes, decrease hospitalizations for HF, and decrease all-cause mortality.[16-19,28-31]

Implications for practice

Evidence-based strategies for management of HF continue to expand each day. Any clinician caring for patients with HF or at risk for HF should be comfortable staging or classifying HF based on the ACC/AHA heart failure stages or NYHA classes. Once HF has been staged/classified appropriately, clinicians should utilize evidence-based guidelines from the ACC, AHA, and HFSA in determining the patient's plan of care including use of SGLT2 inhibitors to prevent MACEs, such as CV death, and hospitalizations for HF.[11]

As with all medications, cost is a concern for both clinician and patient. Reports have indicated that cost of SGLT2 inhibitors can be exponentially high, even in patients who have Medicare Part D coverage. For example, median annual out-of-pocket expense in 2019 for the SGLT2 inhibitor empagliflozin was approximately $1,097 for patients covered by Medicare Part D, which made it cost-prohibitive for many patients.[32] However, several pharmaceutical companies supplying SGLT2 inhibitors have patient assistance programs in place to assist with alleviating copays and in some instances, the entire cost of the drug. Clinicians should utilize these programs to ensure that patients are able to afford these medications and are receiving evidence-based care.

For clinicians who want to further expand their knowledge base in regards to HF innovation, research, and advocacy, the HFSA provides excellent resources that are appropriate for advanced practice registered nurses, physician assistants, physicians, and pharmacists.[33] NP

REFERENCES

1. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y, Ritchey MD. National burden of heart failure events in the United States, 2006 to 2014. *Circ Heart Fail*. 2018;11(12):e004873. doi:10.1161/CIRCHEARTFAILURE.117.004873.
2. Lam CSP, Chandramouli C, Ahooja V, Verma S. SGLT-2 inhibitors in heart failure: current management, unmet needs, and therapeutic prospects. *J Am Heart Assoc*. 2019;8(20):e013389. doi:10.1161/JAHA.119.013389.
3. Dunlay SM, Givertz MM, Aguilar D, et al. Type 2 diabetes mellitus and heart failure: a scientific statement from the American Heart Association and the Heart Failure Society of America. *Circulation*. 2019;140(7):e294-e324. doi:10.1161/CIR.0000000000000691.
4. Lehrke M, Marx N. Diabetes mellitus and heart failure. *Am J Med*. 2017; 130(6S):S40-S50. doi:10.1016/j.amjmed.2017.04.010.
5. Young JB, Dunlap ME, Pfeffer MA, et al. Mortality and morbidity reduction with candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM Low-Left ventricular ejection fraction trials. *Circulation*. 2004;110(17):2618-2626. doi:10.1161/01.CIR.0000146819.43235.A9.
6. Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev*. 2017;3(1):7-11.
7. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. *Circulation*. 2013;128(16):e240-e327. doi:10.1161/CIR.0b013e31829e8776.
8. Hollenberg SM, Stevenson LW, Ahmad T, et al. 2019 ACC expert consensus decision pathway on risk assessment, management, and clinical trajectory of patients hospitalized with heart failure: a report of the American College of Cardiology solution set oversight committee. *J Am Coll Cardiol*. 2019;74(15): 1966-2011. doi:10.1016/j.jacc.2019.08.001.
9. Quesada Q, Klein LK. Heart failure with reduced ejection fraction. In: Edmonson K, Yoo C, eds. *Current Diagnosis & Treatment: Cardiology*. 5th ed. New York: McGraw-Hill Education; 2017:335-366.
10. Lampert BC, Dyke DB, Koelling TM. Heart failure due to left ventricular systolic dysfunction. In: Baliga R, Eagle K, eds. *Practical Cardiology: Evaluation and Treatment of Common Cardiovascular Disorders*. 3rd ed. Switzerland: Springer; 2020:149-175.
11. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Failure Society of America. *Circulation*. 2017;136(6):e137-e161.
12. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507-520. doi:10.1001/jama.2013.284427.
13. Broglio K, Walsh A. Referring patients to hospice or palliative care. *Nurse Pract*. 2017;42(4):49-55. doi:10.1097/01.NPR.0000511008.14090.1d.
14. Guglin M, Zucker MJ, Borlaug BA, et al. Evaluation for heart transplantation and LVAD implantation: JACC council perspectives. *J Am Coll Cardiol*. 2020;75(12):1471-1487.
15. Kavalieratos D, Gelfman LP, Tycon LE, et al. Palliative care in heart failure: rationale, evidence, and future priorities. *J Am Coll Cardiol*. 2017;70(15): 1919-1930. doi:10.1016/j.jacc.2017.08.036.
16. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720.
17. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. doi:10.1056/NEJMoa1611925.
18. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357. doi:10.1056/NEJMoa1812389.
19. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019; 381(21):1995-2008. doi:10.1056/NEJMoa1911303.
20. Das SR, Everett BM, Birtcher KK, et al. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes. *J Am Coll Cardiol*. 2020;76(9):1117-1145. doi:10.1016/j.jacc.2020.05.037.
21. Melillo G. FDA approves dapagliflozin to treat heart failure, breaking new ground in SGLT2 competition. AJMC. 2020. www.ajmc.com/view/fda-approves-dapagliflozin-to-treat-heart-failure-breaking-new-ground-in-sglt2-competition.
22. Sano R, Shinozaki Y, Ohta T. Sodium-glucose cotransporters: functional properties and pharmaceutical potential. *J Diabetes Investig*. 2020;11(4): 770-782. doi:10.1111/jdi.13255.
23. Garcia-Ropero Á, Vargas-Delgado AP, Santos-Gallego CG, Badimon JJ. Inhibition of sodium glucose cotransporters improves cardiac performance. *Int J Mol Sci*. 2019;20(13):3289. doi:10.3390/ijms20133289.
24. Halimi S, Vergès B. Adverse effects and safety of SGLT-2 inhibitors. *Diabetes Metab*. 2014;40(6 suppl 1):S28-S34. doi:10.1016/S1262-3636(14)72693-X.

25. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI. Sodium glucose cotransporter-2 inhibition in heart failure potential mechanisms, clinical applications, and summary of clinical trials. *Circulation*. 2017;136(17):1643-1658. doi:10.1161/CIRCULATIONAHA.117.030012.

26. U.S. Food and Drug Administration. FDA removes Boxed Warning about risk of leg and foot amputations for the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). 2020. www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin.

27. Invokana (canagliflozin) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2020.

28. Anker SD, Kumbhani DJ, Bavry AA. Empagliflozin Cardiovascular Outcome Event Trial in type 2 diabetes mellitus patients – EMPA-REG OUTCOME. American College of Cardiology. 2019. www.acc.org/latest-in-cardiology/clinical-trials/2015/09/17/10/11/empa-reg-outcome.

29. Packer M, Anker SD, Butler J, et al. EMPEROR-Reduced trial investigators Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413-1424. doi:10.1056/NEJMoa2022190.

30. Januzzi JL, Bavry AA. Canagliflozin Cardiovascular Assessment Study. American College of Cardiology. 2019. www.acc.org/latest-in-cardiology/clinical-trials/2017/06/12/16/25/canvas.

31. Bonaca MP, Kumbhani DJ. Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58 – DECLARE-TIMI 58. American College of Cardiology. 2019. www.acc.org/latest-in-cardiology/clinical-trials/2018/11/08/23/09/declare-timi-58.

32. Luo J, Feldman R, Rothenberger SD, Hernandez I, Gellad WF. Coverage, formulary restrictions, and out-of-pocket costs for sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists in the Medicare Part D Program. *JAMA Netw Open*. 2020;3(10):e2020969. doi:10.1001/jamanetworkopen.2020.20969.

33. Heart Failure Society of America (HFSA). HFSA Learning Center. https://learningcenter.hfsa.org/Public/Catalog/Main.aspx.

34. Farxiga (dapagliflozin) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020.

35. Jardiance (empagliflozin) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2021.

Christy McDonald Lenahan is associate professor and Nurse Practitioner Coordinator at the University of Louisiana at Lafayette Lafayette, La., Family Nurse Practitioner at Serenity MedAesthetics Youngsville, La., and Family and Emergency Nurse Practitioner at Ochsner Lafayette General Medical Center Lafayette, La.

Deedra Harrington is associate professor/BSN Coordinator at the University of Louisiana College of Nursing and Allied Health Professions at Lafayette, La.

Frances Stueben is assistant professor at the University of Louisiana at Lafayette, La.

The authors and planners have disclosed no potential conflicts of interests, financial or otherwise.

DOI-10.1097/01.NPR.0000753832.85114.65