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Review Article

The role of SGLT2 inhibitors in heart failure

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ABSTRACT

Heart failure (HF) is a highly prevalent disease worldwide. Its prevalence is expected to grow for the foreseeable future increasing the need for continuous assessment and optimization of guideline-directed medical therapy. The purpose of this article is to review available data assessing the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors for management of HF. An independent literature search using PubMed was performed by each author to identify all pertinent articles. In addition, reference sections of each article were reviewed. Articles were eligible for inclusion if they assessed the use of SGLT2 inhibitors on therapeutic outcomes related to HF. Among patients with HF, SGLT2 inhibitors reduced the risk of cardiovascular mortality and HF hospitalization regardless of the presence of diabetes. These agents increased the risk of urinary and genital infections. These data support the addition of SGLT2 inhibitors to guideline-directed medical therapy in HF patients, especially those with a reduced ejection fraction.

Keywords: Cardiology, Heart failure, SGLT2 inhibitor, Sodium-glucose co-transporter 2 inhibitor

INTRODUCTION

Heart failure (HF) affects over 6 million adults in the United States (U.S.), and the prevalence is expected to increase to >8 million by 2030.[1,2] HF is associated with considerable morbidity and mortality, resulting in substantial economic and public health burden. It is a leading cause of hospitalization in the U.S. with over one million hospitalizations occurring annually and up to 25% of patients being readmitted within 30 days.[1-6]

Several organizations have published guidelines for HF treatment including, the 2013 American College of Cardiology Foundation/American Heart Association guideline with an update published in 2017, the 2017 ACC Expert Consensus Decision Pathway for Optimization of HF Treatment, and the 2016 European Society of Cardiology (ESC) guideline.[7-10] Guideline-directed medical therapy (GDMT) is indicated in select patients, depending on ejection fraction (EF), classification, and staging. GDMT reduces hospitalizations, morbidity, and mortality as well as prevents HF progression. Most data supporting medication use for mortality reduction are available for patients with HF with reduced EF (HFrEF). Per guidelines, established GDMT may include the following agents: beta-blockers, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitor (ARNI), aldosterone antagonist, and loop diuretics.[7-10] The most recent guidance document, the 2021 ACC Expert Consensus, recommends addition of a sodium-glucose co-transporter 2 (SGLT2) inhibitor in patients with HFrEF in addition to the aforementioned agents.[11]

Table 1: Inclusion and exclusion criteria for SGLT2 inhibitor trials in HF patients.

Study	Inclusion criteria	Exclusion criteria
DAPA-HF[21]	EF ≤40% NYHA II, III, or IV NT-proBNP ≥600 pg/mL or ≥400pg/mL if hospitalized for HF within 12 months or ≥900 pg/mL if AF Receiving standard HF device therapy Receiving standard HF drug therapy (ACEi/ARB/ARNi and beta-blocker with AA encouraged)	Recent treatment with or unacceptable side effects associated with an SGLT2 inhibitor Type 1 diabetes mellitus Symptomatic hypotension or a SBP <95 mmHg eGFR <30 ml/min/1.73 m^2 (or rapidly declining renal function)
REFORM[30]	EF <45% NYHA II or III Diabetes Stable HF symptoms for ≥3 months Receiving stable HF therapy for ≥3 months No HF hospitalization for ≥3 months Maximum furosemide dose of 80 mg/day	Severe hepatic disease eGFR <45 ml/min/1.73 m^2 SBP <95 mmHg Hemoglobin A1c <6%
DEFINE-HF[31]	EF ≤40% NYHA II or III NT-proBNP ≥600 pg/mL and/or BNP ≥100 pg/mL (NT-proBNP ≥600 pg/mL and/or BNP ≥125 pg/mL if AF) No change in diuretic management for 1 week	Decompensated HF Type 1 diabetes mellitus eGFR< 30ml/min/1.73 m^2 Admission for ACS, PCI, or cardiac surgery within 30 days Admission for cardiac resynchronization therapy within 90 days Planned CV revascularization, major cardiac surgery, or cardiac resynchronization therapy within 90 days Volume depletion Current or recent treatment with any SGLT2 inhibitor within 12 weeks Past or current history of bladder cancer SBP <90 mmHg HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, severe stenotic valve disease, and hypertrophic obstructive cardiomyopathy
EMPEROR-Reduced[22]	EF ≤40% plus 1 of the following: • EF 36–40: NT-proBNP ≥2500pg/mL (or ≥ 5000 pg/mL if AF) • EF 31–35: NT-proBNP ≥1000pg/mL (or ≥ 2000 pg/mL if AF) • EF ≤30: NT-proBNP ≥600 pg/mL (or ≥1200 pg/mL if AF) • EF ≤40 with HF hospitalization within 12 months: NT-proBNP ≥600 pg/mL (or ≥1200 pg/mL if AF) NYHA II, III, or IV NT-proBNP ≥600pg/mL or ≥400 pg/mL if hospitalized for HF within 12 months or ≥900 pg/mL if AF Receiving standard HF device therapy Receiving standard HF drug therapy (ACEi/ARB/ARNi, beta-blocker, AA, diuretic, and ivabradine) No change in diuretic management for 1 week BMI <45kg/m2	MI, CABG, major CV surgery, stroke, or TIA within 90 days Heart transplant recipient or listed for transplant Cardiomyopathy due to infiltrative diseases, accumulation diseases, muscular dystrophies, reversible cause, hypertrophic obstructive cardiomyopathy, or pericardial constriction Severe valvular heart disease expected to lead to surgery Acute decompensated HF requiring IV diuretics, vasodilators, inotropic agents, or mechanical support within 1 week ICD or cardiac resynchronization therapy within 3 months Symptomatic hypotension and/or SBP< 100mmHg eGFR <20 ml/min/1.73 m^2 Current or recent treatment with any SGLT2 inhibitor within 12 weeks History of ketoacidosis
RECEDE CHF[33]	EF <50% NYHA II or III Stable loop diuretic dose for 1 month Stable HF therapy for 3 months No HF hospitalizations within 3 months Stable T2DM BNP >100 pg/mL	SBP <95 mmHg eGFR <45 ml/min/1.73 m^2 Use of thiazide diuretic Chronic liver disease and/or liver enzymes 2 times ULN

(Contd...)

Table 1: (Continued)

Study	Inclusion criteria	Exclusion criteria
SOLOIST-WHF[36]	HF diagnosis ≥3 months before screening History of chronic treatment with loop diuretic HF hospitalization requiring intravenous diuretic therapy T2DM Use of beta-blocker and RAAS inhibitor if EF <40% BNP ≥150 pg/mL (or ≥450 pg/mL if atrial fibrillation) or NT-proBNP ≥600 pg/mL (or ≥1800 pg/mL if atrial fibrillation)	End-stage HF Acute coronary syndrome within 3 months Stroke within 3 months Percutaneous coronary intervention or coronary artery bypass surgery within 1 month eGFR < 30ml/min/1.73 m^2 diabetic ketoacidosis or nonketotic hyperosmolar coma within 3 months lower extremity diabetic complications

SGLT2: Sodium-glucose co-transporter 2, HF: Heart failure, ARB: Angiotensin receptor blocker, ACEi: Angiotensin converting enzyme inhibitor, ARNI: Angiotensin receptor-neprilysin inhibitor, CV: Cardiovascular, EF: Ejection fraction, T2DM: type 2 diabetes mellitus

Table 2: Baseline characteristics for SGLT2 inhibitor trials in HF patients.

Study/Baseline characteristic	DAPA-HF[21]	REFORM[30]	DEFINE-HF[31]	EMPEROR-Reduced[22]	RECEDE CHF[33]	SOLOIST-WHF[36]
Age (years)	66.4	67.1	61.3	66.9	69.8	69.5
Male (%)	76.6	66.1	73.4	76.1	73.9	66.3
Diabetes (%)	41.8	100	63.1	49.8	100	100
NYHA classification (%)						
II	67.6	42.9	65.8	75.1	---	---
III	31.6	12.5	34.2	24.4	---	---
IV	0.9	N/A	N/A	0.6	---	---
LVEF (%)	31.1	45.5	26.5	27.5	≥45%: 30.4 36–45: 47.8 ≤35: 21.7	35% <50%: 79.1%
NT-proBNP (pg/mL) (median)	1437	---	1136	1907	2381	1779
HF cause						
Ischemic	56.4	53.6	52.9	51.8	---	---
Nonischemic	35.6	---	---	48.3	---	---
Unknown	8.1	3.6	---	---	---	---
HF medications (%)						
Diuretic	93.5	100	85.6	100	100	95.0
ACE inhibitor/ARB	83.7	89.3	59.3	69.7	73.9	82.7
ARNI	10.7	---	32.4	19.5	13.0	16.8
Beta-blocker	96.1	82.1	96.7	94.7	87.0	92.1
AA	71.1	41.1	60.8	71.4	47.8	64.5

SGLT2: Sodium-glucose co-transporter 2, HF: Heart failure, ARB: Angiotensin receptor blocker, ACE: Angiotensin converting enzyme, ARNI: Angiotensin receptor-neprilysin inhibitor

At present, four SGLT2 inhibitors are approved by the Food and Drug Administration (FDA) including: empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin.[12-15] These agents were initially approved for treatment of type 2 diabetes mellitus (T2DM); however, compelling data demonstrate that these agents are potential therapeutic options for other disease states. Five randomized controlled trials (RCTs) have been published assessing the use of SGLT2 inhibitors in the patients with T2DM and established atherosclerotic cardiovascular disease (CVD) or with multiple CVD risk factors.[16-20] Data from these trials led to FDA approval of canagliflozin and empagliflozin for reduction in major adverse cardiovascular (CV) events and CV death, respectively.[16,18] Interestingly, all five studies demonstrated a reduction in hospitalizations for HF.[16-20] These findings prompted clinicians to assess the benefit of SGLT2 inhibitors in HFrEF patients, resulting in the completion and publication of the DAPA-HF and EMPEROR-Reduced trials.[21,22]

In patients with diabetes, SGLT2 inhibitors inhibit the SGLT2 in the proximal renal tubules, thereby reducing reabsorption of filtered glucose and increasing urinary excretion of glucose.[12-15] The proposed mechanism of benefit from SGLT2 inhibitors in HF patients is not completely understood and numerous mechanisms have been proposed. These benefits may be mediated by the inhibition of sodium-hydrogen

Table 3: Key results of SGLT2 inhibitor trials in HF patients.

Study/Results (SGLT2i vs. placebo)	DAPA-HF[21]	REFORM[30]	DEFINE-HF[31]	EMPEROR-Reduced[22]	RECEDE CHF[33]	SOLOIST-WHF[35]
HF hospitalization and CV death	16.3% vs. 21.2% HR: 0.74, 95% CI: 0.65–0.85, *P*<0.001; NNT: 21	---	---	19.4% vs. 24.7% HR: 0.75, 95% CI: 0.65–0.86, *P*<0.001; NNT: 19	---	51.0 vs. 76.3/100 patient years HR: 0.67, 95% CI: 0.52–0.95, *P*<0.001
HF hospitalization	9.7% vs. 13.4% HR: 0.7, 95% CI: 0.59–0.83; NNT: 27	---	---	13.2% vs. 18.3% HR: 0.69, 95% CI: 0.59–0.81; NNT: 20	---	40.4 vs. 63.9/100 patient years; HR: 0.64, 95% CI: 0.49–0.83, *P*<0.001
CV death	9.6% vs. 11.5% HR: 0.82, 95% CI: 0.96–0.98; NNT: 53	---	---	10.0% vs. 10.8% HR: 0.92, 95% CI: 0.75–1.12	---	51.0 vs. 58/100 patients years; HF: 0.84, 95% CI: 0.58–1.22, *P*=0.36

SGLT2: Sodium-glucose co-transporter 2, HF: Heart failure, CV: Cardiovascular, vs.: Versus

exchange, a decrease in preload due to diuresis, a decrease in afterload due to blood pressure and atrial stiffness lowering effects, and preservation of renal function.[23,24] Sotagliflozin is a dual SGLT1 and 2 inhibitor. SGLT1 is found primarily in the small intestine and serves as the main transporter for glucose absorption. This expanded mechanism of action may result in improved glucose control.[25]

A comprehensive review of major RCTs is needed to assess the safety and efficacy of SGLT2 inhibitors in patients with established HF. This review aims to provide a comprehensive review of the published studies assessing the use of SGLT2 inhibitors in HF and provide recommendations for optimal use of these agents.

MATERIALS AND METHODS

A literature search was performed to identify RCTs assessing use of SGLT2 inhibitors on therapeutic outcomes related to HF. In addition, *post hoc* analyzes of RCTs selected for inclusion were also included if they provided additional information pertaining to patients with HF within the original study. A search was completed using the MEDLINE, PubMed and the Medical Subject Headlines terms "HF," "reduced EF," "preserved EF," "CD," "drug therapy," "diabetes," "SGLT2 inhibitor," "SGLT2," "sodium glucose co-transporter 2 inhibitor," "empagliflozin," "dapagliflozin," "canagliflozin," and "ertugliflozin" in September of 2020. The search was repeated in April 2021 and June 2021 with an additional search term of "sotagliflozin." Each author performed an independent search to ensure all pertinent articles were identified. The studies using any SGLT2 inhibitor dose were included. The reference sections of each included article as well as current guidelines were reviewed to ensure all pertinent literature was identified. Each author evaluated relevant articles and a consensus among all authors was used to select studies for narrative inclusion. A total of 13 trials were selected for inclusion, six of which studied solely HF patients.

RESULTS

Canagliflozin

The CANVAS program combined data from two trials. These trials were randomized, controlled, multicenter trials assessing the use of canagliflozin in patients with T2DM and either established CVD or the presence of multiple CVD risk factors. The patients received canagliflozin 100 mg, 300 mg, or placebo added to standard of care. A total of 10,142 patients were enrolled. The patients were followed for a mean of 3.6 years. In the full population, HF hospitalization was lower with canagliflozin (5.5% vs. 8.7%, HR: 0.67, 95% CI: 0.52–0.87; NNT: 32).[16] Of the included patients, 14.4% had HF at baseline. In the subgroup of HF patients, canagliflozin did not provide a statistical reduction in the composite of CV death, nonfatal MI, or nonfatal stroke (HR: 0.80, 95% CI: 0.61–1.05); however, this lack of benefit may be due to the low sample size. However, in the HF group, canagliflozin reduced the composite of CV death or HF hospitalizations (16.3 vs. 20.8 events/1000 patient-years; HR: 0.78, 95% CI: 0.67–0.91). It also decreased the risk of fatal or hospitalized HF (HR: 0.70, 95% CI: 0.55–0.89) and hospitalized HF alone (HR: 0.67, 95% CI: 0.52–0.87).[26]

The CREDENCE trial was a randomized, controlled, multicenter trial assessing the use of canagliflozin in patients with T2DM and chronic kidney disease. Patients received canagliflozin 100 mg or placebo added to ACEi or ARB therapy. A total of 4401 patients were enrolled. Patients were followed for a median of 2.6 years. In the full population, HF hospitalization was lower with canagliflozin (4.0% vs. 6.4%, HR: 0.61, 95% CI: 0.47–0.80; NNT: 42). Of the included patients, 14.8% had HF at baseline. In the subgroup of HF patients, canagliflozin did not provide a statistical reduction in the composite of CV death, nonfatal MI, or nonfatal stroke (HR: 0.91, 95% CI: 0.62–1.34); however, this lack of benefit may be due to the low sample size.[20,27]

Dapagliflozin

The DECLARE-TIMI 58 trial is a randomized, controlled, multicenter trial assessing the use of dapagliflozin in patients with T2DM and either established CVD or the presence of multiple CVD risk factors. The patients received dapagliflozin 10 mg or placebo added to standard of care. A total of 17,160 patients were enrolled. Patients were followed for a mean of 4.2 years. In the full population, HF hospitalization was lower with dapagliflozin (2.5% vs. 3.3%, HR: 0.73, 95% CI: 0.61–0.88; $P = 0.002$; NNT: 44). Of the included patients, 10.1% had HF at baseline. In HF patients, dapagliflozin provided a greater reduction in the composite of CV death and HF hospitalizations (16.7% vs. 19.7%, HR: 0.79, 95% CI: 0.63–0.99).[17] A subgroup analysis was conducted assessing the use of dapagliflozin in patients with HFrEF. When assessing HF hospitalizations alone, dapagliflozin reduced the risk as compared to placebo in those patients with HF (HR: 0.64, 95% CI: 0.43–0.95).[28]

The DAPA-CKD trial is a randomized, controlled, multicenter trial assessing the use of dapagliflozin in patients with chronic kidney disease defined as an estimated glomerular filtration rate of 25–75 mL/min/1.73m^2 plus a urinary albumin-to-creatinine ratio of 200–500 mg/g. Patients received dapagliflozin 10 mg or placebo added to an ACEi or ARB (if tolerated). A total of 4304 patients were enrolled. The patients were followed for a mean of 2.4 years. In the full population, the composite of death from CV causes or HF hospitalization was lower with dapagliflozin (4.6% vs. 6.4%, HR: 0.71, 95% CI: 0.55–0.92; $P = 0.009$). Of the included patients, 10.9% had HF at baseline.[29] Table 1 provides an overview of the most pertinent inclusion and exclusion criteria for each reviewed study specifically assessing SGLT2 inhibitor use in HF. The REFORM trial is a randomized, controlled, single center trial assessing the use of dapagliflozin in patients with T2DM with symptomatic HF. Patients received dapagliflozin 10 mg or placebo added to standard of care. A total of 56 patients were enrolled. The patients were followed for 1 year. Table 2 provides an overview of the pertinent baseline characteristics. The mean EF of included patients was 45%. Dapagliflozin provided no significant change in the left ventricular end-systolic volume, left ventricular end-diastolic volume, left ventricular mass index, or left ventricular EF. Patients receiving dapagliflozin required lower doses of diuretic therapy.[30]

The DAPA-HF trial is a randomized, controlled, multicenter trial assessing the addition of dapagliflozin to standard treatment for HFrEF. Patients received dapagliflozin 10 mg daily or placebo added to ACEi, ARB, or ARNI plus beta-blockade. The use of aldosterone antagonists was encouraged. A total of 4744 patients were enrolled. The patients were followed for a median of 18.2 months. Table 3 provides an overview of the hard outcomes assessed in HF patients. The composite of worsening HF or CV death was lower with dapagliflozin (16.3% vs. 21.2%, HR: 0.74, 95% CI: 0.65–0.85, $P < 0.001$; NNT: 21). When assessed individually, each of these outcomes were significant favoring use of dapagliflozin with HF hospitalizations (9.7% vs. 13.4%, HR: 0.70, 95% CI: 0.59–0.83; NNT: 27) and CV death (9.6% vs. 11.5%, HR: 0.82, 95% CI: 0.69–0.98; NNT: 53). In addition, dapagliflozin provided a reduction in death from any cause and provided a greater change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score.[21]

The DEFINE-HF is a randomized, multicenter trial assessing the use of dapagliflozin for patients with HFrEF. Patients were included if they had an EF <40% and were required to be on a stable dose of loop diuretic. Patients received dapagliflozin 10 mg daily or placebo. A total of 263 patients were enrolled. After 12 weeks, dapagliflozin provided an improvement of 5 points or greater in KCCQ score in more patients (OR 2.4, 95% CI: 1.31–4.2, $P < 0.01$). Of the patients receiving dapagliflozin that experienced adverse effects, 9.2% were due to volume depletion.[31]

Empagliflozin

The EMPA-REG Outcome trial is a randomized, controlled, multicenter trial assessing the use of empagliflozin in patients with T2DM with established CVD. Patients received empagliflozin 10 mg, 25 mg, or placebo added to standard of care. A total of 7028 patients were enrolled. The patients were followed for a median of 3.1 years. In the full population, HF hospitalization was lower with empagliflozin (2.7% vs. 4.1%, HR: 0.65, 95% CI: 0.50–0.85, $P = 0.002$; NNT: 72). Of the included patients, 10% had HF at baseline. In the subgroup of HF patients, empagliflozin did not provide a statistical reduction in HF hospitalizations (10.4% vs. 12.3%, HR: 0.75, 95% CI: 0.48–1.19); however, this lack of benefit may be due to the low sample size.[18,32]

The EMPEROR-Reduced trial is a randomized, controlled, multicenter trial assessing the addition of empagliflozin to standard treatment for HFrEF. Patients received empagliflozin 10 mg daily or placebo added to ACEi, ARB, or ARNI, beta-blockade, and aldosterone antagonist therapy. A total of 3730 patients were enrolled. The patients were followed for a median of 16 months. The composite of worsening HF or CV death was lower with empagliflozin (19.4% vs. 24.7%, HR: 0.75, 95% CI: 0.65–0.86, $P < 0.001$; NNT: 19). When assessed individually, HF hospitalizations were decreased with use of empagliflozin (13.2% vs. 18.3%, HR: 0.69, 95% CI: 0.59–0.81; NNT: 20). CV death was similar between groups.[22]

The RECEDE-CHF trial is a randomized, controlled, single-center trial assessing the use of empagliflozin for patients with HF and T2DM. Patients were included if they had an EF <50% and were required to be on a stable dose of loop diuretic. Patients received empagliflozin 25 mg daily or placebo. A total

of 23 patients were enrolled. The patients were followed for a median of 14 weeks. This study assessed whether empagliflozin augmented the diuretic effect of loop diuretics. Empagliflozin increased the 24-h urinary volume at day 3 and week 6 as compared to placebo with a mean difference of 535 mL and 545 mL, respectively. No difference in 24-h urinary sodium was found at either time point. In addition, no difference was found in systolic blood pressure or NT-proBNP. A greater reduction in weight was found with empagliflozin with a difference of 1 kg at day 3 and 1.71 kg at week 6. For those patients allocated to empagliflozin, 5 patients required a 50% loop diuretic dose reduction by day 3. No occurrences of hyponatremia, hypokalemia, diabetic ketoacidosis, or severe hypoglycemia occurred. Two empagliflozin patients had worsening renal function within 48 h of initiation of empagliflozin; however, the renal function return to baseline by week 6.[33]

Ertugliflozin

The VERTIS CV trial is a randomized, controlled, multicenter trial assessing the use of ertugliflozin in patients with T2DM and established atherosclerotic CVD. Patients received ertugliflozin 5 mg, 15 mg, or placebo added to standard of care. A total of 8246 patients were enrolled. Patients were followed for a mean of 3.5 years. In the full population, HF hospitalization was lower with ertugliflozin (2.5% vs. 3.6%, HR: 0.70, 95% CI: 0.54–0.90; NNT: 91). Of the included patients, 24% had HF at baseline. In HF patients, ertugliflozin provided a greater reduction in HF hospitalizations (1.69 vs. 2.62 events/100 patient years, HR: 0.63, 95% CI: 0.44–0.90). The benefit of ertugliflozin in HF patients was found in those patients with EF ≤45%.[19,34]

Sotagliflozin

The SCORED trial is a randomized, controlled, multicenter trial assessing the use of sotagliflozin in patients with T2DM, CKD, and additional CV risk. Patients received sotagliflozin 200 mg, 400 mg, or placebo added to standard of care. A total of 10,584 patients were enrolled, of which 19.9% had HF. The patients were followed for a median of 16 months. In the full population, HF hospitalization and urgent visits for HF were lower with sotagliflozin (3.5 vs. 5.1 events/100 patient years (HR: 0.67, 95% CI: 0.55–0.82).[35]

The SOLOIST-WHF trial is a randomized, controlled, multicenter trial assessing use of sotagliflozin in patients with T2DM that had a recent HF hospitalization. No specific EF cut point was required. Patients received sotagliflozin 200 mg, 400 mg, or placebo added to ACEi, ARB, or ARNI, beta-blockade, and aldosterone antagonist therapy. A total of 1222 patients were enrolled, 20% of which has an EF >50%. The patients were followed for a median of 9.2 months. The composite of HF hospitalization, urgent HF visit, or CV death was lower with sotagliflozin at 51.0 versus 76.3/100 patient years (HR: 0.67, 95% CI: 0.52–0.85). When assessed individually, HF hospitalizations and urgent HF visits were decreased with use of sotagliflozin (40.4 vs. 63.9/100 patient years, HR: 0.64, 95% CI: 0.49–0.83). CV death and adverse effects were similar between groups. It should be noted that the trial ended early due to loss of funding from the sponsor.[36]

DISCUSSION

The effect of SGLT2 inhibitors on HF outcomes has been studied in multiple RCTs. An important comparison between studies is whether the populations included patients with T2DM, patients with HF, or both. Six large-scale RCTs have been conducted in patients with diabetes regardless of the presence of HF.[18-20,26,28,35] In these studies, the incidence of patients with HF ranged from 10.1% to 31%, with an average across all 6 studies of 17.4%. This average reflects rates of HF among patients with diabetes in the United States which is four times higher than the general population and ranges from 9% to 22%.[37] Although not assessing HF as a primary outcome, all 6 studies showed significant reductions in HF hospitalizations, with NNTs ranging from 42 to 91. Subgroup and *post hoc* analyses of these studies yielded mixed results as to the benefit among patients with HF. These inconsistent findings could be attributed to the low sample size of HF patients.

Six studies included patients with HF, with RECEDE-CHF, REFORM, and SOLOIST-WHF also requiring patients to have T2DM.[21,22,30,31,33,36] For EMPEROR-Reduced, DAPA-HF and DEFINE-HF, the incidence of diabetes was 49.8%, 41.8%, and 63.1%, respectively.[21,31,32] For the large-scale RCTs, the average incidence of 45.8% is reflective of the rates of diabetes among patients with HF in the United States, which ranges from 10% to 47%.[1] RECEDE-CHF, DEFINE-HF, and REFORM were small in scale and assessed surrogate markers for clinically important outcomes. These surrogate markers included changes in measures of left ventricular function, NT-proBNP, KCCQ-CS scores, and measures of diuretic effect.[30,31,33] Large-scale trials evaluating clinically important outcomes included assessments of hospitalization rates and CV death.

DAPA-HF and EMPEROR-Reduced were large-scale RCTs that evaluated use of SGLT2 inhibitors in patients with HFrEF.[21,22] Use of GDMT was prioritized in both studies with the majority of patients receiving ACEi/ARBs/ARNI, beta-blockers, and aldosterone antagonists. These therapies are reflective of current guidelines recommendations which recommend use of SGLT2 inhibitors in patients already receiving these medication classes.[11] Of note, approximately, 30% of patients were not receiving aldosterone antagonists. Subgroup analysis in both studies showed the composite endpoint maintained statistical significance in patients not receiving aldosterone antagonists at baseline. Consistent benefits were also seen for patients receiving ARNIs; however, this was limited to a smaller number of patients. While both trials found significant reductions in the

composite outcome of HF failure hospitalization and CV death, only DAPA-HF found a significant reduction in mortality with an NNT: of 53.[21,22] From a therapeutic perspective, the mortality benefit with dapagliflozin could support preferential use over empagliflozin. A meta-analysis of DAPA-HF and EMPEROR-Reduced found an overall significant reduction in mortality when assessing both trials.[38]

In contrast to DAPA-HF and EMPEROR-Reduced, SOLOIST-WHF was a large-scale trial in patients with diabetes and HF. While most evidence is limited to patients with HFrEF, SOLOIST-WHF based eligibility for inclusion on HF hospitalization rather than EF.[36] This study offers insight on the use of SGLT2 inhibitors in patients with HF with preserved EF (HFpEF), a population with limited data regarding use of SGLT2 inhibitors. Subgroup analysis showed significant improvements in the primary composite endpoint regardless of EF, indicating a possible benefit in patients with HFpEF. It should be noted that only 21% of patients had an EF above 50% and that use of SGLT2 inhibitors is not currently recommended in patients with HFpEF due to limited data supporting its use.[36]

Use of SGLT2 inhibitors in practice can be guided by clinical trial findings. Clinicians should prioritize use of large-scale trials that assess clinically important outcomes in patients with HF, including DAPA-HF, EMPEROR-Reduced, and SOLOIST-WHF. Providers should also consider the approved FDA indications for each agent. At present, dapagliflozin is the only SGLT2 inhibitor with an FDA approved indication for the management of HF in patients with New York Heart Association classes II, III, or IV.[13] Ertugliflozin is the only available agent without an FDA approved indication for use to reduce CV events.[15] Of note, sotagliflozin is not

Table 4: Clinical considerations pertaining to SGLT2 inhibitor use.

Patients with T2DM and HF		
When to consider initiating an SGLT2 inhibitor	Trials found significant reductions in HF hospitalization. Most patients did not have a history of HF.	2021 ADA guidelines recommend considering SGLT2 inhibitor therapy in all patients with diabetes and HF regardless of baseline A1c.
Patients with HF		
When to consider initiating an SGLT2 inhibitor	Patient-specific factors to guide therapy: HFrEF vs. HFpEF Majority of literature shows a benefit in HFrEF. Benefit in HFpEF not well established. NYHA Classification Majority of literature in patients with class II and III, limited data in class IV	Consider SGLT2 inhibitor in patients with HFrEF and NYHA class of II or III. 2021 ACC Expert Consensus suggests consideration for use in NYHA class IV as well.
What other GDMT should a patient receive before initiating an SGLT2 inhibitor?	Majority of patients in trials were already receiving an ACEi/ARBs/ARNI, beta-blockers, and aldosterone antagonists. Most patients received an ACEi or ARB, not an ARNI.	Consider an SGLT2 inhibitor in patients already receiving an ACEi/ARBs/ARNI, beta-blockers, and aldosterone antagonists, or in patients not receiving these medications due to tolerability or safety concerns. Initiation of an ARNI is not needed prior to consideration of an SGLT2 inhibitor.
Which SGLT2 inhibitor should be initiated?	Dapagliflozin, empagliflozin, and sotagliflozin have large-scale RCTs in HF. Dapagliflozin and empagliflozin were studied regardless of the presence of diabetes. Only dapagliflozin significantly reduced mortality in RCT data, however meta-analysis data showed a combined mortality benefit.	2021 ACC Expert Consensus recommends use of either dapagliflozin or empagliflozin, with a starting and target dose of 10 mg by mouth daily.
Is initiation of an SGLT2 inhibitor safe in patients with renal disease?	DAPA-HF excluded patients with an eGFR <30 mL/min/1.73 m^2. EMPEROR-Reduced excluded patients with an eGFR <20 mL/min/1.73 m^2.	Prior to initiation, ensure eGFR ≥30 mL/min/1.73 m^2 for dapagliflozin and ≥20 mL/min/1.73 m^2 for empagliflozin. Use is contraindicated in dialysis.
What adverse effects should be monitored after initiation?	EMPEROR-Reduced found higher rates of uncomplicated genital tract infections, though overall rates were low. Both EMPEROR-Reduced and DAPA-HF found similar rates of other adverse effects between groups.	Though well tolerated in trials, it is reasonable to monitor all patients for adverse effects. Monitor for hypotension, volume depletion, hypoglycemia, and urinary/genital infections.

SGLT2: Sodium-glucose co-transporter 2, HF: Heart failure, ARB: Angiotensin receptor blocker, ACEi: Angiotensin converting enzyme inhibitor, ARNI: Angiotensin receptor-neprilysin inhibitor, T2DM: type 2 diabetes mellitus

FDA approved at this time. Based on the available data, dapagliflozin or empagliflozin should be added to HF patients GDMT if they have HFrEF and NYHA class of II or III. This recommendation is also supported by the 2021 ACC Expert Consensus Decision Pathway.[11] Table 4 summarizes clinical considerations and application strategies that can be used in practice. Other factors to assess include patient preference and medication cost. Medication adherence and cost should also be regularly assessed and strategies to improve medication adherence should be prioritized. Finally, adverse effects must be considered. Each of the SGLT2 inhibitors has been found to increase the risk of genital mycotic infections and urinary tract infections.

CONCLUSION

Multiple morbidity and mortality reducing agents are available for management of HF. SGLT2 inhibitors provide morbidity and mortality reduction in the HF population, especially those with a reduced ejection fraction. These agents should be added to HF GDMT in the absence of contraindications.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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