Review

Prevention and Management of Heart Failure: Role of SGLT2 Inhibitors in Patients With and Without Diabetes

A Kherlopian, T Doctorian, JE Udelson & AR Vest

Abstract

Certain antidiabetic therapies have adverse cardiovascular (CV) consequences. The recommendations for CV safety studies for new antidiabetic therapies led to the discovery that the sodium-glucose cotransporter-2 inhibitors (SGLT2is) have benefits in heart failure (HF) management. Mounting evidence from large, international, randomized, placebo-controlled trials have consistently demonstrated a reduction in hospitalizations for heart failure (HHF) among populations with type 2 diabetes or with HF with reduced ejection fraction. In vitro, animal and human studies have attempted to identify the cardioprotective mechanisms of SGLT2is, although these are not yet clearly defined. This review will summarize the major SGLT2i trials, which have resulted in valuable additions to CV care that are expected to significantly reduce both incident HF and established HF progression.

Keywords

Sodium-glucose cotransporter-2 inhibitors, Cardiovascular outcomes, Heart failure, Left ventricular remodeling, antidiabetic therapy, Guideline-directed medical therapy

Key points

- Sodium-glucose cotransporter-2 inhibitors (SGLT2is) are associated with multiple favorable outcomes, including reduced cardiovascular death and hospitalization for heart failure
- The cardioprotective mechanisms of SGLT2is are not clearly defined
- The consistent demonstration of a reduction in hospitalization for heart failure across many rigorous well-powered trials, independent of type 2 diabetes status, suggests a class effect of SGLT2is on heart failure with reduced ejection fraction (HFrEF)
- SGLT2 inhibitor (SGLT2i) use among patients with symptomatic HFrEF may lead to reverse left ventricular remodeling
- Additional research is needed to fill current gaps in knowledge pertaining to the cardioprotective mechanisms of SGLT2is and the influence of SGLT2is among those with heart failure with preserved ejection fraction

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Introduction

Diabetes mellitus is known to increase the risk of incident cardiovascular disease (CVD).[1] However pharmacological glycemic control does not necessarily reduce CVD risk and some antidiabetic medications have even been associated with increased cardiovascular (CV) events such as myocardial infarction (MI) and heart failure (HF).[2] In response to post-marketing analysis of the antidiabetic drug rosiglitazone, the United States Food and Drug Administration (FDA) published a Guidance for Industry in 2008 outlining recommendations for the evaluation of CV risks for type 2 diabetes mellitus (T2D) pharmacotherapies.[3,4] This document recommended clinical trials of antidiabetic therapy demonstrate no impermissible increased CV risk by evaluating CV mortality, MI, and stroke outcomes. In line with the FDA recommendations large cardiovascular outcome trials (CVOTs) of sufficient sample size to rigorously evaluate those outcomes were performed for the sodium-glucose cotransporter-2 inhibitors (SGLT2is). Remarkably, many of the SGLT2is demonstrated CV benefits for their primary outcomes of CV mortality, MI, and stroke. Somewhat unexpectedly, there was also a consistent signal across trials of patients with T2D and elevated CV risk for a reduction in HF hospitalizations with SGLT2is.[5-7] The favorable HF outcomes for patients with T2D led to trials in patients with established HF, to prevent worsening and progression. To date, all of these trials have been positive, and the sodium-glucose cotransporter-2 inhibitor (SGLT2i) class is rapidly becoming established as a component of medical therapy for heart failure with reduced ejection fraction (HFrEF).[8,9]

This review will summarize these remarkable data, which in a relatively short period of time have resulted in significant changes in clinical practice and an important impact on prevention and on the progression of HF.

Prevention and Management of Heart Failure:
Role of SGLT2 Inhibitors in Patients With and Without Diabetes

Prevention of Heart Failure in Patients with Type 2 Diabetes

Between 2015 and 2020, five multinational randomized controlled trials assessed the effect of SGLT2is on CV outcomes among individuals with T2D.[5-7,10,11] Each of these trials assessed the impact of the SGLT2i therapy compared to placebo on 3-point major adverse cardiovascular events (3P-MACE), namely death from CV causes, nonfatal MI, or nonfatal stroke. These Randomized Control Trials (RCTs) also specifically evaluated hospitalization for HF (HHF) as a secondary outcome, which was of particular interest because some thiazolidinediones and dipeptidyl peptidase-4 inhibitor antidiabetic therapies had previously been associated with increased risk of HHF.[12]

The first SGLT2i CVOT to be reported was the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME).[5] The study assigned 7,020 mostly older, male patients with T2D, elevated CV risk, and predominantly normal or mildly reduced eGFR to 10mg or 25mg daily of empagliflozin or placebo; the patients were followed for a median 3.1 years. Nearly all the patients had established CVD (99%), although cardiac failure term was included in the definition of CVD unlike subsequent CVOTs. Only 10.0% of patients had investigator-reported HF at baseline.[5] The empagliflozin-treated patients were pooled (n=4687) and compared to the placebo group (n=2333), demonstrating a significant reduction in the primary outcome of 3P-MACE (10.5% vs 12.1%; HR 0.86, p<0.04). Secondary outcome analysis demonstrated a reduction in HHF in the pooled empagliflozin group relative to placebo [2.7% vs 4.1%; HR 0.65 (95% CI, 0.50-0.85)] (see Table 1).[5] Subsequent analyses showed the two empagliflozin doses (10mg or 25mg) both significantly reduced the following HF outcomes compared to placebo: (1) HHF, (2) composite HHF or cardiovascular death, or (3) composite HHF or death from HF. Moreover, those taking empagliflozin had lower diuretic requirements compared to placebo [HR 0.62 (95% CI: 0.53–0.73)].[13] Participants without a HF history had a similar reduction in HHF or cardiovascular death with empagliflozin [HR 0.63 (95% CI, 0.51-0.78)] relative to those with a HF history [HR 0.72 (95% CI, 0.50-1.04)], suggesting empagliflozin may provide not only HF primary prevention, but may also deter clinical progression of established HF.[13]

The subsequent CANagliflozin cardioVascular Assessment Study (CANVAS) Program combined data from the CANVAS and CANVAS-Renal multinational trials. Evaluation of CV events in CANVAS and eight other phase II-III studies was sufficient for FDA approval of canagliflozin to manage T2D in 2013, with the caveat that additional post-marketing monitoring was required to confirm CV safety. Since the CANVAS trial unblinded some of their data related to increased LDL-C among canagliflozin users, enrollment of additional patients to show long-term CV safety could not ensue.[14] The CANVAS-Renal trial commenced in 2013 to provide sufficient power with the existing CANVAS trial data to address the post-marketing CV safety objective as well as evaluate renal disease progression.[15] Both CANVAS and CANVAS-R had the same inclusion criteria and randomized treatment groups; the collective data is shown in Table 1.[15] The CANVAS Program assigned 10,142 mostly older, male patients with T2D, symptomatic CVD or risk factors for CVD, and predominantly normal or mildly reduced eGFR to 100mg or 300mg daily canagliflozin or placebo; the patients were followed for a mean of 3.6 years.[6,15] About 65% of patients had a history of CVD, and 14% had a physician-reviewed history of HF. Similar to the EMPA-REG study, the canagliflozin-treated dose groups were pooled (n=5795) and compared to the placebo group (n=4347), demonstrating a significant reduction in the primary outcome of 3P-MACE (26.9 vs 31.5 participants per 1000 patient-years; HR 0.86, p=0.02). Secondary outcome analysis demonstrated a reduction in HHF [5.5 vs 8.7 participants per 1000 patient-years; HR 0.67 (95% CI, 0.52-0.87)] among the canagliflozin group relative to placebo group.[6] CV death was similar between both canagliflozin and placebo groups; the composite of CV death and HHF was significantly lower in the canagliflozin group [16.3 vs 20.8 participants per 1000 patient-years; HR 0.78 (0.67–0.91)] owing to the notable reduction in HHF.[6] Participants with a HF history had a greater reduction in HHF or cardiovascular death with canagliflozin [HR 0.61 (95% CI, 0.46-0.80)] relative to those without a HF history [HR 0.87 (95% CI, 0.72-1.06) P for interaction=0.02], suggesting canagliflozin may provide secondary HF prevention.[16]

The third SGLT2i CVOT published was the Dapagliflozin Effect on CardiovascuLAR Events-Thrombolysis In Myocardial Infarction 58 (DECLARE-TIMI 58) trial. DECLARE-TIMI 58 assigned 17,160 mostly older, male patients with T2D, CVD or risk factors for CVD, and predominantly normal or mildly reduced eGFR to 10mg daily dapagliflozin or placebo; the patients were followed for a median of 4.2 years. At baseline, 40.6% of patients had CVD and only 10.0% of patients had HF. Compared to the placebo group, the dapagliflozin group experienced a significant reduction in the primary outcome of CV death or HHF (4.9% vs 5.8%; HR 0.83, p<0.005). However, there was no statistically significant difference in the other primary composite outcome of CV death, MI, or ischemic stroke (8.8% vs 9.4%; HR 0.93, p=0.17). Secondary outcome analysis demonstrated a reduction in HHF in the dapagliflozin group (2.5% vs 3.3%; HR 0.73 (95% CI, 0.52-0.87)).[7] DECLARE-TIMI 58 was the first of these CVOTs to characterize left ventricular ejection fraction (LVEF) among participants. Dapagliflozin decreased CV death or HHF risk more extensively among patients with HF with reduced EF (HFrEF) [HR 0.62 (95% CI, 0.45-0.86)] relative to participants without HFrEF [HR 0.88 (95% CI, 0.76-1.02) P for interaction=0.046], again supporting the hypothesis that dapagliflozin may provide secondary HF prevention.[17]

The fourth SGLT2i CVOT was the eValuation of ERTugliflozin efficacy and Safety CardioVascular outcomes trial (VERTIS CV). VERTIS CV assigned 8,246 mostly older, male patients with T2D, established CVD, and predominantly

normal or mildly reduced eGFR to 5 or 15mg of ertugliflozin or placebo; the patients were followed for a mean of 3.5 years. Similar to the EMPA-REG and CANVAS Program trials, the ertugliflozin-treated patients were pooled (n=5499) and compared to the placebo group (n=2747). The study demonstrated ertugliflozin was non-inferior to placebo for the primary outcome of 3P-MACE (11.9% vs 11.9%; HR 0.97, p<0.001). However, ertugliflozin was not superior to placebo for key CV and/or renal secondary outcomes, including the composite of CV death or HHF. Nevertheless, when CV death was excluded as an endpoint of interest, a notable reduction in HHF with ertugliflozin was identified [2.5% vs 3.6%; HR 0.70 (95% CI, 0.54-0.90)].[10] The VERTIS CV trial also recorded LVEF for 76% of patients with baseline HF; when comparing the ertugliflozin group to placebo group, the risk of CV death or HHF was similar for those with or without a history of HF, regardless of LVEF.[18]

The fifth SGLT2i CVOT was the Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED). Distinct from other CVOTs, SCORED studied a combined SGLT1/2 inhibitor (sotagliflozin), and included patients with predominantly mild to moderately reduced eGFR and a higher percentage of women (45%). About 48% of patients had CVD history and 31% had baseline HF. The trial assigned 10,464 mostly older patients with T2D, CV risk factors and CKD to sotagliflozin 200mg daily or placebo; the patients were followed for a median of 1.3 years. The study ended prematurely due to withdrawal of funding from the sponsor, leading to adjustment of the primary endpoints to meet the desired target number of events and statistical power. Compared to placebo, sotagliflozin was associated with a significant decrease in the primary outcome of composite death from CV cause, admission for HF, and urgent care visit for HF (5.6 vs 7.5 events per 100 patient-years; HR 0.74, p<0.001). Compared to the placebo group, the sotagliflozin group experienced a reduction in HHF and urgent visits for HF [3.5 vs 5.1 events/100 patient-years; HR 0.67 (95% CI, 0.55-0.82)].[11] Sotagliflozin significantly reduced HF even among those with more advanced renal dysfunction.[11]

In addition to the five large CVOTs, a large multinational RCT evaluated the effect of canagliflozin on renal outcomes for subjects with T2D and CKD, regardless of CVD history. The trial was designed based on the hypothesis-generating results of previous CVOTs that suggested SGLT2is prevented renal disease progression.[5-7] The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial assigned 4,401 mostly older, male patients to canagliflozin 100mg daily or placebo; the patients were followed for a mean of 2.6 years. About 50% of the patients had a history of CVD. Canagliflozin was associated with a significant reduction in the primary composite outcome of end-stage kidney disease, doubling of serum creatinine (SCr), or renal or CV death (11.1% vs 15.5%; HR 0.70, p=0.00001). There was also a significant reduction in many secondary CV endpoints among the canagliflozin group, including HHF [HR 0.61 (95% CI, 0.47-0.80)], CV death or HHF [HR 0.69 (95% CI, 0.57–0.83)], and CV death, MI, or stroke [HR 0.80 (95% CI, 0.67–0.95)].[19]

A summary of the above six trials is illustrated in Table 1. The consistency across RCTs despite different SGLT2i therapies suggests a class effect of SGLT2is in decreasing incident HHF among those with T2D. HHF reductions among subgroups with a baseline HF history also indicates a potential for secondary HF prevention, meaning deterring clinical progression of the HF syndrome in those with established HF. Moreover, the very modest impact of these agents on glucose control and the broad mechanistic effects not involving diabetes or glucose metabolism suggested the possibility of favorable effects on the HF syndrome even without T2D. These concepts led to the design and execution of a remarkable series of HF trials, reviewed in the next section.

Prevention of Heart Failure Progression Among Patients With Chronic Heart Failure

Several trials have been designed to evaluate the impact of SGLT2is among patients with HFrEF and heart failure with preserved ejection fraction (HFpEF) in the presence or absence of T2D. The HF outcome benefit has been consistent across the studies completed to date among patients with HFrEF, irrespective of the T2D status or background HF medications.

In the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, 4744 patients with HFrEF (EF≤40%) with New York Heart Association (NYHA) functional class II through IV were randomized to dapagliflozin 10mg daily versus placebo groups.[9] About 42% of patients had T2D. Baseline characteristics are shown in Table 2. The treatment group received dapagliflozin in addition to existing guideline-directed medical therapy (GDMT). The primary endpoint was the composite of HHF, urgent HF visit for intravenous therapy, or CV death. After a mean follow up of 18.2 months, 16% of the dapagliflozin group versus 21% of the placebo group experienced an event (HR 0.74, p<0.001). The primary outcome favored dapagliflozin regardless of the presence or absence of T2D (see Table 2). A subgroup analysis demonstrated similar dapagliflozin benefits and no significant safety differences regarding volume depletion or renal adverse events among those taking or not taking sacubitril/valsartan.[20]

In the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced), 3730 adult patients with HFrEF (EF ≤40%) with NYHA Class II through IV were randomized to empagliflozin 10mg daily or placebo.[8] Similar to DAPA-HF, about half (49.8%) of enrolled patients in EMPEROR-Reduced had T2D. The baseline eGFR could be as low as 20 mL/min/1.73 m^2. Over a median follow up period of 16 months, the primary outcome - a composite of CV death or HHF - was 19.4% versus 24.7% (HR 0.75, p<0.001) for empagliflozin versus placebo, respectively. The annual rate of eGFR decline was lower in the dapagliflozin group compared to the placebo group: -0.5 versus -2.28 mL/

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Table 1. SGLT2 inhibitor trials among patients with diabetes mellitus type 2*

Trial Parameters	EMPA-REG OUTCOME (2015)	CANVAS Program (2017)[‖]	DECLARE-TIMI 58 (2019)	CREDENCE (2019)	VERTIS-CV (2020)	SCORED (2020)
Intervention	Empagliflozin 10mg or 25mg daily vs placebo	Canagliflozin 100mg or 300mg daily[¶] vs placebo	Dapagliflozin 10mg daily vs placebo	Canagliflozin 100mg daily vs placebo	Ertugliflozin 5mg or 15mg daily vs placebo	Sotagliflozin 200mg daily[€] vs placebo
Number of participants[†]	7,020[§]	10,142[**]	17,160	4,401	8,246[‡]	10.584
Population and Baseline Characteristics[‡]	T2D and increased risk of CVD with eGFR ≥ 30	T2D, eGFR >30, and symptomatic CVD or multiple risk factors for CVD	T2D, CrCl ≥ 60 and established CVD or risk factors for CVD	T2D and CKD with eGFR 30 to <90 and albuminuria	T2D, eGFR>30, and established CVD	T2D, CV risk factor(s), and CKD with eGFR 26-60
Age (years)	63.1	63.3	63.9	63.0	64.4	69
Female	28.6%	35.8%	37.4%	33.9%	29.7%	44.9%
BMI	30.6	32.0	32.0	31.3	31.9	31.8
HgbA1c	8.07%	8.2%	8.3%	8.3%	8.2%	8.3%
eGFR	74.1	76.5	85.2	56.2	75.9	44.5
CVD history	99.2%	65.6%	40.6%	50.4%	100%	48.6%
HF History	10.0%	14.4%	10%	14.8%	23.7%	31%
Average follow-up (years)	3.1 (median)	3.6 (mean)	4.2 (median)	2.6 (mean)	3.5 (mean)	1.3 (median)
Primary Outcome(s)	**3P-MACE:** 10.5% vs 12.1% (HR 0.86, p<0.04)	**3P-MACE:** 26.9 vs 31.5 per 1000 pt-years (HR 0.86, p=0.02)	**CV death or HHF:** 4.9% vs 5.8% (HR 0.83, p=0.005) **MACE[††]:** 8.8% vs 9.4% (HR 0.93, p=0.17)	**Composite of ESKD, doubling SCr, or renal or CV death:** 11.1% vs 15.5% (HR 0.70, p=0.00001)	**3P-MACE:** 11.9% vs 11.9% (HR 0.97, p<0.001)[§§]	**Composite of death from CV cause, HHF, or urgent care visit for HF:** 5.6% vs 7.5% (HR 0.74, p<0.001)
Heart Failure Outcome(s)	**HHF:** 2.7% vs. 4.1%, HR 0.65 (95% CI, 0.50–0.85)	**HHF:** 5.5 vs 8.7 per 1000 pt-years, HR 0.67 (95% CI, 0.52–0.87)	**HHF:** 2.5% vs 3.3%, HR 0.73 (95% CI, 0.61–0.88)	**HHF:** 2.8% vs 4.5%, HR 0.61 (95% CI, 0.47–0.80)	**HHF:** 2.5% vs 3.6%, HR 0.70 (95% CI, 0.54 – 0.90)	**HHF/urgent HF visits** 3.5 vs 5.1 per 100 pt-yrs, HR 0.67 (95% CI, 0.55–0.82)

*T2D: type 2 diabetes mellitus; CV: cardiovascular; CVD: cardiovascular disease; HF: heart failure; HR: hazard ratio; ASCVD: Atherosclerotic cardiovascular disease; eGFR: estimated Glomerular Filtration Rate (ml/min/1.73m^2); BMI: Body Mass Index (kg/m^2); HgbA1c: Glycated hemoglobin; 3P-MACE: 3-point major adverse cardiovascular events (death from CV causes, nonfatal MI, or nonfatal stroke); CrCl: Creatinine Clearance (mL/min); ESKD: End-Stage Kidney Disease; SCr: Serum Creatinine; Pt: patient

[†]Includes treatment and placebo arms; all patients in SGLT2i and placebo arms received standard-of-care treatments

[‡]Characteristics of SGLT2i arm are balanced with placebo arm. Age, BMI, and eGFR are reflected as averages.

[§] Data from the patients receiving 10-mg or 25-mg dose of empagliflozin were pooled

[¶] Canagliflozin dose increased to 300mg once daily after 13 weeks of 100mg daily in 71.4% of patients in CAVAS-R

[‖]Includes CANVAS and CANVAS-Renal trials (i.e. Integrated CANVAS Program)

[**]Data from the patients receiving 100-mg or 300-mg dose of canagliflozin from the Integrated CANVAS Program were pooled, and data from the placebo groups in the Integrated CANVAS Program were pooled

[††] Major Adverse Cardiovascular Event - cardiovascular death, myocardial infarction, or ischemic stroke

[‡‡]Data from the patients receiving 5-mg or 15-mg dose of ertugliflozin were pooled

[§§]one-sided P value for the test of noninferiority

[€]Sotagliflozin dose increased to 400mg once daily after 6 months of the treatment period if unacceptable side effects did not occur - 74.5% had an increase in dose to 400mg

min/1.73 m^2 per year (p<0.001), suggesting a longer term renal protective effect of empagliflozin. Similar to DAPA-HF, the primary outcome benefit of empagliflozin was observed regardless of the presence or absence of T2D[8] (see Table 2).

Both DAPA-HF and EMPEROR-Reduced trials demonstrated a reduction in composite risk of CV death and HHF for HFrEF patients treated with dapagliflozin or empagliflozin in the presence or absence of T2D, although CV death alone was only significantly reduced in DAPA-HF.[8,9] A meta-analysis by Zannad et al. of these two trials (8474 patients total) demonstrated 13% reduction of all cause death, 14% reduction in CV death, as well as 26% relative reduction in CV death or HHF, and 25% reduction in composite HHF or CV death.[21] The risk of adverse renal outcomes (50% reduction eGFR, ESKD, renal transplantation, or renal death) was significantly reduced in patients receiving dapagliflozin or empagliflozin. Patients with NYHA class II experienced fewer CV deaths or HHF (HR 0.67, CI 0.59-0.67, p=0.0087), than patients with NYHA class III or IV (HR 0.87, CI 0.75-1.01).[21]

In the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial, 1222 patients aged 18 to 85 with T2D and chronic HF were randomized to sotagliflozin versus placebo and followed for a median of 9 months.[22] In contrast to the DAPA-HF and EMPEROR-Reduced trials, this study had no EF threshold. However, a majority of participants had HFrEF and the mean baseline EF was 35% (Table 2). Unlike DAPA-HF and EMPEROR-Reduced, all enrolled patients in the SOLOIST trial had a concomitant diagnosis of T2D. Fifty-one percent of the sotagliflozin group experienced a primary outcome event (death from a CV cause, HHF or urgent care visits) versus 76% of the placebo group (HR 0.67, p<0.001). These benefits were observed in patients with both reduced (<50%) and preserved (≥50%) EF [HR 0.72, 95% CI (0.56–0.94) and HR 0.48, 95% CI (0.27–0.86), respectively].[22]

Table 2. SGLT2 inhibitor trials in patients with heart failure*

Trial parameters	DAPA-HF (2019)	EMPEROR-Reduced (2020)	SOLOIST-WHF (2021)
Intervention	Dapagliflozin 10mg daily vs placebo	Empagliflozin 10mg daily vs placebo	Sotagliflozin 200mg daily§ vs placebo
Number of participants†	4,744	3,730	1,222
Population and Baseline Characteristics‡	HFrEF (EF≤ 40%), NYHA class II-IV, and eGFR ≥ 30	HFrEF (EF ≤ 40%), NYHA class II-IV, eGFR ≥ 20	Worsening HF (any EF)¶, T2D, eGFR ≥ 30
Age (years)	66	67	70
Female	23.4%	24.0%	33.7%
EF	31%	27%	35%ǀ
NYHA class II	67.5%	75.0%	45.2%††
T2D history	41.8%	49.8%	100%
eGFR	65.7	62.0	49.7
Average follow-up (months)	18.2	16	9
Primary Outcome	**CV death, HHF, or urgent HF visit:** 16% vs 21% (HR 0.74, p<0.001)	**CV death or HHF:** 19.4% vs 24.7% (HR 0.75, p<0.001)	**CV death, HHF, or urgent HF visit:** 51% vs 76% (HR 0.67, P<0.001)
Primary Outcome by T2D status**			
T2D	0.75 (0.63–0.90)	0.72 (0.60–0.87)	0.67 (0.52–0.85)
No T2D	0.73 (0.60–0.88)	0.78 (0.64–0.97)	N/A‡‡
Key Secondary Heart Failure Outcome	**CV death or HHF:** 16.1% vs 20.9% HR 0.75 (95% CI, 0.65–0.85)	**HHF:** HR 0.70 (95% CI, 0.58–0.85)	**HHF and urgent visits for HF:** HR 0.64 (95% CI, 0.49–0.83)

*SGLT2i: sodium-glucose cotransporter-2 inhibitor; T2D: type 2 diabetes mellitus; CV: cardiovascular; HF: heart failure; HR: hazard ratio; HHF: hospitalization for heart failure; EF: ejection fraction; eGFR: estimated glomerular filtration rate (ml/min/1.73m²)

†Includes treatment and placebo arms; all patients in SGLT2i and placebo arms received standard-of-care treatments

‡Characteristics of SGLT2i arm are balanced with placebo arm. Age, EF, and eGFR are reflected as averages.

§Dose increased to 400 mg once daily as early as 2 weeks to 8 months of the treatment period if unacceptable side effects did not occur.

¶Patient admitted to the hospital or had urgent HF visit to ED, HF Unit, or infusion center for WHF associated with intravascular volume overload (the Index Event), as determined by Investigator

ǀ79% of patients enrolled in SOLOIST-WHF had EF<50%

**Results expressed as hazard ratio and 95% confidence interval based on T2D status

††Similar proportion of patients with NYHA class II and III (45.2% vs 45.8%, respectively)

‡‡All enrolled patients had T2D

In summary, empagliflozin, dapagliflozin, and sotagliflozin each reduced the composite of HHF and CV death among patients with reduced EF and NYHA class II-III symptoms. The DAPA-HF and EMPEROR-Reduced trials furthermore demonstrated that the benefit of SGLT2i for the primary composite outcome was independent of T2D status. Moreover, the subgroup analysis of SOLOIST-WHF trial raises the potential that SGLT2is may improve outcomes specifically for patients with HF and EF $\geq$ 50%, although within EMPEROR-Reduced the subgroup with the lowest LVEFs had the clearest demonstration of benefit. Given the lack of evidence-based therapies for HFpEF, the results of ongoing SGLT2i clinical trials for patients with HFpEF are eagerly awaited.[23-25]

Mechanisms of Action

SGLT2is inhibit the SGLT2 protein in the proximal convoluted renal tubules, thereby reducing reabsorption of filtered glucose and sodium, causing glucosuria and natriuresis, and ultimately decreasing serum glucose and HgbA1c independent of insulin.[26-28] Some drugs in this class have combined SGLT2 and SGLT1 inhibitor properties. SGLT1 proteins are found in the small intestine epithelium and the proximal convoluted tubule downstream to the SGLT2 proteins. Inhibiting SGLT1 predominantly reduces the intestinal uptake of glucose, and to a lesser degree in the proximal convoluted tubule, thereby promoting glycemic control with the potential side effect of diarrhea.[28,29] A naturally existing form of SGLT1/2i from apple-tree bark, called phlorizin, was initially studied in the 1830s; its glucosuria property was then discovered in 1885. The first SGLT2i drug was FDA approved for glycemic control among patients with T2D in 2013.[28,30]

Mechanisms of SGLT2i CV benefits appear to extend beyond simple glycemic control.[27,31,32] Potential mechanisms for improved HF clinical stability include decreased ventricular loading, improved myocardial fuel efficiency, and reduction in adipose tissue.[27,32,33] Decreased ventricular loading may occur by decreased preload via osmotic diuresis and natriuresis as well as decreased afterload via decreased blood pressure and arterial stiffness.[33,34] Evidence for decreased body sodium levels in skin tissue was demonstrated among patients with T2D treated with dapagliflozin,[35] and volume contraction without significant intravascular volume depletion was reported during dapagliflozin or empagliflozin treatment.[36,37] However other studies have not demonstrated a sustained loss of extracellular water and have even suggested an upregulation of the renin-angiotensin-aldosterone system.[38]

On a cellular level, it has been proposed that SGLT2 inhibition may promote myocardial metabolic substrate flexibility and energy efficiency. The failing heart transitions from the predominant fatty acid fuel source towards glucose utilization, but the mild increase in circulating ketones induced by SGLT2i has been suggested in animal models to encourage myocardial substrate preference away from glucose and towards ketone bodies, fatty acids and branched chain amino acids.[39-41] Serum metabolomics analyses in humans corroborate an association between empagliflozin and augmented ketone and amino acids utilization in the tricarboxylic acid cycle.[40] Existing human studies indicate that increased circulating ketone levels are associated with improved cardiac output without deterioration in myocardial energy efficiency, in both healthy controls and patients with HFrEF.[42] Further studies are required to determine whether the degree of circulating ketosis induced by SGLT2i significantly influences myocardial substrate preference in the failing human heart and whether this can achieve improved cardiovascular hemodynamics.

SGLT2is also reduce adipose tissue volume in both the visceral and epicardial locations, which may also be a mechanism of cardioprotection via reduction in systemic or paracrine hormonal signaling.[34,43-45] The combination of decreased LV preload and afterload, potentially combined with the improved metabolic signaling, may explain the regression in left ventricular hypertrophy (LVH) and diastolic dysfunction demonstrated by dapagliflozin and empagliflozin in the Does Dapagliflozin Regress Left Ventricular Hypertrophy In Patients With Type 2 Diabetes (DAPA-LVH) and Effects of Empagliflozin on Cardiac Structure in Patients With Type 2 Diabetes (EMPA-HEART) trials.[43,46]

Overall the mechanistic data explaining the cardioprotective effects of SGLT2is remains limited and at times contradictory, such that we are currently unable to confidently ascribe definitive mechanisms of benefit.[34,41] Although knowledge of the effects of SGLT2is on HF natural history and CV outcomes have rapidly accelerated beyond our more slowly evolving understanding of the mechanisms, this does not diminish the clinical opportunities for this novel addition to HFrEF therapy.

Effect of SGLT2 inhibitors on Serum and Imaging Biomarkers in Heart Failure

Biomarkers play a supportive role in the diagnosis, prognosis, and management of CV disease and HF.[47] Several studies have examined the impact of SGLT2 inhibitors on serum and imaging biomarkers in HF using N-terminal pro-B-type natriuretic peptide (NT-proBNP), magnetic resonance imaging (MRI), and/or echocardiography. There are discrepant findings regarding the effect of SGLT2 inhibitors on serum biomarkers and limited evidence that SGLT2 inhibitors provide clinically significant improvement upon imaging biomarkers.

Therapies that reverse or slow LV remodeling are generally associated with mortality benefits in HFrEF, and LV metrics from MRI and echocardiography can serve as imaging biomarkers.[48,49] Six placebo-controlled trials evaluated the influence of dapagliflozin or empagliflozin on LV remodeling using MRI,[43,46,50-52] or echocardiography.[53] DAPA-LVH and EMPA-HEART showed modest though statistically significant reductions in LV mass index in patients with T2D and a baseline mean preserved LVEF without a significant decrease in NTproBNP.[43,46] Four trials evaluated the impact of SGLT2 inhibitors on LV remodeling with a baseline mean reduced LVEF.[50-53] Three of these studies showed a statistically significant decrease in the primary outcome of LV volume

relative to baseline in the SGLT2i group compared to the change in the placebo group, after at least 3 months of therapy added to guideline-directed HF medical therapy.[50,52,53] Similarities of these three trials were: (1) use of empagliflozin in the treatment arm, (2) baseline dilated LV, and (3) majority of patients with at least NYHA class II symptom.[50,52-54] One trial showed no effect of dapagliflozin on LV volume parameters after one year of therapy using MRI[51] (see Table 3). The evidence to date of clinically significant reverse LV remodeling with only empagliflozin and not dapagliflozin, despite relatively similar effects on outcomes, suggests that the mechanisms of clinical benefit for this drug class may be mediated via multiple pathways.

The effect of SGLT2is on serum biomarkers, specifically on the natriuretic peptides, has been inconsistent across studies to date among patients with T2D or HF. In a post-hoc analysis, Januzzi et al observed only an attenuation of serum NT-proBNP among a population of diabetics without reported LVEF in the canagliflozin group relative to the placebo group over a two year period.[31] DEFINE-HF (Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in Patients with HF with Reduced Ejection Fraction) and Empire HF (Empagliflozin in Heart Failure Patients With Reduced Ejection Fraction) trials demonstrated no significant change over 12 weeks in mean serum NT-proBNP levels among patients with HFrEF treated with dapagliflozin or empagliflozin, respectively, compared to placebo.[55,56] In EMPA-RESPONSE-AHF (a randomized, double-blind, placebo-controlled, multicenter pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated HF), empagliflozin did not significantly decrease NT-proBNP levels after 4 days of treatment, compared to placebo.[57] These findings contrast with DAPA-HF, which showed 20% reduction in NT-proBNP

Table 3. SGLT2 inhibitor trials and remodeling in patients with heart failure*

Trial parameters	REFORM (2020)	EMPIRE-HF (2021)	SUGAR-DM-HF (2020)	EMPA-TROPISM (2021)
Intervention†	Dapagliflozin 10 mg daily vs placebo	Empagliflozin 10 mg daily vs placebo	Empagliflozin 10 mg daily vs placebo	Empagliflozin 10 mg daily vs placebo
Number of participants	56	190	105	84
Population and Baseline Characteristics	HFrEF (EF<45%) or worsening LV dysfunction	HFrEF (EF≤40%)	HFrEF (EF≤40)	HF (EF<50%)
EF	45%	29%	33%	36%
NYHA class II	43%‡	83%	77%	100% (NYHA II-III)§
T2D history	100%	13%	78%	0%
Imaging modality	MRI	Echocardiography	MRI	MRI
Average follow-up (weeks)	52	12	36	26
Endpoints‖	**Change in LVESV¶:** 4.82 mL (95% CI -13.28 to 22.93, p=0.594) **Change in LVEDV:** 7.83 mL (-15.05 to 30.70, p=0.495) **Change in LVMi:** 2.5 g/m² (-3.95 to 8.95, p=0.440)	**Change in LVESVi¶ (vs placebo):** -4.3 mL/m² (95% CI, -8.5 to -0.1, p=0.04) **Change in LVEDVi¶ (vs placebo):** -5.5 mL/m² (-10.6 to -0.4, p=0.03) **Change in LVMi (vs placebo):** -9.0 g/m² (-17.2 to -0.8, p=0.03)	**Change in LVESVi¶ (vs placebo):** -6.0 ml/m² (95% CI, -10.8 to -1.2, p=0.015) **Change in LVEDVi¶ (vs placebo):** -8.2 ml/m² (95% CI, -13.7 to -2.6, p=0.0042)	**Change in LVESV¶ (vs placebo):** -26.6 ml vs -0.5 mL, p<0.001) **Change in LVEDV¶ (vs placebo):** -25.1 mL vs -1.5 mL, p<0.001) **Change in LVM (vs placebo):** -17.8 g vs +4.1 g, p<0.001)

*SGLT2: sodium-glucose cotransporter-2; T2D: type 2 diabetes mellitus; HFrEF: heart failure with reduced ejection fraction; HF: heart failure; CI: confidence interval; EF: ejection fraction; NYHA: New York Heart Association; eGFR: estimated glomerular filtration rate (ml/min/1.73m²); LVM: left ventricular mass; LVMi: left ventricular mass index; LVESV: left ventricular end systolic volume; LVESVi: left ventricular end systolic volume index; LVEDV: left ventricular end diastolic volume; LVEDVi: left ventricular end diastolic volume index; mL: milliliter; g: grams; m²: meters squared; MRI: magnetic resonance imaging

†Includes treatment and placebo arms; all patients in SGLT2i and placebo arms received standard-of-care treatments

‡ 44.6% with NYHA class I

§ Unknown proportion of patients with NYHA class II

¶ Primary endpoint

‖The first three columns reflect a between-group difference, whereas the fourth column reflects within-group changes

levels over 8 months in HFrEF patients who were treated with dapagliflozin.[9] Among studies that compared an SGLT2i to another antidiabetic drug, there were no consistent significant reductions in NT-proBNP. In the randomized trial by de Boer et al., 12 weeks of treatment with licogliflozin significantly decreased NT-proBNP levels in patients with T2D and HF.[58] In the CANDLE trial (Effects of canagliflozin in patients with type 2 diabetes and chronic heart failure: a randomized trial), patients with HF treated with canagliflozin experienced a non-significant reduction in NT-proBNP levels compared to glimepiride after 24 weeks of treatment.[59] In another trial, 12 weeks of luseogliflozin therapy in patients with T2D and HFpEF (EF>45%) versus voglibose resulted in no significant differential change in serum BNP levels.[60]

Ongoing Studies and Future Directions

In light of major trials showing significant benefits of SGLT2is on patients with HFrEF regardless of T2D status and the findings of the SOLOIST-WHF trial discussed above, there are ongoing studies evaluating the impact of SGLT2 inhibitors on HFpEF patients with EF >40%. In PRESERVED-HF (Dapagliflozin in PRESERVED Ejection Fraction Heart Failure), investigators are evaluating the impact of dapagliflozin on HFpEF (EF>40%) with respect to functional status as measured by the Kansas City Cardiomyopathy Questionnaire[23] and in DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure), 6100 patients with HFpEF are being randomized to dapagliflozin versus placebo.[25] In EMPEROR-Preserved (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction), 5988 patients with HFpEF with or without T2D were randomized to empagliflozin versus placebo for the primary outcome of time to CV death or HHF.[24] While SOLOIST showed mortality and morbidity benefits for patients with T2D and HF treated with sotagliflozin, future studies should also evaluate the impact of sotagliflozin on patients with HF without T2D. To further affirm a class effect of SGLT2 inhibitors upon CV and HF outcomes, future studies on canagliflozin in patients with HFrEF with or without T2D may be considered.

Conclusions and Applications

The utility of SGLT2is extends beyond glycemic control, as demonstrated by several recent major clinical trials showing significant CV benefits, and specifically a reduction in HHF among patients with T2D or HF when SGLT2is are added to standard care. The consistent demonstration of a reduction in HHF across the many rigorous well-powered trials discussed above suggests a class effect. Dapagliflozin has received FDA approval in adults with HFrEF to reduce the risk of CV death and HHF, with a similar FDA indication under review for empagliflozin. The use of dapagliflozin or empagliflozin is endorsed by the American College of Cardiology Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment for patients with stage C HFrEF, NYHA Class II through IV.[61] This document cautions against use if eGFR <30 mL/min/m^2 for dapagliflozin or <20 mL/min/m^2 for empagliflozin, although these thresholds are lower than those currently recommended by the FDA for SGLT2i initiation. It remains to be seen how future iterations of the HF practice guidelines will integrate the SGLT2i data, and how the logistics of SGLT2i initiation within the expanding repertoire of HFrEF GDMT will evolve. Bassi et al. have projected that 2.1 million patients with HFrEF are candidates for SGLT2is in the United States and that treatment of all eligible patients would prevent or delay approximately 34,125 deaths per year.[62] Ongoing trials will elucidate whether there is a role among patients with HFpEF.

The SGLT2i story represents a remarkable journey, emanating initially from regulatory guidance intended to show CV safety of agents for diabetes, with resultant large CVOTs having sufficient statistical power to demonstrate benefits on CV outcomes, including robust secondary findings that opened the door to large HF trials. In just over 10 years, this class of agents has moved from a new therapy for diabetes to a cornerstone agent in the prevention and treatment of HF.

Prevention and Management of Heart Failure:
Role of SGLT2 Inhibitors in Patients With and Without Diabetes

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