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Sodium glucose cotransporter 2 inhibitors: New horizon of the heart failure pharmacotherapy

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Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have gained momentum as the latest class of antidiabetic agents for improving glycemic control. Large-scale clinical trials have reported that SGLT2 inhibitors reduced cardiovascular outcomes, especially hospitalization for heart failure in patients with type 2 diabetes mellitus who have high risks of cardiovascular disease. Accumulating evidence has indicated that beneficial effects can be observed regardless of the presence or absence of type 2 diabetes mellitus. Accordingly, the Food and Drug Administration approved these agents specifically for treating patients with heart failure and a reduced ejection fraction. It has been concluded that canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin can be recommended for preventing hospitalization associated with heart failure in patients with type 2 diabetes and established cardiovascular disease or those at high cardiovascular risk. In the present review, we explore the available evidence on SGLT2 inhibitors in terms of the cardioprotective effects, potential mechanisms, and ongoing clinical trials that may further clarify the cardiovascular effects of the agents.

Key Words: Sodium glucose cotransporter 2 inhibitors; Heart failure; Clinical trials; Potential mechanisms; Diuretics

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Core Tip: Sodium glucose cotransporter 2 inhibitors are newly approved by the Food and Drug Administration as treatment choice for heart failure based on evidence from several large-scale clinical trials demonstrating reduction in cardiovascular outcomes, especially hospitalization for heart failure or cardiovascular death. The background of the approval and potential mechanisms are discussed in this review. As well, summary of available evidence from clinical trials and ongoing trials examining beneficial effects of the agents are written.

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INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as the latest class of antidiabetic agents for improving glycemic control. Interestingly, the EMPA-REG OUTCOME trial, which evaluated empagliflozin in patients with type 2 diabetes and cardiovascular disease, demonstrated a greater-than-expected reduction in cardiovascular death, hospitalization for heart failure, and all-cause death[1,2]. Subsequent cardiovascular outcome trials assessing other SGLT2 inhibitors reported similar results; for instance, the Canagliflozin Cardiovascular Assessment Study (CANVAS), involving 10142 type 2 diabetic patients with high cardiovascular risk, demonstrated that canagliflozin decreased the risk of the primary outcome of a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke by 14%[3-5]. In the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial, dapagliflozin lowered the rate of cardiovascular death or heart failure hospitalization by 17% in patients with type 2 diabetes who had or were at risk for cardiovascular disease. Those trials are summarized in Table 1. A recent meta-analysis including these clinical trials reported that SGLT2 inhibitors reduced the risk of cardiovascular death or heart failure hospitalization by 23% (HR, 0.77; 95%CI, 0.71-0.84; $P < 0.0001$), with a similar benefit in patients with and without a history of heart failure[6]. The magnitude of benefit associated with SGLT2 inhibitors varied with baseline renal function, with greater reductions in hospitalization for heart failure (P for interaction = 0.0073) observed in patients with more severe renal dysfunction at baseline. Additionally, sotagliflozin, a dual inhibitor of SGLT1 and SGLT2, has reduced the risk of cardiovascular death or heart failure events in patients with type 2 diabetes and chronic kidney disease[7] or type 2 diabetes complicated with heart failure[8] (Table 2). Despite these positive findings, the benefit of SGLT2 inhibitors on heart failure events was not primarily investigated in these studies, where study participants were patients with diabetes; accordingly, background medical therapy for heart failure might not be optimized. When investigating new heart failure pharmacotherapies, it is crucial to consider whether the therapies provide any additional benefits to established therapies. Therefore, it is uncertain whether these benefits can be generalized.

CARDIOPROTECTIVE EFFECTS IN PATIENTS WITH HEART FAILURE WITH REDUCED EJECTION FRACTION, REGARDLESS OF DIABETIC STATUS

A meta-analysis incorporating data from EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 revealed that the decrease in the composite of cardiovascular death or heart failure hospitalization did not statistically differ among patients with (HR, 0.71; 95%CI, 0.61-0.84) or without (HR, 0.79; 95%CI, 0.71-0.88) history of heart failure at baseline (P for interaction = 0.51). However, the cardioprotective effects of SGLT2 inhibitors in patients with heart failure, regardless of the presence or absence of diabetes, are uncertain. The question was answered by the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, wherein 4744

Table 1 Landmark clinical trials of sodium-glucose cotransporter 2 inhibitors

Ref.	Population (n)	Age, yr (mean)	Intervention	Follow-up period (median)	Patients with a history of HF	Patients with a history of CVD	Main results
EMPA-REG[1]	T2DM (7028)	63.1	Empagliflozin	3.1 yr	10.1%	100%	CV death or HF (HR, 0.66; 95%CI, 0.55–0.79) HF (HR, 0.65; 95%CI, 0.50–0.85) CV death (HR, 0.62; 95%CI, 0.49–0.77)
CANVAS[3]	T2DM (9734)	63.3	Canagliflozin	2.4 yr	14.4%	65.6%	CV death or HF (HR, 0.78; 95%CI, 0.67–0.91) HF (HR, 0.67; 95%CI, 0.52–0.87) CV death (HR, 0.87; 95%CI, 0.72–1.06)
DECLARE-TIMI 58[4]	T2DM (17160)	63.9	Dapagliflozin	4.2 yr	10.0%	40.6%	CV death or HF (HR, 0.83; 95%CI, 0.73–0.95) HF (HR, 0.73; 95%CI, 0.61–0.88) CV death (HR, 0.98; 95%CI, 0.82–1.17)
VERTIS-CV[5]	T2DM (8246)	64.4	Ertugliflozin	3.5 yr (mean)	23.7%	71.4% ¹	CV death or HF (HR, 0.88; 95%CI, 0.75–1.03) HF (HR, 0.70; 95%CI, 0.54–0.90) CV death (HR, 0.92; 95%CI, 0.77–1.11)

¹Numbers are % of patients with coronary artery disease. T2DM: Type 2 diabetes mellitus; CV: Cardiovascular; HF: Heart failure; CVD: Cardiovascular disease; HR: Hazard ratio; CI: Confidence interval.

Table 2 Summary of clinical trials of sotagliflozin

Ref.	Population (n)	Age, yr (median)	Follow-up period (median)	Patients with a history of HF	Patients with a history of CAD	Main results
SCORED[7]	T2DM and CKD (10584)	63	16 mo	31.0%	22.4%	CV death or HF (HR, 0.74; 95%CI, 0.63–0.88) CV death (HR, 0.90; 95%CI, 0.73–1.12)
SOLOIST-WHF [8]	T2DM and HF (1222)	70	9.2 mo	100%	58.3%	CV death or HF (HR, 0.67; 95%CI, 0.52–0.85) CV death (HR, 0.84; 95%CI, 0.58–1.22)

HF: Heart failure; CAD: Coronary artery disease (numbers indicate % of patients with coronary revascularization in the SCORED trial and % of those with ischemic heart disease in the SOLOIST-WHF trial); T2DM: Type 2 diabetes mellitus; CKD: Chronic kidney disease; CV: Cardiovascular; HF: Heart failure; HR: Hazard ratio; CI: Confidence interval.

patients with heart failure with reduced left ventricular ejection fraction (LVEF) were randomly assigned to receive either dapagliflozin or placebo, in addition to standard therapy for heart failure. Among the participants, 41.8% had diabetes mellitus. During a median follow-up of 18 months, the incidence of cardiovascular death or worsening heart failure was significantly lower in the dapagliflozin group than in the placebo (16.3% *vs* 21.2%; HR, 0.74; 95%CI, 0.65–0.85; $P < 0.001$). Subgroup analysis indicated that the benefit was observed regardless of diabetic status. The empagliflozin outcome trial in patients with chronic heart failure with reduced LVEF (EMPEROR-Reduced) followed the results, examining the potential benefit of empagliflozin in 3730 patients

with heart failure and reduced LVEF[9]. As observed in DAPA-HF, 50.2% of the study participants did not present with diabetes mellitus. The two trials are summarized in Table 3. The study participants in the EMPEROR-Reduced presented greater severity of heart failure than those in the DAPA-HF, with a mean LVEF of 27% *vs* 31% and a median N-terminal prohormone of brain natriuretic peptide (NT-proBNP) value of 1907 *vs* 1437. Furthermore, more than 70% of the patients enrolled in EMPEROR-Reduced had a LVEF less than 30%. As in the DAPA-HF, the empagliflozin group had lower incidence of cardiovascular death or hospitalization for heart failure than the placebo (19.4% *vs* 24.7%; HR, 0.75; 95%CI, 0.65–0.86; $P < 0.001$) during the median follow-up of 16 months. Moreover, the benefit was observed regardless of the diabetes status. A meta-analysis that included DAPA-HF and EMPEROR-Reduced reported that SGLT2 inhibitors reduced both cardiovascular (HR, 0.86; 95%CI 0.76–0.98) and all-cause mortality (HR, 0.87; 95%CI, 0.77–0.98), without evident statistical heterogeneity between dapagliflozin and empagliflozin[10]. Similarly, SGLT2 inhibitors reduced the risk for the first hospitalization for heart failure (HR, 0.69; 95%CI, 0.62–0.78), the total number of heart failure hospitalizations or cardiovascular death (HR, 0.75; 95%CI, 0.68–0.84), and worsening renal function (HR, 0.62; 95%CI, 0.43–0.90). These findings were generally consistent in subgroup analyses (Table 4). Furthermore, both agents showed no excess risk of adverse events when compared with placebo, including renal adverse events, volume depletion, severe hypoglycemia, or bone fractures. Based on this evidence, the Heart Failure Association of the European Society of Cardiology has recently issued a position paper highlighting results of clinical trials on the role of SGLT2 inhibitors in patients with heart failure[11]. On May 5, 2020, the Food and Drug Administration approved dapagliflozin, specifically, to treat patients with heart failure and reduced ejection fraction. The position paper has concluded that canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin can be recommended to prevent hospitalization for heart failure in type 2 diabetic patients with established cardiovascular disease or high cardiovascular risk[11]. Dapagliflozin and empagliflozin are recommended to reduce the risk for heart failure hospitalization and cardiovascular death in symptomatic patients with heart failure with reduced LVEF already receiving guideline-directed medical therapy, regardless of diabetic status. The Canadian Cardiovascular Society and the Canadian Heart Failure Society have recommended that SGLT2 inhibitors are to be used in patients with mild or moderate heart failure who have an LVEF of 40% or less to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular death[12].

MECHANISMS LINKING SGLT2 INHIBITORS AND REDUCTIONS IN CARDIOVASCULAR EVENTS ARE UNKNOWN

Potential mechanisms

The mechanisms underlying the cardioprotective effects of SGLT2 inhibitors have not been comprehensively elucidated. SGLT2 is predominantly located in the proximal tubule of the kidney and reabsorbs glucose and sodium. Thus, SGLT2 inhibitors reduce not only glucose reabsorption but also sodium reabsorption. These inhibitors behave as diuretics presenting mechanisms such as natriuresis and enhanced diuresis, which can be attributed to an osmotic effect dependent on glycosuria, resulting in a decrease in blood pressure. Research has reported that the drug provides cardiovascular benefits by reducing plasma volume, blood pressure, arterial stiffness, and vascular resistance[2,13]. Blood pressure reduction and renal protection could be the main mechanisms contributing to favorable outcomes. Recently, basic research has suggested that SGLT2 inhibitors induce sympathetic nervous system inhibition[14]. Other studies have reported that SGLT2 inhibitors improved the circadian rhythm of sympathetic activity and reduced high fat diet-induced elevation of tyrosine hydroxylase and noradrenaline in animal models[15,16]. In agreement with this evidence, cardiovascular events that were reduced by SGLT2 inhibitors included sudden cardiac death and hospitalization for heart failure[3]. This evidence presents the hypothesis that the inhibition of sympathetic nervous activity could explain the cardiovascular benefits of SGLT2 inhibitors. Several other hypotheses beyond effects on glycemia, blood pressure lowering, and weight loss have been postulated, including improvement in myocardial energetic efficiency[17] and inhibition of sodium-hydrogen exchangers in the heart, which could prevent cardiomyocyte injury [18].

Table 3 Summary of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure and the EMPEROR-Reduced trials

Ref.	Population (n)	Patients with T2DM	Intervention	Follow-up period (median)	Main results
DAPA-HF[22]	HFrEF with or without T2DM (4744)	42%	Empagliflozin	18 months	CV death or HF (HR, 0.71; 95%CI, 0.65–0.85) HF (HR, 0.70; 95%CI, 0.59–0.83) CV death (HR, 0.82; 95%CI, 0.69–0.98)
EMPEROR-Reduced[9]	HFrEF (3730)	49.8%	Empagliflozin	16 months	CV death or HF (HR, 0.75; 95%CI, 0.65–0.86) HF (HR, 0.69; 95%CI, 0.59–0.81) CV death (HR, 0.92; 95%CI, 0.75–1.12)

T2DM: Type 2 diabetes mellitus; CV: Cardiovascular disease; HF: Heart failure; HR: Hazard ratio; CI: Confidence interval.

Table 4 Subgroup analyses for the primary outcomes in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure and the EMPEROR-Reduced trials

Subgroup	HR (95%CI) of dapagliflozin compared to placebo	HR (95%CI) of empagliflozin compared to placebo
Age		
≤ 65 yr	0.78 (0.63–0.96)	0.71 (0.57–0.89)
> 65 yr	0.72 (0.60–0.85)	0.78 (0.66–0.93)
Sex		
Male	0.73 (0.63–0.85)	0.80 (0.68–0.93)
Female	0.79 (0.59–1.06)	0.59 (0.44–0.80)
T2DM		
Yes	0.75 (0.63–0.90)	0.72 (0.60–0.87)
No	0.73 (0.60–0.88)	0.78 (0.64–0.97)
eGFR < 60 mL/min/1.73 m ²		
Yes	0.72 (0.59–0.86)	0.83 (0.69–1.00)
No	0.76 (0.63–0.92)	0.67 (0.55–0.83)

T2DM: Type 2 diabetes mellitus; HR: Hazard ratio; CI: Confidence interval.

Differences between SGLT2 inhibitors and loop diuretics

Loop diuretics that act in the ascending limb of the Henle loop alleviate symptoms related to heart failure by promoting urinary sodium excretion. Despite their clinical usefulness, diuretics have failed to demonstrate prognostic effects, partly due to counter-regulatory responses through activation of the renin-angiotensin system, neurohormonal activation, and development of diuretic resistance[19]. SGLT2 inhibitors lower plasma glucose by blocking glucose reabsorption in the proximal tubule, resulting in glucose excretion into the urine. The diuretic effect of SGLT2 inhibitors was initially assumed to originate from mild osmotic diuresis owing to glycosuria. Griffin *et al*[20] recently conducted a double-blind, placebo-controlled, crossover study involving treatment with either empagliflozin of 10 mg or matched placebo for 2 wk, followed by a 2-wk washout period and crossover at 2 wk with the alternative treatment in diabetic patients with heart failure[20]. They reported that the natriuretic effect was synergistic with loop diuretics, resulting in a reduced blood and plasma volume, which did not activate the sympathetic nervous system or renin-angiotensin system. Renal dysfunction did not affect the natriuretic effect.

Table 5 Summary of ongoing heart failure outcome trials of sodium-glucose cotransporter 2 inhibitors

	PRESERVED-HF	DELIVER	DAPA ACT HF-TIMI 68	EMPEROR-Preserved	EMPULSE
NCT number	03030235	03619213	04363697	03057951	04157751
Population	HFpEF with or without T2DM	HFpEF with or without T2DM	Acute heart failure with reduced ejection fraction	HFpEF with or without T2DM	Acute Heart Failure
Sample size	320	4700	2400	5750	500
Intervention	Dapagliflozin/placebo	Dapagliflozin/placebo	Dapagliflozin/placebo	Empagliflozin/placebo	Empagliflozin/placebo
Primary endpoint	Change from baseline in NT-proBNP	Time-to-first occurrence of CV death, HF hospitalization, or urgent HF visit	CV death or worsening HF	Time-to-first event of HF hospitalization	Death, number of HF events
Status	Estimated completion; February 2021	Estimated completion; June 2021	Estimated completion; October 2022	Estimated completion; April 2021	Estimated completion; June 2021

HFpEF: Heart failure with preserved ejection fraction; T2DM: Type 2 diabetes mellitus; CV: Cardiovascular; HF: Heart failure; NT-proBNP: N-terminal pro-brain natriuretic peptide.

OPTIMAL TIME FOR ADMINISTERING THE AGENT

The EMPA-RESPONSE-AHF study is a multicenter pilot study that included 80 patients with acute heart failure receiving standard diuretic therapy, randomized to receive either empagliflozin of 10 mg or matched placebo daily for 30 d[21]. Empagliflozin did not demonstrate reduction in the primary outcomes of the visual analog scale of dyspnea, diuretic response, change in NT-proBNP, or length of hospital stay. A secondary composite outcome of in-hospital exacerbation of heart failure, re-hospitalization for heart failure, or death within 60 d reportedly occurred less frequently in the empagliflozin group (10% *vs* 13%, $P = 0.014$). The occurrence of adverse events related to renal function, blood pressure, and heart rate was comparable between the groups. Future trials investigating the benefits of SGLT2 inhibitors in patients with acute heart failure are warranted.

Another clinical question remains whether the effects of SGLT2 inhibitors are affected by the left ventricular ejection fraction. Heart failure treatments in patients with HFrEF have long been established, while evidence is scarce in patients with heart failure with preserved ejection fraction (HFpEF). Similarly, available evidence has revealed that the beneficial effects of SGLT2 inhibitors have been observed in HFrEF but not necessarily in HFpEF. Ongoing studies may provide some data on this issue. The ongoing heart failure outcome trials for SGLT2 inhibitors are summarized in Table 5.

CONCLUSION

Accumulated evidence from large-scale randomized placebo-controlled trials has demonstrated the consistent effect of SGLT2 inhibitors on the clinical course of heart failure, mainly driven by a substantial decrease in hospitalization for heart failure. These benefits were attained regardless of the presence or absence of diabetes, with agents administered once daily and requiring no up-titration; additionally, no serious adverse effects were observed. This evidence supports the role of SGLT2 inhibitors as a new standard of care for HFrEF. Further studies are needed to clarify the optimal time for administering these agents, proper candidates who most benefit from these agents, and mechanisms explaining the cardioprotective effects of SGLT2 inhibitors.

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