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MINIREVIEWS

Sodium glucose cotransporter 2 inhibitors in the management of heart failure: Veni, Vidi, and Vici

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Abstract

Heart failure (HF) is a chronic disease associated with high morbidity and mortality rates. Renin-angiotensin-aldosterone system blockers (including angiotensin receptor/neprilysin inhibitors), beta-blockers, and mineralocorticoid receptor blockers remain the mainstay of pharmacotherapy for HF with reduced ejection fraction (HFrEF). However, despite the use of guideline-directed medical therapy, the mortality from HFrEF remains high. HF with preserved ejection fraction (HFpEF) comprises approximately half of the total incident HF cases; however, unlike HFrEF, there are no proven therapies for this condition. Sodium glucose cotransporter-2 inhibitors (SGLT-2is) represent a new class of pharmacological agents approved for diabetes mellitus (DM) that inhibit SGLT-2 receptors in the kidney. A serendipitous finding from seminal trials of SGLT-2is in DM was the significant improvement in renal and cardiovascular (CV) outcomes. More importantly, the improvement in HF hospitalization (HHF) in the CV outcomes trials of SGLT-2is was striking. Multiple mechanisms have been proposed for the pleiotropic effects of SGLT-2is beyond their glycemic control. However, as patients with HF were not included in any of these trials, it can be considered as a primary intervention. Subsequently, two landmark studies of SGLT-2is in patients with HFrEF, namely, an empagliflozin outcome trial in patients with chronic HF and a reduced ejection fraction (EMPEROR-Reduced) and dapagliflozin and prevention of adverse outcomes in HF (DAPA-HF), demonstrated significant improvement in HHF and CV mortality regardless of the presence of DM. These impressive results pitchforked these drugs as class I indications in patients with HFrEF across major guidelines. Thereafter, empagliflozin outcome trial in patients with chronic HF with preserved ejection fraction (EMPEROR-Preserved) and dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction HF (DELIVER) trials successively confirmed that SGLT-2is also benefit patients with HFpEF with or without DM. These results represent a watershed as they constitute the first clinically meaningful therapy for HFpEF in the past three decades of evolution of HF management. Emerging positive data for the use of

SGLT-2is in acute HF and post-myocardial infarction scenarios have strengthened the pivotal role of these agents in the realm of HF. In a short span of time, these classes of drugs have captivated the entire scenario of HF.

Key Words: Heart failure with preserved ejection fraction; Gliflozins; Diuresis; Natriuresis; N terminal-pro brain natriuretic peptide; Heart failure hospitalization

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Core Tip: Heart failure (HF) is associated with high morbidity and mortality rates. Sodium glucose cotransporter-2 inhibitors (SGLT-2is) are approved for diabetes mellitus (DM), and have also demonstrated improvement in renal and cardiovascular (CV) outcomes along with good glycemic control. Two landmark studies of SGLT-2is in patients with HF demonstrated improvement in HF hospitalization and CV mortality, irrespective of DM status. Subsequent clinical trials proved that SGLT-2is also benefit patients with HF with preserved ejection fraction with/without DM. Emerging positive data for SGLT-2is in acute HF and post-myocardial infarction scenarios have bolstered their pivotal role in the full diapason of HF.

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INTRODUCTION

Heart failure (HF) is the chronic outcome of several cardiac illnesses such as coronary artery disease, hypertension, repaired cyanotic congenital defects, and cardiomyopathies. HF is caused by the functional or structural impairment of ventricular filling or ejection[1]. Worldwide, there are approximately 37.7 million cases of HF, and the prevalence of this condition is increasing[2]. The classification of HF includes HF with reduced ejection fraction (HFrEF) (*i.e.* HF with a left ventricular ejection fraction [LVEF] of ≤ 40%), HF with mildly reduced ejection fraction (HFmrEF) (*i.e.* HF with LVEF of 41%-49%), and HF with preserved ejection fraction (HFpEF) (*i.e.* HF with LVEF of ≥ 50%). A new entity recently described in literature is HF with improved ejection fraction (*i.e.* HF with a baseline LVEF of ≤ 40%, a ≥ 10-point increase from baseline LVEF, and a second measurement of LVEF > 40%)[3]. The standard treatment for HFrEF comprises beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers with mineralocorticoid receptor blockers, and diuretics[4]. These medications have offered immense clinical benefits to patients with HFrEF and are supported by evidence from large clinical trials. All of these drugs were introduced into clinical practice in the early 1990s and 2000s. Since then, only angiotensin receptor neprilysin inhibitor (ARNI)-sacubitril-valsartan has shown superiority over angiotensin-converting enzyme (ACE) inhibitors in reducing cardiovascular (CV) mortality and HF hospitalization (HHF) in 2014[5]. Although strong evidence is available for the benefits of these drugs in HFrEF, they have failed to offer comparable benefits in patients with HFpEF. Table 1 depicts the number needed to treat (NNT) of major guideline-approved HF medications derived from the seminal trials. The much anticipated PARAGON-HF trial, which compared ARNI with valsartan, did not report significant benefits in patients with HFpEF. However, certain benefits were observed in women and in those with HFmrEF. Thus, evidence-based therapies to enhance the outcomes of patients with HFpEF are lacking[6].

Sodium glucose cotransporter-2 inhibitors (SGLT-2is), which were initially approved as antidiabetic agents, are now used to treat HF and constitute one of the four pillars of HF pharmacotherapy. The indication for SGLT-2is as major HF medications came after the landmark trial of dapagliflozin in HFrEF, which proved the potential of the drug in reducing CV outcomes irrespective of the presence or absence of diabetes[7,8]. Subsequently, the efficacy of empagliflozin, another SGLT-2i, was confirmed in a major trial on empagliflozin outcome trial in patients with chronic HF and a reduced ejection fraction (EMPEROR-Reduced), which showed that empagliflozin significantly reduced HHF regardless of the presence of diabetes; however, mortality reduction was not noted[9]. Moreover, the most recently published articles on SGLT-2is in HFpEF (Empagliflozin outcome trial in patients with chronic HF with preserved ejection fraction [EMPEROR-Preserved] and dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction HF [DELIVER trial]) have shown promising results. Based on these findings, the latest guidelines recommend their use in HFpEF therapy[10,11].

SGLT-2IS IN HF: MECHANISM OF ACTION

SGLT-2is are a class of drugs that inhibits SGLT-2 receptors in the proximal convoluted tubules of nephrons in the kidney, resulting in the failure of glucose reabsorption in the kidney. However, the benefits in CV outcomes cannot be explained by these simple mechanisms alone. Conventional and direct cardiac mechanisms of action of SGLT-2is can confer CV benefits (Figure 1).

Table 1 Number needed to treat in major heart failure trials

Study	Drug tested	Primary endpoints	Results	NNT	Year	Number of patients	Follow-up
EMPEROR-Reduced trial	Empagliflozin *vs* placebo	CV death or HF hospitalization	19.4% *vs* 24.7% HR: 0.75 (95%CI: 0.65-0.86)	19	2020	3730	16 months
DAPA-HF trial	Dapagliflozin *vs* placebo	CV death or HF hospitalization	16.3% *vs* 21.2% HR: 0.74 (95%CI: 0.65-0.85)	21	2019	4744	18.2 months
SOLOIST-HF trial	Sotagliflozin *vs* placebo	CV death or HF hospitalization	70% *vs* 98% HR: 0.67 (95%CI: 0.52-0.85)	4	2021	1222	9 months
PARADIGM-HF trial	ARNI *vs* enalapril	CV death or HF hospitalization	21.8% *vs* 26.5% HR: 0.80 (95%CI: 0.73-0.87)	21	2014	8442	27 months
RALES trial	Spironolactone *vs* placebo	Death from all causes	35% *vs* 46% HR: 0.70 (95%CI: 0.60-0.82)	9	1999	1663	24 months
EMPHASIS-HF	Eplerenone *vs* placebo	CV death or HF hospitalization	18.3% *vs* 25.9% HR: 0.63 (95%CI: 0.54-0.74)	19	2011	2737	1.8 years
EPHESUS	Eplerenone *vs* placebo	Death any cause CV death or HF hospitalization	HR: 0.85 (95%CI: 0.75-0.96); HR: 0.87 (95%CI: 0.79-0.95)	50 to prevent 1 death; 33 to prevent 1 CV death or HF hospitalization	2003	6642	16 months
MERIT-HF trial	Metoprolol *vs* placebo	All-cause death	7.2% *vs* 11% HR: 0.66 (95%CI: 0.53-0.81)	27	1999	3991	2.4 years
CIBIS II-HF trial	Bisoprolol *vs* placebo	All-cause death HF hospitalization	11.8% *vs* 17.3%; 33% *vs* 39%	18; 17	1999	2647	1.3 years
COPERNICUS trial	Carvedilol *vs* placebo	All-cause death and HF hospitalization	36.8% *vs* 44.7%	13	2001	2289	10 months
CHARM trial	Candesartan *vs* placebo	CV death and HF hospitalization	22% *vs* 24% HR: 0.89 (95%CI: 0.77-1.03)			3023	36.6 months
VA-HEFT Trial	Valsartan *vs* placebo	Mortality plus morbidity	No difference 28.8% *vs* 32.1% HR: 0.87 (95%CI: 0.77-0.97)		2001	5010	23 months
SHIFT trial	Ivabradine *vs* placebo	CV death and HF hospitalization	24% *vs* 29% HR: 0.82 (95%CI: 0.75-0.90)	27	2010	6558	22.9 months
SOLVD trial	Enalapril *vs* placebo	Mortality HF hospitalization			1991	2569	22-55 months

CHARM: Candesartan in heart failure assessment of reduction in mortality and morbidity; CI: Confidence interval; CIBIS II: The cardiac insufficiency bisoprolol study II; COPERNICUS: Carvedilol prospective randomized cumulative survival; CV: Cardiovascular; HF: Heart failure; HR: Hazard ratio; DAPA: Dapagliflozin and prevention of adverse outcomes; EMPEROR: Empagliflozin outcome trial in patients with chronic heart failure and a reduced ejection fraction; EMPHASIS: Eplerenone in mild patients hospitalization and survival study; EPHESUS: Eplerenone post–acute myocardial infarction heart failure efficacy and survival study; MERIT: Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients; NNT: Number needed to treat; PARADIGM: Prospective comparison of angiotensin receptor–neprilysin inhibitor with angiotensin-converting–enzyme inhibitor to determine impact on global mortality and morbidity; RALES: Randomized Aldactone evaluation study; SHIFT: Systolic heart failure treatment with the if inhibitor ivabradine trial; SOLOIST: Effect of Sotagliflozin on cardiovascular events in patients with type 2 diabetes worsening post heart failure; SOLVD: Studies of left ventricular dysfunction; VA-HEFT: The vasodilator-heart failure trial.

Conventional effects

Natriuresis and osmotic diuresis occur because of glucosuria. However, the coadministration of loop diuretics and dependence of the degree of osmotic diuresis and glycosuria on blood glucose levels indicate alternative mechanisms of benefit. Similar benefits were observed in patients without diabetes. Studies have suggested that SGLT-2is decrease only interstitial fluid and not plasma volume and thus can act synergistically[12,13]. SGLT-2is reduce blood pressure secondary to improvement in endothelial function, reduction in arterial stiffness, and alterations in sympathetic nervous activity[14,15]. However, these drugs exert only a modest antihypertensive effect. Weight loss occurs because of an

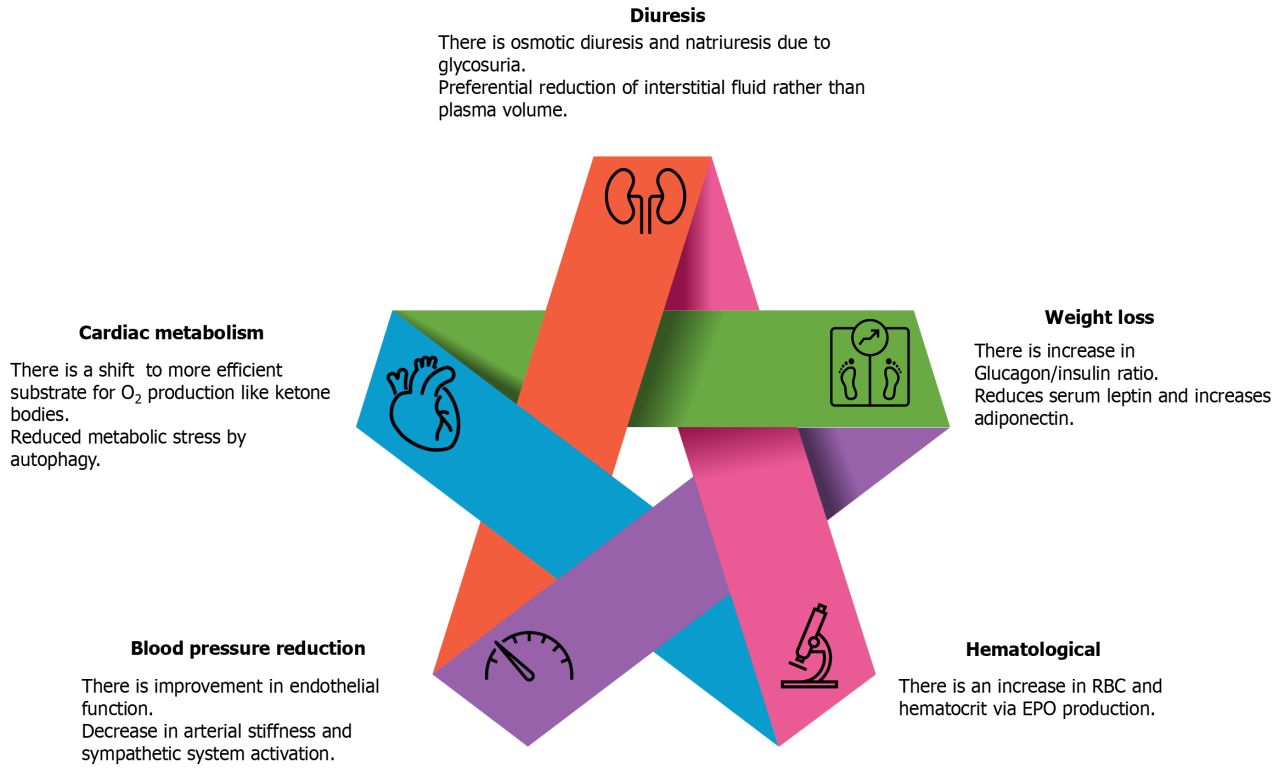

Figure 1 Mechanism of action of sodium glucose cotransporter-2 inhibitors in heart failure. EPO: Erythropoietin; O_2: Oxygen; RBC: Red blood cell.

increased glucagon: insulin ratio, which augments lipid mobilization[16,17]. Hematocrit and red blood cell mass increase with an elevation in erythropoietin production in the kidneys[18].

Direct effects

SGLT-2i therapies reverse adverse cardiac remodeling[19,20]. This effect has been demonstrated in patients with left ventricular hypertrophy and type 2 diabetes mellitus (T2DM) but not in those with HF, and a direct novel cardioprotective effect may be plausible[20,21]. Other effects include changes to more oxygen-efficient ketone bodies, cardiac metabolism of fatty acids, and glucose oxidation, which improve cardiac efficiency[22]. Furthermore, SGLT-2is inhibit sodium-hydrogen exchanger 1 and SGLT-1 transporters and improve the levels of cytosolic sodium[23,24]. Autophagy exerts a favorable effect on HF by alleviating metabolic stress. Continuous glycosuria simulates a state of nutrient depletion and catabolism, which induces autophagy[25,26]. SGLT-2is reduce the serum leptin-to-adiponectin ratio, exerting cardioprotective effects[27,28].

Role in improving cardiac metabolism

SGLT-2is were initially postulated to increase fasting ketone levels, which might act as an additional substrate for myocyte energy production; however, this theory was not supported by experimental data[29,30]. SGLT-2is maintain cytosolic calcium levels by inhibiting the sodium-hydrogen exchanger[23,24]. Certain preclinical studies have suggested that SGLT-2is induce a myocardial substrate switch, thereby improving myocardial energetics. However, in the EMPA-VISION trial (assessment of cardiac energy metabolism, function and physiology in patients with HF taking empagliflozin), treatment with 10 mg empagliflozin once daily for 12 weeks did not enhance cardiac energetics or alter the levels of circulating serum metabolites associated with energy metabolism compared with placebo. Thus, enhanced cardiac energy metabolism is unlikely to mediate the beneficial effects of SGLT-2is in HF[31].

ADVERSE EFFECTS OF SGLT-2IS

The most common adverse effects of SGLT-2is are mycotic genital infections in women, urinary tract infections, nausea, and constipation. Other adverse events include lower limb amputation, which is especially seen with canagliflozin. Predisposing factors to limb amputation with the use of SGLT-2is are preexisting peripheral arterial disease, neuropathy, and diabetic foot ulcers. Hence, in patients with foot ulcers, SGLT-2is should be avoided or discontinued. The risk of euglycemic diabetic ketoacidosis (DKA) is also seen with SGLT-2is, which can be up to three-fold higher, and is again most noted with the use of canagliflozin. This finding could be attributed to noninsulin-dependent glucose clearance, hyperglucagonemia, and volume depletion. Thus, in patients with suspected DKA, the drug should be discontinued. A modest but reversible decrease in estimated glomerular filtration rate (eGFR) and rise in serum creatinine may also be noted in the initial period with the use of these drugs due to intravascular volume contraction. Therefore, the patient's

volume status should be corrected, especially in the elderly, before initiating treatment. Other rare side effects include bone fractures, bladder cancer (to be avoided in patients with active bladder cancer), and hyperkalemia.

CONTRAINDICATIONS OF SGLT-2IS

The contraindications for therapy include T1DM, dialysis-dependent kidney disease and hypersensitivity reactions, such as anaphylaxis or angioedema, to any of the four agents.

HHF IN PRIMARY PREVENTION STUDIES OF SGLT-2IS

The combined analysis of the canagliflozin cardiovascular assessment study (CANVAS) and CANVAS-renal trials, which compared CV events in patients with T2DM taking the SGLT-2i canagliflozin *vs* those taking placebo, was conducted as a part of the CANVAS program[32]. The findings showed a significant reduction in major adverse cardiac events (26.9 participants per 1000 patient-years in the canagliflozin group *vs* 31.5 per 1000 patient-years in the placebo arm). Equal benefits were observed in patients with HFrEF and those with HFpEF, with greater benefits in those with a history of HF.

The empagliflozin cardiovascular outcome event trial in T2DM patients (EMPA-REG outcome) was conducted to evaluate the CV safety of empagliflozin in patients with T2DM with atherosclerotic CV disease (ASCVD). The trial reported a 14% reduction in major adverse cardiovascular outcomes (MACEs) with empagliflozin compared with placebo, along with a relative risk (RR) reduction of 38% for CV deaths, 32% for all-cause deaths, and 35% for HHF[33].

The dapagliflozin effect on cardiovascular events-thrombolysis in myocardial infarction 58 (DECLARE-TIMI 58) study examined the CV safety of dapagliflozin in patients with T2DM having ASCVD or a high risk for the condition. Although dapagliflozin significantly improved glycemic control, it did not significantly reduce MACEs. Nonetheless, in patients with HFrEF, hospitalization and CV death rates significantly decreased[34].

In the effect of sotagliflozin on cardiovascular and renal events in patients with T2DM and moderate renal impairment who are at cardiovascular risk (SCORED) trial, 10584 patients with T2DM (glycated hemoglobin level ≥ 7%), chronic kidney disease (eGFR 25-60 mL/min/1.73 m^2 of body surface area), and CV disease risk were randomly assigned in a 1:1 ratio to receive either sotagliflozin or placebo. The primary endpoint of this study was the composite of CV death, HHF, and urgent HF visits. The rates of primary endpoint events were 5.6 and 7.5 events per 100 patient-years in the sotagliflozin and placebo groups, respectively (hazard ratio [HR]: 0.74; 95% confidence interval [CI]: 0.63-0.88; P = 0.001). Diarrhea, DKA, genitourinary infections, and dehydration occurred more frequently in the sotagliflozin group than in the placebo group. Hence, in patients with diabetic nephropathy with or without albuminuria, sotagliflozin treatment reduced the rates of primary endpoints, especially HHF[35].

META-ANALYSIS OF PRIMARY PREVENTION TRIALS OF SGLT-2IS

The meta-analysis performed by Zelniker *et al*[36] included data from 34322 patients (60.2% with established ASCVD) and three identified trials, namely, EMPA-REG outcomes, CANVAS program, and DECLARE-TIMI-58. A total of 3342 MACEs, 2028 CV deaths and HHF events, and 766 renal composite outcomes were documented. Although the rate of MACEs was reduced to 11% (HR: 0.89; 95%CI: 0.83-0.96; P = 0.0014), the benefit was evident only in patients with ASCVD (HR: 0.86; 95%CI: 0.80-0.93) and not in those without ASCVD (HR: 1.00; 95%CI: 0.87-1.16; P for interaction = 0.0501). However, the risk of CV death or HHF was decreased by 23% (HR: 0.77; 95%CI: 0.71-0.84; P = 0.0001) both in patients with and without established ASCVD and irrespective of the presence or absence of HF. Similarly, SGLT-2is alleviated the risk of renal disease progression by 45% (HR: 0.55; 95%CI: 0.48-0.64; P = 0.0001) regardless of the presence or absence of ASCVD. The extent of benefits offered by SGLT-2is in reducing HHF and the progression of renal impairment was the highest in patients with advanced renal disease[36].

Another meta-analysis of four trials of SGLT-2is in patients with diabetes conducted by Lo *et al*[37] demonstrated benefits in reducing CV events. This meta-analysis examined the results based on renal impairment. The pooled RR (95%CI) for the composite CV outcome was 0.93 (0.87-0.99) in the general study population (NNT: 167 and 0.89 (0.77-1.02) in patients with eGFR 60 mL/min/1.73 m^2; that for all-cause mortality was 0.9 (0.84-0.97) with NNT = 143; that for CV death was 0.89 (0.81-0.99) in the general population and 0.82 (0.62-1.07) in patients with eGFR 60 mL/min/1.73 m^2; and that for HHF was 0.71 (0.63-0.79) with NNT = 91. Regarding renal outcomes, the pooled RR (95%CI) for the composite renal outcome was 0.63 (0.56-0.71) with NNT = 67 in the general population and 0.67 with eGFR 60 mL/min/1.73 m^2. In addition, the risk for albuminuria progression was reduced (RR = 0.80).

These meta-analyses confirm that SGLT-2is are associated with significantly lower MACEs, HHF, and all-cause mortality, with the strongest evidence for HHF reduction. Although the evidence was weaker in the population subset with eGFR 60 mL/min/1.73 m^2, SGLT-2is significantly reduced the number of adverse renal events and also possibly retarded the progression of renal disease, with these effects being obvious even in the population with eGFR 60 mL/min/1.73 m^2[37].

SECONDARY PREVENTION TRIALS OF SGLT-2IS

These trials are shown in Table 2 and Figure 2.

Trials in HFrEF

Dapagliflozin and prevention of adverse outcomes in HF (DAPA-HF): This trial randomized 4744 patients with New York Heart Association (NYHA) class II-IV symptoms and LVEF 40% to either dapagliflozin (10 mg once a day) or placebo along with guideline-directed medical therapy. The primary endpoint was a composite of CV death and hospitalization because of worsening HF symptoms. After a follow-up of 18.2 months, dapagliflozin significantly reduced the primary outcome (16.3% *vs* 21.2%, HR: 0.74, 95%CI: 0.65-0.85; P = 0.001). The first HF event occurred at a significantly lower rate with dapagliflozin than with placebo (10.0% *vs* 13.7%, HR: 0.70, 95%CI: 0.59-0.83). The incidence rate of CV death was 9.6% in the dapagliflozin group and 11.5% in the placebo arm (HR: 0.82, 95%CI: 0.69-0.98), whereas those of non-CV death were 11.6% and 13.9%, respectively (HR: 0.83, 95%CI: 0.71-0.97). These results remained the same irrespective of the patients' diabetes status. The frequency of adverse events was comparable in both treatment groups[7].

EMPEROR-Reduced: In this trial, patients with NYHA II-IV HF and LVEF 40% were randomized to receive either empagliflozin (10 mg once daily) or placebo. The major endpoint was a composite of hospitalization, worsening HF symptoms, and CV death. After 16 months of follow-up, the primary outcome event occurred at a significantly lower rate with empagliflozin than with placebo (19.4% *vs* 24.7%, HR: 0.75, 95%CI: 0.65-0.86; P = 0.001). These benefits were noted irrespective of the patients' glycemic status. Moreover, the rate of HHF was significantly lower with empagliflozin than with placebo (HR: 0.70, 95%CI: 0.58-0.85; P = 0.001)[8].

Trials of SGLT-2is in HFpEF

EMPEROR-Preserved: In this double-blind trial, 5988 patients with NYHA class II-IV HF and LVEF > 40% were randomized to receive either empagliflozin (10 mg once daily) or placebo in addition to the routine therapy and followed up for 2 years. The primary outcome was a combination of hospitalization for worsening HF symptoms and CV death. The findings indicated that empagliflozin significantly reduced the primary endpoints compared with placebo (13.8% *vs* 17.1%, HR: 0.79, 95%CI: 0.69-0.90; P = 0.001). These outcomes were predominantly driven by a reduction in the rate of HHF with empagliflozin (HR: 0.73, 95%CI: 0.61-0.88; P = 0.001) and were similar in patients with and without diabetes. Uncomplicated genital and urinary tract infections and hypotension were reported more often with empagliflozin than with placebo[10].

DELIVER trial: This trial comprised 6263 stable patients with HF who had LVEF of > 40% with or without diabetes. The patients received dapagliflozin 10 mg once daily or placebo in addition to guideline-directed medical therapy. Those with LVEF 40% and elevated natriuretic peptide levels with structural heart disease were eligible for the study. The time to first CV death or the worsening of HF events (HHF or urgent HF visits) was the primary endpoint. After a median follow-up of 2.3 years, the primary outcome occurred in 16.4% of the patients in the dapagliflozin arm and 19.5% in the placebo group (HR: 0.82, 95%CI: 0.73-0.92; P = 0.001). The rate of HF worsening was 11.8% *vs* 14.5% (HR: 0.79, 95%CI: 0.69-0.91) and that of CV death was 7.4% *vs* 8.3% (HR: 0.88, 95%CI: 0.74-1.05) in the dapagliflozin *vs* placebo group. Comparable results were obtained in the prespecified subgroups, including patients with and without diabetes, and the incidence of adverse events was also similar[11].

Effect of empagliflozin on exercise ability and HF symptoms in patients with chronic HF (EMPERIAL) trial: Patients with HFrEF (EF < 40%) (EMPERIAL-Reduced, n = 312) or HFpEF (EF 40%) (EMPERIAL-Preserved, n = 315), with and without T2DM, were randomized to receive either empagliflozin 10 mg or placebo for 12 weeks. The primary endpoint was a 6-minute walk test distance change at week 12. Key secondary endpoints included the Kansas city cardiomyopathy questionnaire total symptom score (KCCQ-TSS) and Chronic HF questionnaire self-administered standardized format dyspnea score. The 6-minute walk test distance median differences (95%CI) for the empagliflozin and placebo groups at week 12 were -4.0 meters (-16.0 to 6.0; P = 0.42) and 4.0 m (-5.0 to 13.0; P = 0.37) in EMPERIAL-Reduced and EMPERIAL-Preserved, respectively, which were nonsignificant. All secondary endpoints were considered exploratory, indicating an improvement only in the EMPERIAL-Reduced trial[38].

Although HFpEF is not as malignant as HFrEF, considerable morbidity and mortality are associated with it because of comorbidities. In a retrospective study of HFpEF, patients who were admitted for acute or chronic HF exhibited a readmission rate of 21%, which led to increased mortality and resource consumption. Thus, there is a need for better management of these patients, for which SGLT2-is can be helpful[39].

SGLT-2IS IN AHF

Effects of sotagliflozin on cardiovascular events in patients with type 2 diabetes post worsening HF (SOLOIST-worsening HF) study

Sotagliflozin is a combined of SGLT-2 and SGLT-1 receptor inhibitor. SGLT-1 inhibition reduces postprandial glucose levels by delaying intestinal glucose absorption. In this trial, 1222 patients with HF and recent HF worsening were randomized in a 1:1 ratio to receive either sotagliflozin or placebo, with a median follow-up of 9 months. The patients received either sotagliflozin or placebo before discharge (48.8%) and at a median of 2 days after discharge (51.2%). The

Table 2 Landmark trials of sodium glucose cotransporter-2 inhibitors in heart failure

Trial	Year	Number of patients	SGLT-2i used *vs* placebo	Endpoints		*P* value
				SGLT-2 arm	Placebo arm	
EMPAREG outcomes	2015	7028	Empagliflozin 10 or 25 mg	CV death, non-fatal MI or stroke: 10.5%	CV death, non-fatal MI or stroke: 12.1%	< 0.001
				All-cause mortality: 3.8%	All-cause mortality 5.1%	< 0.01
				HHF: 2.7%	HHF: 4.1%	0.002
DECLARE TIMI 58	2018	17160	Dapagliflozin 10 mg	CV death, MI, stroke: 8.8%	CV death, MI, stroke: 9.4%	0.17
				CV death or HHF: 4.9%	CV death or HHF: 5.8%	0.005
CANVAS	2017	10142	Canagliflozin	Composite of CV death, non-fatal MI or stroke: 26.9%	Composite of CV death, non-fatal MI or stroke: 31.5%	< 0.0001
				CV death or HHF: 16.3%	CV death or HHF: 20.8%	
DAPA-HF	2019	4744	Dapagliflozin 10 mg	CV death or WHF: 16.3%	CV death or WHF: 21.2%	0.001
EMPEROR-Reduced	2020	3730	Empagliflozin 10 mg	CV death or HHF: 19.4%	CV death or HHF: 24.7%	< 0.001
EMPEROR-Preserved	2021	5988	Empagliflozin 10 mg	CV death or HHF: 13.8%	CV death or HHF: 17.1%	< 0.001
DELIVER	2022	6263	Dapagliflozin 10 mg	CV death or WHF: 16.4%	CV death or WHF: 19.5%	< 0.001
SOLOIST WHF	2021	1222	Sotagliflozin	CV death, HHF, urgent visit for HF: 51%	CV death, HHF, urgent visit for HF: 76%	0.001
EMPA RESPONSE	2020	80	Empagliflozin 10 mg	Change in VAS dyspnea score, wt. change, change in NT-proBNP, hospital stay length: 10%	Change in VAS dyspnea score, wt. change, change in NT-pro-BNP, hospital stay length: 13%	0.014
EMPULSE	2022	530	Empagliflozin 10 mg	Net clinical benefit: 53.9%	Net clinical benefit: 39.7%	0.0054
				CV death: 4.2%	CV death: 8.3%	
				HF events: 10.6%	HF events: 14.7%	
				Change in KCCQ-TSS: 4.5	Change in KCCQ-TSS	0.035
				Wt. change: -1.5 Kg	Wt. change	0.014
EMMY	2022	476	Empagliflozin 10 mg	Change in NT-pro-BNP: 15% lower *vs* placebo		0.026
				LVEF: 1.5% *vs* placebo		0.029
				E/e': 6.8% *vs* placebo		0.015
				LVESV: 7.5 mL *vs* placebo		0.0003
				LVEDV: 9.7 mL *vs* placebo		0.0015

CANVAS: Canagliflozin cardiovascular assessment study; CV: Cardiovascular; DAPA: Dapagliflozin and prevention of adverse outcomes; DECLARE TIMI 58: Dapagliflozin effect on cardiovascular events-thrombolysis in myocardial infarction 58; DELIVER: Dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction heart failure; E/e': Mitral inflow E wave velocity/annular tissue' wave velocity; EMMY: Empagliflozin in patients with acute myocardial infarction; EMPAREG: Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients; EMPA-RESPONSE: Effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure; EMPEROR: Empagliflozin outcome trial in patients with chronic heart failure; EMPULSE: Effect on clinical benefit, safety and tolerability of once daily oral empagliflozin 10 mg compared to placebo, initiated in patients hospitalized for acute heart failure who have been stabilized; HF: Heart failure; HHF: Heart failure hospitalization; KCCQ-TSS: Kansa city cardiomyopathy questionnaire total symptom score; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end systolic volume; MI: Myocardial infarction: NT-pro-BNP: N-terminal pro-B-type natriuretic peptide; SGLT-2is: Sodium glucose cotransporter-2 inhibitors; SOLOIST-WHF: Effect of Sotagliflozin on cardiovascular events in patients with type 2 diabetes post worsening heart failure; VAS: Visual analogue scale; WHF: Worsening heart failure; Wt.: Weight.

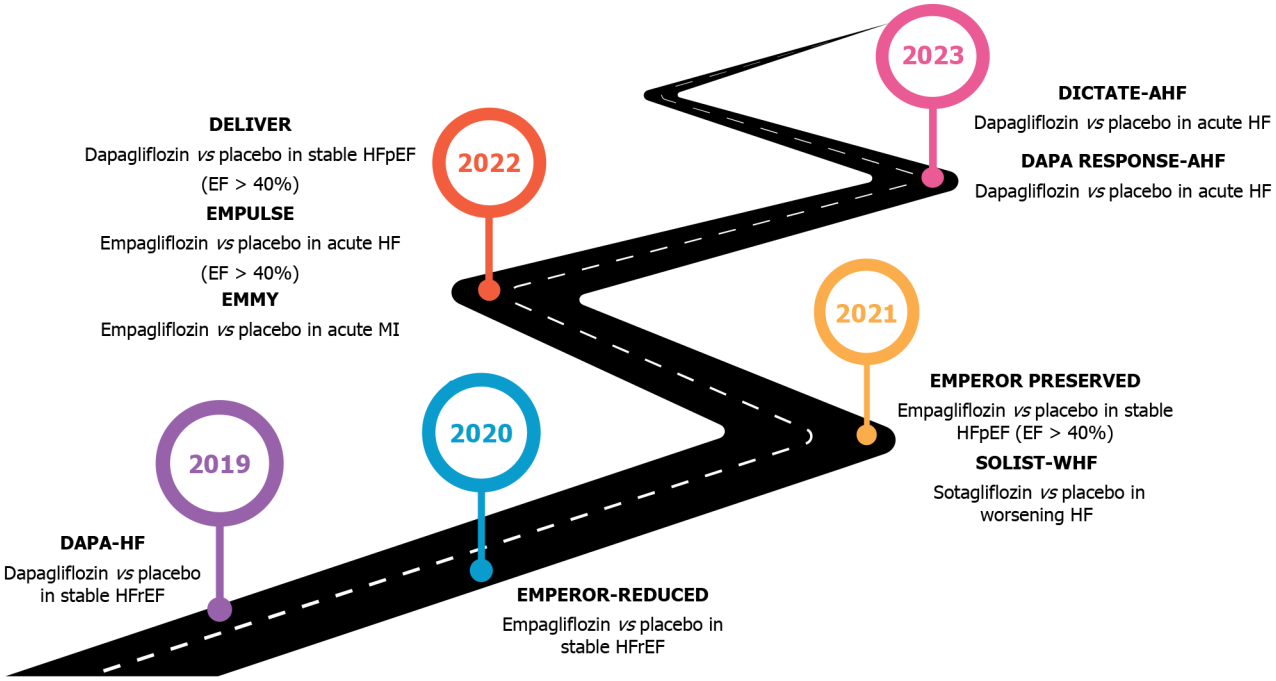

Figure 2 Roadmap of various landmark trials of sodium glucose cotransporter-2 inhibitors in heart failure. HF: Heart failure; MI: Myocardial infarction; EF: Ejection fraction.

primary endpoint was a combination of CV death, hospitalization, and urgent visits for worsening HF (first and subsequent).

In total, 600 primary endpoint events were reported (245 in the sotagliflozin group and 355 in the placebo group). The rate of primary endpoint events was significantly reduced in the sotagliflozin group compared with the placebo group (51.0 *vs* 76.3, HR: 0.67, 95%CI: 0.52-0.85; P = 0.001). Moreover, the rates of CV death were 10.6% with sotagliflozin and 12.5% with placebo (HR: 0.84, 95%CI: 0.58-1.22) and those of non-CV death were 13.5% in the sotagliflozin group and 16.3% in the placebo group (HR: 0.82, 95%CI: 0.59-1.14). However, more episodes of diarrhea (6.1% *vs* 3.4%) and severe hypoglycemia (1.5% *vs* 3.0%) were reported in the sotagliflozin group than in the placebo group. Furthermore, the percentages of patients with hypotension (6.0% *vs* 4.6%) and acute renal injury (4.1% *vs* 4.6%) were slightly higher in the sotagliflozin group[40].

Effects of empagliflozin on clinical outcomes in patients with acute decompensated HF (EMPA-RESPONSE-AHF) trial: In this randomized, placebo-controlled, double-blind, parallel-group, multicenter pilot study, 80 patients with AHF with and without diabetes were randomized to receive either empagliflozin 10 mg/day or placebo for 30 days. The primary endpoints were alterations in the visual analog scale (VAS) dyspnea score, diuretic response (weight change per 40 mg furosemide), change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, and the length of stay. The secondary outcomes comprised safety and clinical endpoints. The mean age was 76 years, 33% were women, 47% had *de novo* HF, and the median NT-proBNP level was 5236 pg/mL. Differences were not observed in the primary endpoints between the empagliflozin and placebo groups. Nevertheless, empagliflozin decreased the combined endpoint of in-hospital HF worsening, rehospitalization for HF, or death at 60 days compared with placebo (4 [10%] *vs* 13 [33%]; P = 0.014). Moreover, urinary output was higher in the empagliflozin group than in the placebo group. Empagliflozin was well tolerated, safe, and did not exert any adverse effects on the patients' blood pressure or renal function[41].

Effects on clinical benefit, safety, and tolerability of once daily oral empagliflozin 10 mg compared to placebo, initiated in patients hospitalized for acute heart failure who have been stabilized (EMPULSE) trial: In this trial, patients with AHF who exhibited a systolic blood pressure of 100 mmHg and did not receive inotropic support during the last 24 hours were randomized to receive either empagliflozin 10 mg (n = 265) or placebo (n = 265). Any intravenous (IV) diuretic or vasodilator use was discontinued within the last 6 hours of randomization. Patients with NT-proBNP of ≥ 1600 pg/mL or BNP of ≥ 400 pg/mL during hospitalization or within 72 hours prior to admission were included. The median LVEF was 31%. The primary endpoints were the composite of death, number of HF events, time to first HF event, and the KCCQ-TSS score from baseline to 90 days (P = 0.0054). In patients with acute decompensated HF (ADHF), empagliflozin was linked to a significant clinical benefit at 90 days and resulted in improved weight loss (decongestion) compared with placebo[42].

Efficacy and safety of dapagliflozin in AHF (DICTATE-AHF): The DICTATE-AHF trial investigated the efficacy and safety of dapagliflozin initiated within 24 hours of hospital admission on the diuretic response in patients with hypervolemic ADHF. Adult patients with T2DM admitted to the hospital with ADHF and underwent current or planned treatment with IV loop diuretics were included in this study. The findings were presented at the European Society of Cardiology (ESC) congress 2023. Early initiation of dapagliflozin did not significantly improve the diuretic efficiency

compared with structured routine care in patients with ADHF. However, it did not worsen any prespecified safety outcomes. Exploratory analyses revealed that the drug alleviated decongestion and resulted in early discharge from the hospital[43].

Effect of adjuvant dapagliflozin on improving the treatment of congestion in patients with AHF (DAPA-RESPONSE AHF): This randomized double-blind study included 87 patients with ADHF who presented with dyspnea. The patients were randomized to receive either dapagliflozin (10 mg/day, n = 45) or placebo (n = 42) for 30 days within 24 hours of admission. The primary outcome was the difference in the area under the curve (AUC) of the VAS dyspnea score between the groups over the first 4 days. The secondary endpoints were urinary sodium concentration 2 hours after randomization, percent change in NT-proBNP, cumulative urine output (UOP), and differences in mortality and hospital readmission rates. The results revealed that dapagliflozin significantly reduced the AUC of the VAS dyspnea score compared with placebo (3192.2 ± 1631.9 mm × hr *vs* 4713.1 ± 1714.9 mm × hr; P < 0.001). Moreover, the relative change in NT-proBNP compared with baseline was larger with dapagliflozin than with placebo (-34.89% *vs* -10.085%; P = 0.001). In addition, a higher cumulative UOP was observed with dapagliflozin on day 4 (18600 mL *vs* 13700 mL; P = 0.031). Dapagliflozin also reduced the rehospitalization rates within 30 days after discharge; however, it did not affect spot urinary sodium concentration, incidence of HF worsening, or mortality rates[44].

SGLT-2is in acute myocardial infarction

Empagliflozin in patients with acute myocardial infarction (EMMY) trial: In this randomized, double-blind trial, 476 patients with acute myocardial infarction (MI) were randomly assigned to receive either empagliflozin 10 mg or a matching placebo once daily within 72 hours of percutaneous coronary intervention (PCI). The primary endpoint was the change in NT-proBNP level over 26 weeks, and the secondary endpoint was alterations in echocardiographic parameters. The baseline median (interquartile range) NT-proBNP level was 1294 (757-2246) pg/mL. NT-proBNP reduction was significantly higher in the empagliflozin group than in the placebo group, which was 15% lower (95%CI: -4.4 to -23.6) after adjusting for baseline NT-proBNP level, sex, and diabetes status (P = 0.026). In addition, significant improvements were noted in LVEF, E/e', and left ventricle volume. Seven patients (three in the empagliflozin group) were hospitalized for HF[45].

EFFECT OF SGLT-2IS ON INTRACARDIAC DEFIBRILLATOR DEVICE IMPLANTATIONS

Sudden cardiac death (SCD) is the most devastating complication of HF. Current guidelines recommend intracardiac defibrillator device implantation in patients with HFrEF who have LVEF of ≤ 35% even after receiving optimized HF treatment for at least 3 months. ACE inhibitors/angiotensin II receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, and ARNIs prevent adverse cardiac remodeling and thus reduce the risk of SCD. Moreover, SGLT-2is also reduce the risk of ventricular arrhythmia, thereby preventing SCD.

In a population-based cohort study involving 399810 patients with recently diagnosed T2DM, SGLT-2is decreased the risk of all-cause mortality and new-onset arrhythmias (17% lower risk of new-onset arrhythmia) compared with placebo [46]. Furthermore, the EMPA-REG outcome study reported a significant reduction in CV deaths, including SCD, with empagliflozin[47].

Moreover, post-hoc analysis of the DAPA-HF (dapagliflozin and prevention of adverse outcomes in HF) study indicated that patients on dapagliflozin [140/2373 patients (5.9%)] exhibited significantly fewer arrhythmic events and SCD than those on placebo [175/2371 patients (7.4%); HR: 0.79; 95%CI: 0.63-0.99; P = 0.037)[48]. The mechanism was, in this case too, a reduction in wall stress and adverse remodeling.

In a recent meta-analysis of 22 trials that comprised 52115 patients, SGLT-2is were found to alleviate the risks of atrial fibrillation and ventricular tachyarrhythmia by 18% and 28%, respectively[49].

HYPERURICEMIA AND GOUT REDUCTION BY SGLT-2IS

The pathogenesis of hyperuricemia and gout is intricately linked to that of T2DM and HF. Visceral obesity, diabetes, and HF increase the incidence of hyperuricemia, which in turn exacerbates the risk of diabetes and HF. Hyperuricemia worsens glucose tolerance in patients with diabetes and causes ventricular dysfunction in those with HF. Nutrient surplus and signal deprivation are deranged, which leads to urate overproduction and underexcretion. SGLT-2is induce starvation mimicry in a state of nutrient surplus and decrease flux *via* the pentose phosphate pathway. These changes attenuate purine and urate synthesis and promote renal urate excretion, thus alleviating hyperuricemia and gout. Hence, the use of SGLT-2is may reduce the need for gout medications in patients with HF[50].

FUTURE STUDIES

EMPA-AHF (NCT05392764) study

A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy of empagliflozin in ADHF.

EMPA (NCT05556044) study

To evaluate the efficacy and safety of in-hospital initiation of empagliflozin in patients hospitalized for new-onset AHF, regardless of LVEF, for up to 90 days of follow-up.

Empagliflozin for patients with acutely decompensated congestive HF, diuretic resistance, and moderate to advanced chronic kidney disease (DRIP-AHF, NCT05305495)

A prospective, single arm, cohort study to evaluate the synergistic empagliflozin and furosemide in acutely decompensated HF patients complicated by hypovolemia and diuretic resistance.

Peri-treatment of SGLT-2is on myocardial infarct size and remodeling index measured by cardiac magnetic resonance imaging in patients with acute myocardial infarction and high risk of HF undergoing percutaneous coronary intervention (PRESTIGE AMI; NCT04899479)

To evaluate whether SGLT-2is is effective in reducing the size of infarction and myocardial remodeling in patients with AMI and at high risk of heart failure. SGLT-2is will be administered before PCI in patients with ST-elevation MI (STEMI) or non-STEMI, and infract size as well as LV end systolic volume will be assessed using cardiac magnetic resonance imaging.

Acute reno-cardiac action of dapagliflozin in advanced HF patients on heart transplant waiting list (ARCADIA AHF; NCT04782245)

To examine whether dapagliflozin use in patients waiting for heart transplant has any effect on soluble urokinase type plasminogen activation receptor-a biomarker useful both in acute kidney injury and HF.

Dapagliflozin on volume vascular outcomes (DAPA VOLVO; NCT04869124)

To investigate the effects of dapagliflozin on volume status (assessed by change in relative plasma volume and blood volume) and vascular function (flow mediated dilatation and pulse wave velocity) in patients with congestive HF.

GUIDELINES

Although SGLT-2is were initially recommended for HFrEF, latest guidelines have extended their use to HFpEF. The 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines for HF provide SGLT-2i class IA indications for HFrEF treatment. In patients with HFmrEF (41%-49%) and HFpEF, SGLT-2is are given a class 2A indication, which is also supported by the 2023 American College of Cardiology expert consensus decision pathway for the management of HFpEF. This guideline recommends that SGLT-2is should be started in all patients in the absence of any contraindications[51,52]. The 2023 Focused Update of ESC provides SGLT-2is a class IA indication in patients with HFrEF and HFmrEF to alleviate the risk of HHF or CV death. In addition, ESC provides a strong class IA indication for SGLT-2is in patients for HFpEF in this recent update[53].

CONCLUSION

SGLT-2is are a class of drugs that were initially introduced as antidiabetic medications but have recently become one of the four essential pillars of HF management. The efficacy of these inhibitors has been proven in the entire HF spectrum, irrespective of LVEF and diabetic status. The mechanisms underlying these benefits, although not well established, are believed to involve various cardiometabolic and biomolecular targets, in addition to the diuretic effects. These inhibitors offer early and sustained benefits without substantial side effects and should therefore be initiated at the earliest in HF management to reduce morbidity and mortality.

FOOTNOTES

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