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Review

SGLT2 inhibitors: a new pillar of the heart failure regimen

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Initially intended as an adjunct treatment for type 2 diabetes mellitus (T2DM), SGLT2-inhibitors (SGLT2i) have transformed into an unexpected pillar of the heart failure (HF) regimen. The past several years have witnessed a meteoric rise of this drug class, starting with the serendipitous results of trials assessing the safety of the glucose-lowering therapy in a broad range of cardiovascular patients and culminating with the demonstration of a reduction in hospitalizations for heart failure and cardiovascular mortality in dedicated heart failure populations. The heart failure benefits of SGLT2i are independent of a patient's glycemic status, but the salient mechanisms of cardioprotection remain a subject of robust debate and ongoing research. Cardiologists as well as physicians of other disciplines should become familiar with the main indications, benefits, and clinical consideration of implementation. In this review, we will discuss the advance of SGLT2i in heart failure, ranging from the results of large randomized clinical trials to potential mechanisms of action.

Keywords

SGLT2-inhibitors; Heart failure; HFrEF; HFpEF; Diabetes; Cardiomyopathy

1. Background

In 2013, canagliflozin became the first SGLT-2 inhibitor (SGLT2i) approved in the United States for type 2 diabetes mellitus (T2DM). Since then, several of these compounds have been developed and approved for clinical use. Currently, there are four SGLT2i available in the United States and Europe, which include, canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin.

In the 2000's, concerns began to develop around the cardiovascular safety of glucose-lowering therapies [1]. This culminated in 2007 when a signal for increased myocardial infarction with the thiazolidinedione rosiglitazone was identified [2], which prompted regulatory agencies to reevaluate the approval process of anti-diabetic therapies. As a result, in 2008, the Food and Drug Administration (FDA), and in 2012, the European Medicines Agency (EMA), issued requirements for the evaluation of cardiovascular safety outcomes of glucose-lowering therapies [3, 4]. This development set the stage for the unexpected results of several large, randomized, placebo-controlled trials of SGLT2i which demonstrated convincing evidence of improved cardiovascular outcomes, including reduction in major adverse cardiovascular events (MACE) and hospitalizations for heart failure (HHF).

2. Biology of SGLT

Cell membranes are composed largely of phospholipids and are impermeable to large, polar molecules such as glucose. Therefore, glucose transport across cell membranes requires specific membrane transport proteins. There are two classes of glucose transporters in humans: the facilitated uniporter, GLUT, and the active symporter, SGLT [5]. Glucose transport via SGLT occurs by active transport, a process that involves glucose absorption against its concentration gradient using the energy provided by the sodium gradient across the membrane, which is maintained by the Na^+/K^+ ATPase [6]. There are 12 members of the human SGLT family [7], with two involved in renal glucose absorption [8]. The first SGLT discovered, designated SGLT-1, was cloned from human intestinal cells in 1987 [9] and was subsequently discovered in several other tissues include the kidney, heart, trachea, and prostate [10]. SGLT-2, which is found almost exclusively in the kidney, was characterized a few years later [11].

SGLT-2 is a low affinity-high capacity transporter [12] located in the epithelium of segment 1 of the proximal convoluted tubule [13] and is responsible for approximately 90% of filtered glucose reabsorption [14]. The remaining ~10% of the filtered load is reabsorbed by SGLT-1, a high-affinity-low capacity transporter [12] located in segment 2 of the proximal convoluted tubule and segment 3 of the proximal straight tubule [15]. However, complete pharmacologic blockade of SGLT-2 leads to only 50–60% excretion of filtered glucose due to downstream upregulation of SGLT-1 [16].

Glucose transport from the glomerular filtrate through the epithelial cell and into the blood is illustrated in Fig. 1 [17]. Once active transport via SGLT leads to glucose uptake across the apical membrane into the epithelial cell, glucose transport to the peritubular capillary occurs via the basolateral facilitated glucose transporters, GLUT1, which colocalizes with SGLT1, and GLUT2, which colocalizes with SGLT2 [18].

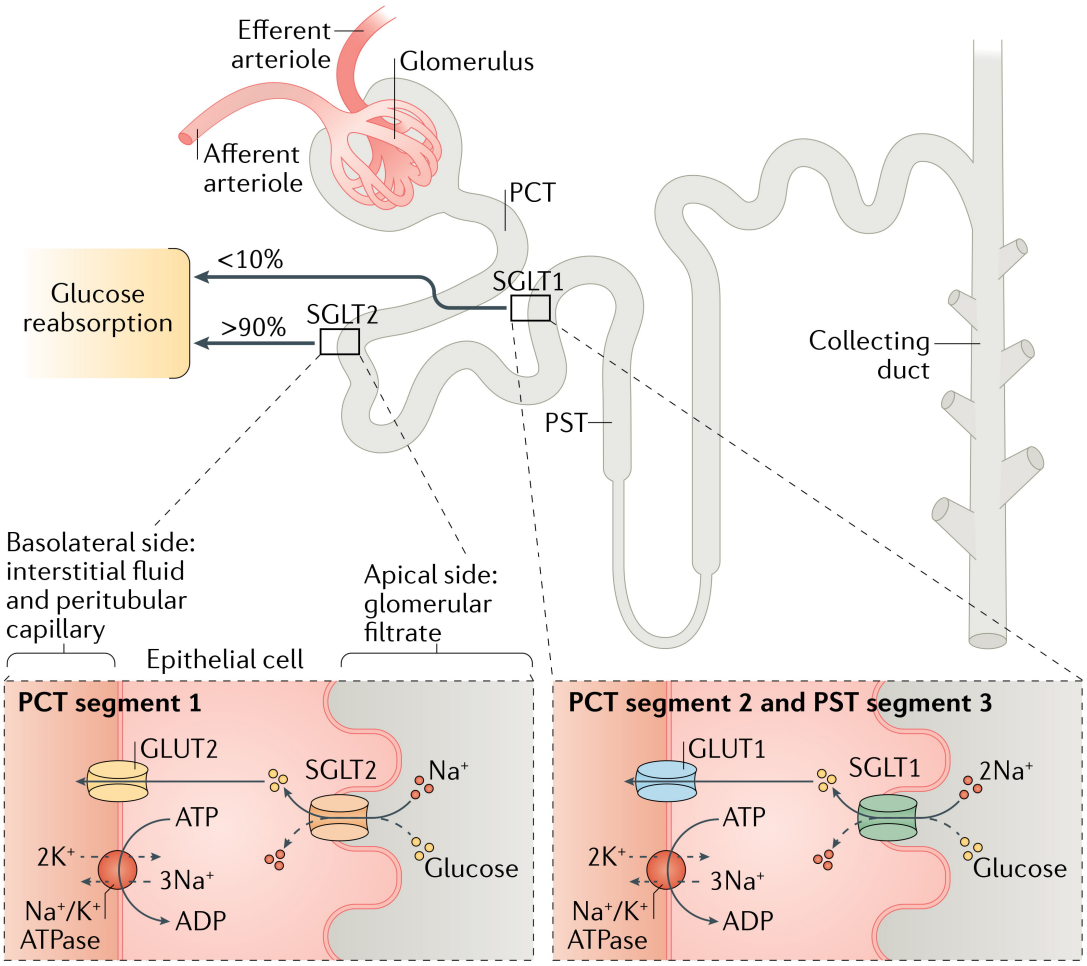

Fig. 1. Glucose reabsorption in the kidney. The majority (>90%) of glucose is reabsorbed via sodium-glucose cotransporter 2 (SGLT2) in segment 1 of the proximal convoluted tubule (PCT) while the remainder (<10%) is reabsorbed in segment 2 of the PCT and segment 3 of the proximal straight tubule (PST). Once active transport via SGLT leads to glucose uptake across the apical membrane into the epithelial cell, glucose transport to the peritubular capillary occurs via the basolateral facilitated glucose transporters, GLUT1, which colocalizes with SGLT1, and GLUT2, which colocalizes with SGLT2. Reproduced with permission from Cowie *et al.* [17].

3. Benefits in heart failure seen in cardiovascular outcomes trials

The first SGLT2i Cardiovascular Outcomes Trial (CVOT) was EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) [19] in 2015, which enrolled 7020 patients with T2DM and established cardiovascular disease. Despite a primary goal of only showing the cardiovascular safety of empagliflozin, the trial unexpectedly demonstrated a 14% reduction in MACE (a composite of cardiovascular death, nonfatal MI, and stroke), a 38% reduction in cardiovascular mortality, a 32% reduction in all-cause mortality, and a 32% reduction in HHF [19]. Given these remarkable results, the investigators conducted post-hoc assessments that showed empagliflozin reduced cardiovascular events regardless of a past clinical diagnosis of heart failure (HF) (not phenotyped with preserved or reduced ejection fraction) [20], baseline risk for HF [21], and baseline cardiovascular risk [22].

These results were followed by the CANVAS (Canagliflozin Cardiovascular Assessment Study) program [23] in 2017, which enrolled 10,142 patients with T2DM and established, or risk factors for, cardiovascular disease. Similar to EMPA-REG OUTCOME, CANVAS showed a 14% reduction in MACE [23]. Approximately 14% of enrolled patients had a history of either heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF) with similar benefits seen in both groups [24]. Furthermore, reduction in cardiovascular death or HHF was greater among those with a history of HF [25].

Published in 2019, DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58) enrolled 17,160 patients with T2DM and established, or risk factors for, cardiovascular disease but did not demonstrate a reduction in MACE [26], which may be related to the large fraction of patients in the trial without

Table 1. Early cardiovascular outcomes trials in SGLT2i.

	EMPA-REG OUTCOME [19]	CANVAS [23]	DECLARE-TIMI 58 [26]
Drug	Empagliflozin 10 mg or 25 mg vs placebo	Canagliflozin 100 mg or 300 mg vs placebo	Dapagliflozin 10 mg vs placebo
Population	• 7020 patients with T2DM and established cardiovascular disease • eGFR $\geq$30 mL/min/m^2	• 10,142 patients with T2DM and established cardiovascular disease or $\geq$2 CV risk factors • eGFR $\geq$30 mL/min/m^2	• 17,160 patients with T2DM and established cardiovascular disease or CV risk factors • eGFR $>$60 mL/min/m^2
History of heart failure (reduced or preserved EF)	706 (10.1%)	1461 (14.4%)	1724 (10.0%)
Primary outcome	3 Point MACE (HR 0.86, 95% CI 0.74–0.99)	3 Point MACE (HR 0.86, 95% CI 0.75–0.97)	3 Point MACE (HR 0.93, 95% CI 0.84–1.03)
HHF outcome	HR 0.65, 95% CI 0.5–0.85	HR 0.67, 95% CI 0.52–0.87	HR 0.73, 95% CI 0.61–0.88
CV mortality	HR 0.62, 95% CI 0.49–0.77	HR 0.87, 95% CI 0.72–1.06	HR 0.98, 95% CI 0.82–1.17
Post-hoc analyses	CV events reduced regardless of • HF history [20] • baseline HR risk [21] • baseline CV risk [22]	• Benefit regardless of HFrEF or HFpEF [24] • Greater benefit with history of HF [25]	• Reduced HHF regardless of HF history [28] • Reduced CV death in HFrEF patients [28]

T2DM, type 2 diabetes mellitus 2; CV, cardiovascular; eGFR, estimated glomerular filtration rate; 3 Point MACE, three-point major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke); HR, hazard ratio; HHF, hospitalization for heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

cardiovascular disease [27]. However, a post hoc analysis assessed patients by baseline HF status and found that dapagliflozin reduced HHF in patients irrespective of a history of HFrEF and reduced cardiovascular mortality and all-cause mortality in patients with HFrEF [28].

A meta-analysis of the original 3 CVOT's showed that SGLT2i reduced the risk of cardiovascular death or HHF by 23% and that this reduction was independent of a documented history of HF (Table 1, Ref. [19–26, 28]) [29]. The same study also showed that there was greater reduction in HHF in patients with worse kidney function [29]. Given the promising data on HF outcomes in all of the CVOT's, it became clear that dedicated SGLT2i studies involving HF populations would be needed.

4. SGLT2i and dedicated heart failure trials

4.1 HFrEF

The first major SGLT2i trial specifically designed to assess HFrEF was DAPA-HF (Dapagliflozin and the Prevention of Adverse-outcomes in Heart Failure), which enrolled 4744 patients with NYHA II–IV symptoms and EF $\leq$40% (Table 2, Ref. [30–43]) [30]. DAPA-HF showed a 26% reduction in the composite endpoint of cardiovascular death, HHF, or urgent HF visit as well as a reduction in its individual components, including an 18% reduction in cardiovascular death. Importantly, the benefits were irrespective of T2DM status, a diagnosis carried by 42% of the study population. Furthermore, post hoc analyses showed consistent benefits of dapagliflozin regardless of baseline use of diuretics [31], mineralocorticoid receptor antagonists (MRA) [32], or sacubitril/valsartan [33]. In addition, subsequent analyses demonstrated that dapagliflozin reduced the total (first and recurrent) HHF [34] and outpatient intensification of HF therapy [35]. The results of DAPA-HF led to a new FDA indication in May 2020 for dapagliflozin to reduce the risk of cardiovascular death and HHF in adults with HFrEF (NYHA II–IV) [44].

DAPA-HF was followed by EMPEROR-REDUCED (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and Reduced Ejection Fraction), which enrolled 3730 patients with NYHA II–IV symptoms and EF $\leq$40% [36]. Empagliflozin demonstrated a 25% reduction in the composite of cardiovascular death and HHF, although did not reach statistical significance for cardiovascular death alone. Similar to DAPA-HF, the results in EMPEROR-REDUCED were irrespective of T2DM. Patients were treated with guideline-directed medical therapy and no interaction was observed with use of MRA [45]. Empagliflozin also demonstrated an early and sustained improvement in Kansas City Cardiomyopathy Questionnaires-Clinical Summary Score (KCCQ-CSS) [37] as well as a reduction in the total number of inpatient and outpatient HF events [38]. The FDA accepted the application of empagliflozin in January 2021 for a HFrEF indication and formal approval is still pending [46].

Published in January 2021, SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) examined the efficacy of sotagliflozin in patients with T2DM and HFrEF or HFpEF who had been stabilized from recent HF admission [39]. Although it was terminated early due to loss of funding in the setting of COVID-19, the trial enrolled 1222 patients (79% with EF <50%) and demonstrated a 29% reduction in the composite of cardiovascular death, HHF, or urgent visit for HF, which achieved significance by 28 days of follow-up. Statistical significance was not achieved for the individual component of cardiovascular death, although this endpoint is difficult to assess in the setting of truncated follow-up. Additionally, pooled data from SOLOIST-WHF and SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who are at Cardiovascular Risk) [43] demonstrated a 27% reduction in composite of cardiovascular death, HHF, or urgent visit for HF, with significance achieved regardless of reduced or preserved EF. Cardiovascular death was not reduced in the pooled intention-to-treat analysis, but a reduction was achieved in the per-protocol analysis (HR 0.77, 95% CI 0.60–0.98). A subsequent analysis focused on patient-centered outcomes also showed that sotagliflozin increased days alive and out of hospital [44]. Several additional SGLT2i HF trials are ongoing (Table 3).

4.2 HFpEF

In the pooled analysis of SOLOIST-WHF and SCORED, sotagliflozin became the first agent to distinctly show benefit in HFpEF. However, SOLOIST-WHF was not designed to assess HFpEF as the primary hypothesis and HFpEF patients comprised only ~21% of the population [47]. As such, a dedicated trial examining SGLT2i in HFpEF was needed.

Published in August 2021, EMPEROR-PRESERVED (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) [46] enrolled 5988 patients with EF >40%, NYHA II–IV symptoms, and an HHF within the prior 12 months. The EF cutoffs ranged from >40% to <50%, $\geq$50% to <60%, and $\geq$60% with an even distribution. After a median follow-up of 26.2 months, empagliflozin demonstrated a significant reduction in the composite of cardiovascular death and HHF (HR 0.79, 95% CI 0.69–0.90), driven by reduction in HHF (HR 0.71, 95% CI 0.60–0.83). However, empagliflozin did not significantly reduce the risk of cardiovascular death (HR 0.91, 95% CI 0.76–1.09). The benefits of empagliflozin were seen irrespective of glycemic status and across the EF spectrum, albeit with a possible attenuation of benefit in those with EF $\geq$60%.

EMPEROR-POOLED [47], a prospective, pooled analysis of EMPEROR-REDUCED and EMPEROR-PRESERVED assessed the effect of empagliflozin on major renal events in HF, defined as profound and sustained decreases in eGFR or renal replacement therapy. The pooled study demonstrated a reduction in major renal events (2.8% vs 3.5% for empagliflozin vs placebo). However, significant heterogeneity was found between the two trials (p = 0.016 for interaction). Specifically, the hazard ratios for major renal events

Table 2. Major large HF and SGLT2i randomized controlled trials.

	DAPA-HF [30]	EMPEROR-REDUCED [36]	SOLOIST-WHF [39]	EMPEROR-PRESERVED [42]
Drug	Dapagliflozin 10 mg vs placebo	Empagliflozin 10 mg vs placebo	Sotagliflozin 400 mg vs placebo	Empagliflozin 10 mg vs placebo
Population	• 4744 patients with chronic, ambulatory HFrEF (EF $\leq$40% with NYHA II–IV class • 45% with T2DM • eGFR $\geq$30 mL/min/m^2	• 3730 patients with chronic, ambulatory HFrEF (EF $\leq$40% with NYHA II–IV class • 50% with T2DM • eGFR $\geq$20 mL/min/m^2	• 1222 patients with HFrEF (79%) or HFpEF (21%) admitted for acute HF • Transitioned to PO diuretics • 100% with T2DM • eGFR $\geq$30 mL/min/m^2	• 5988 patients with chronic, ambulatory HFpEF (EF $>$40% with NYHA II–IV class • 49% with T2DM • eGFR $\geq$20 mL/min/m^2
Primary outcome	Hospitalization for HF or cardiovascular death, including urgent hospital visit with intravenous therapy for HF (HR 0.74, 95% CI 0.65–0.85)	Hospitalization for HF or cardiovascular death (HR 0.75, 95% CI 0.65–0.86)	Hospitalization of HF, urgent visit for HF, or cardiovascular death (HR 0.67, 95% CI 0.52–0.85)	Hospitalization for HF or cardiovascular death (HR 0.79, 95% CI 0.69–0.90)
HHF outcome	HR 0.70, 95% CI 0.59–0.83	HR 0.69, 95% CI 0.59–0.81	Not assessed individually	HR 0.71, 95% CI 0.60–0.83
CV mortality	HR 0.82, 95% CI 0.69–0.98	HR 0.92, 95% CI 0.75–1.12	HR 0.84, 95% CI 0.58–1.22	HR 0.91, 95% CI 0.76–1.09
Post-hoc analyses	• Benefit regardless of background HF therapy [31–33] • Reduced first and recurrent HHF [34] • Reduced outpatient intensification of HF therapy [35]	• Early and sustained reduction in KCCQ-CSS [37] • Reduced first and recurrent HHF [38]	• Pooled analysis with SCORED [40] showed reduction in primary outcome regardless of HFrEF or HFpEF • Increased days alive and out of hospital [41]	• EMPEROR-POOLED [43] showed significant heterogeneity between HFrEF and HFpEF regarding major renal events

HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association Class; T2DM, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; PO, per os; HR, hazard ratio; CI, confidence interval; HHF, hospitalization for heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; SCORED, Sotagliflozin in patients with diabetes and chronic kidney disease; HFpEF, heart failure with preserved ejection fraction.

Table 3. Select ongoing SGLT2i HF trials.

Trial	NCT identifier	Drug	Population	Enrollment	Primary endpoint
Chronic HF					
DETERMINE-REDUCED	03877237	dapagliflozin	HFrEF	313	6MWD and KCCQ
CHIEF-HF	04252287	canagliflozin	HFrEF and HFpEF	476	KCCQ
DELIVER	03619213	dapagliflozin	HFpEF	6263	Time to first CV death, HHF, or urgent HF visit
Acute HF					
DAPA ACT HF-TIMI 68	04363697	dapagliflozin	HFrEF	2400	Time to first CV death or worsening HF
EMPULSE	04157751	empagliflozin	HFrEF and HFpEF	530	All-cause death, HF event, and KCCQ (Win Ratio)
MI and HF					
EMPACT-MI	04509674	empagliflozin	STEMI/NSTEMI with new HF	3312	Time to first HHF or all-cause death
DAPA-MI	04564742	dapagliflozin	STEMI/NSTEMI with new HF	6400	Time to first HHF or CV death

HFrEF, heart failure with reduced ejection fraction; 6MWD, 6-minute walk distance; KCCQ, Kansas City Cardiomyopathy Questionnaire; HFpEF, heart failure with preserved ejection fraction; CV, cardiovascular; HHF, hospitalization for heart failure; MI, myocardial infarction; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction.

were 0.51 (95% CI 0.33–0.79) in EMPEROR-REDUCED compared to 0.95 (95% CI 0.73–1.24) in EMPEROR-PRESERVED, indicating that renal benefit is primarily in HFrEF patients. As the pathophysiology of HFrEF and HFpEF are profoundly different, it should not come as a complete surprise that the cardiorenal interplay between the two HF phenotypes differ as well. Finally, the fact that EMPEROR-PRESERVED demonstrated a significant reduction in mean eGFR slope/year (–1.25 vs –2.62, $p < 0.001$) suggest that eGFR may not be a robust surrogate for renal outcomes in the HF population at large.

The results from EMPEROR-PRESERVED are important given the paucity of options in HFpEF. The next major trial for SGLT2i and HFPEF is DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction) [48] which is scheduled to complete January 2022.

5. Comparison of individual agents in the SGLT2i class

Without a prospective head-to-head comparison, it is challenging to extrapolate similarities and differences between individual SGLT2i to determine superiority. Available data demonstrate variation in "hard" outcomes such as MACE and cardiovascular death as well as relative efficacy in subgroups relating to subgroups of disease state and severity. Differences in patient populations, study protocols, or pharmacology of the drugs may account for these variations. However, the most consistent benefit across multiple populations and subgroups is the reduction in HHF. A meta-analysis of six outcomes trials studying four SGLT2i showed heterogeneity among the class with respect to cardiovascular death with the greatest and most consistent benefit seen in reduction of HHF [49].

DAPA-HF is the only trial thus far to demonstrate a mortality benefit in a dedicated HFrEF population. Various reasons for lack of a mortality benefit in EMPEROR-REDUCED have been proposed. One explanation highlights that, although both trials were underpowered for cardiovascular death, EMPEROR-REDUCED had significantly less power compared to DAPA-HF for mortality (500 cardiovascular deaths in DAPA-HF compared to 389 cardiovascular deaths in EMPEROR-REDUCED) [50]. The investigators of EMPEROR-REDUCED note the study enrolled patients with lower EF and higher NT-proBNP compared to DAPA-HF (27.7% vs 31.2% and 1887 vs 1428 pg/mL, respectively). As such, it may seem curious that a "sicker" population would experience less overall cardiovascular death. However, this discrepancy may be explained by the higher overall event rate of the primary endpoint for EMPEROR-REDUCED, driven primarily by HHF, which led to shorter follow-up (16 vs 18.2 months) and lower accrual of cardiovascular death [50]. Furthermore, a meta-analysis of DAPA-HF and EMPEROR-REDUCED demonstrated a 14% reduction in cardiovascular death (HR 0.86, 0.76–0.98, $p = 0.027$) and perhaps equally as important, failed to show a significant heterogeneity of effect between the two agents (Fig. 2) [51].

SOLOIST-WHF expanded beyond the findings from DAPA-HF and EMPEROR-REDUCED, although the latter two studies required a reduced EF. SOLOIST-WHF was unique in establishing the safety and efficacy of SGLT2i initiation in acute HF patients that have been stabilized, either prior to discharge or shortly thereafter. The cardiovascular mortality outcome was not met, but this must be taken in context with premature termination of the study (due to loss of funding) with a truncated median follow-up of 9 months.

Although SOLOIST-WHF provided evidence that SGLT2i could reduce HHF in HFpEF patients, EMPEROR-PRESERVED was the first large, dedicated HFpEF-SGLT2i trial to show benefit. The heart failure community awaits the results of DELIVER for comparison.

Finally, the relative SGLT selectivity of these agents has not manifested in overt clinical differences in large, randomized controlled trials. Empagliflozin exhibits an SGLT2:SGLT1 selectivity ratio of 2700 compared to 1200 for dapagliflozin and 20 for sotaglifozin [27]. However, the re-

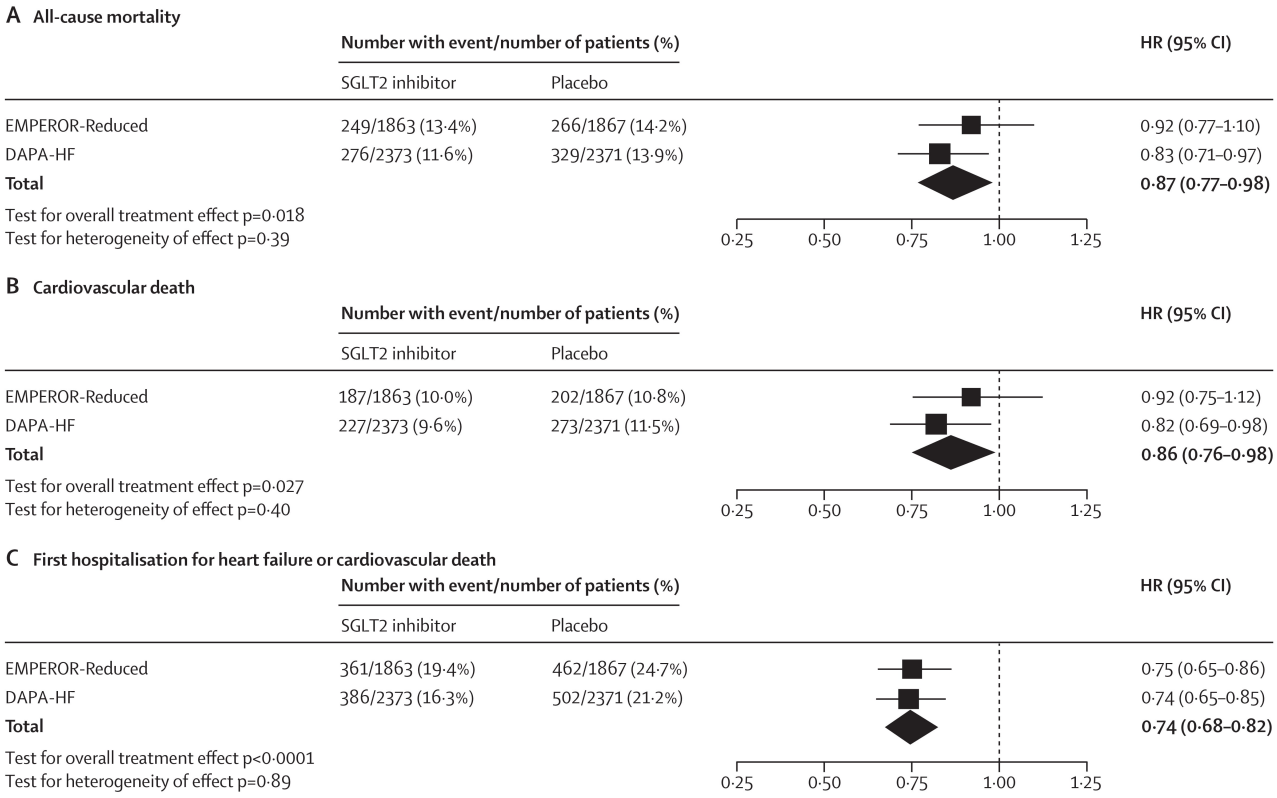

Fig. 2. Meta-Analysis of the DAPA-HF and Emperor Reduced Trials. Note the negative tests for heterogeneity of effect between dapagliflozin and empagliflozin (Reproduced with permission from Zannad *et al.* [51]).

sults of DAPA-HF, EMPEROR-REDUCED, and SOLOIST-WHF are ostensibly comparable.

6. Proposed mechanisms of action

The unexpected results demonstrating cardiovascular benefit of SGLT2i in CVOT's and subsequent trials confirming positive results in HF populations have spurred a flurry of research into these agents' cardiac mechanism of action. SGLT2i appear to exhibit pleotropic effects on multiple molecular and physiologic systems mediated independently of anti-hyperglycemic activity [52]. The actions of these drugs must also be appreciated in the context of a lack of SGLT2 receptors in the myocardium. Here, we will provide an overview of several categories of proposed mechanisms (Fig. 3), divided into direct and indirect cardiomyocyte benefit.

6.1 Mechanisms of direct cardiomyocyte benefit

6.1.1 Reduction in oxidative stress and mitochondrial damage and improved autophagy masquerading as erythrocytosis

A striking feature of SGLT2i has been their ability to consistently increase erythropoietin and erythrocytosis across clinical trials [53]. Interestingly, an increased hematocrit has been the strongest statistical variable associated with reduction in HHF and cardiovascular mortality [54, 55]. However, increasing red blood cell mass through erythropoietin-analogs has not shown benefit in chronic HF patients, even in the setting of low hematocrit [56]. One theory suggests that increased hematocrit may be a biomarker of the underlying mechanisms that provide benefit in HF [57].

SGLT2i induce a state of nutrient-deprivation that leads to transcriptional activation of a series of genes involved in adapting to cellular starvation (Fig. 4, Ref. [57]) [58]. Specifically, the enzymes that act as low energy sensors include sirtuin 1 (SIRT1) and adenosine monophosphate-activated protein kinase (AMPK) [59]. SIRT1 reduces oxidative stress by improving antioxidant activity [60] and AMPK protects mitochondrial function (Fig. 5) [61]. Furthermore, SIRT1 and AMPK signaling stimulates autophagy, a critical process that clears the cell of damaged organelles [62], which are major sources of reactive oxygen species and cellular dysfunction in cardiomyocytes (Fig. 5) [63].

How then is SIRT1/AMPK signaling related to erythrocytosis? In addition to inducing a fasting-like state, SGLT2i also lead to a state of hypoxia mimicry [56]. Specifically, SIRT1 (induced by SGLT2i) activates hypoxia-inducible factor-2a (HIF-2a) [64, 65], a hypoxia sensor that is a principal regulator of erythropoietin synthesis [57, 59]. Thus, the increase in hematocrit demonstrated in SGLT2i clinical trials may serve as the laboratory marker of a complex enzymatic cascade of reduced oxidative stress and improved mitochondrial function.

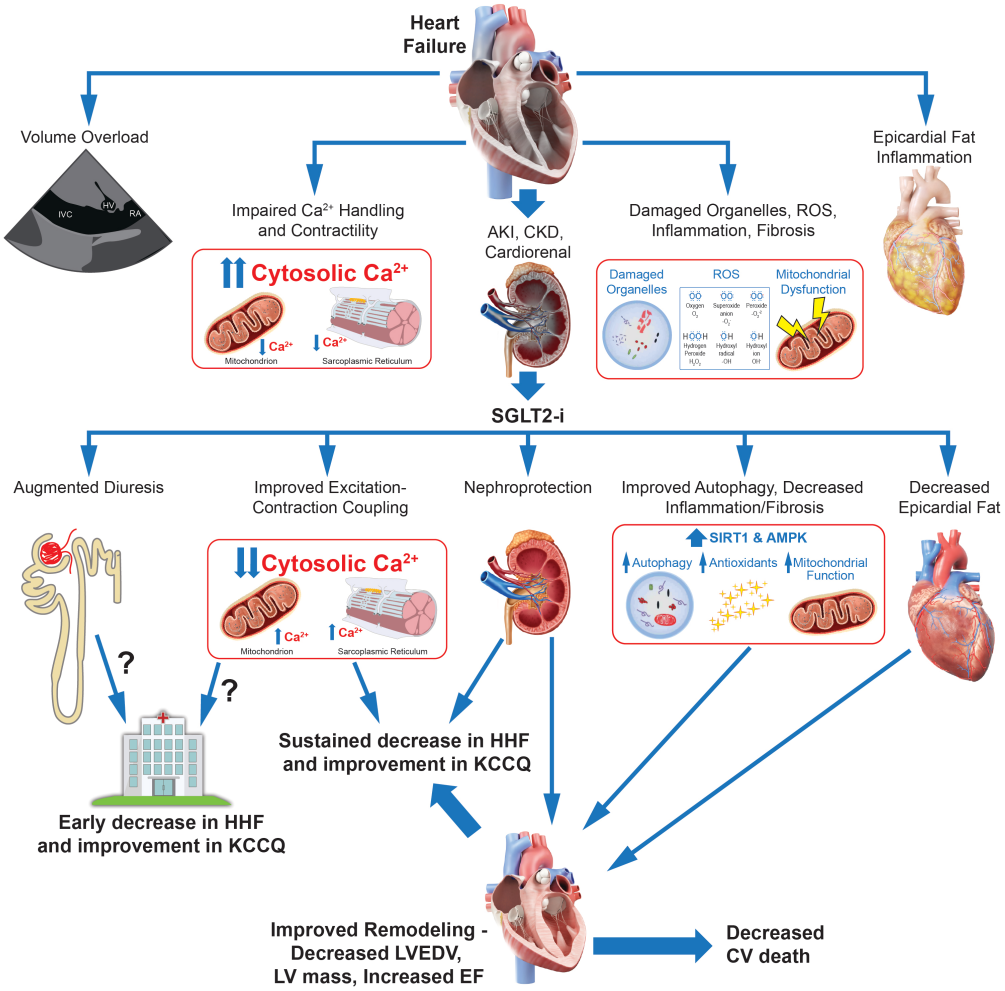

Fig. 3. Proposed Mechanisms of SGLT2i HF Benefit. Several mechanisms of SGLT2i benefit in heart failure have been postulated, including augmented diuresis, improved calcium handling, protection of the cardiorenal axis, and reduced inflammation from multiple pathways, including those emanating from epicardial fat. The mechanisms for early reduction in hospitalizations for heart failure (HHF) and increase in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) remain unclear but may be related to augmented diuresis and improved contractility. Imaging data have demonstrated positive long-term remodeling, which may be explained by off-target attenuation of inflammatory pathways and fibrosis.

6.1.2 Reduction in fibrosis and improvement in LV remodeling

Some clinical trials involving SGLT2i, such as DAPA-HF, have demonstrated a reduction in mortality, with survival curves separating after several months. This may suggest the ability to promote favorable long-term remodeling, as seen with beta-blockers, renin-angiotensin-aldosterone system (RAAS) and neprilysin inhibitors, and MRA [66, 67].

Indeed, several mouse models studying SGLT2i have shown reduction in cardiac fibrosis via reduced expression of transforming growth factor-β [68], collage type I and III [68], matrix metalloproteinase 7 [69], and fibronectin 1 [69] as well as upregulation of signal transducer and activator of transcription 3 (STAT3) signaling [70].

These laboratory findings were supported with clinical data in EMPA-HEART CardioLink -6 (Effect of Empagliflozin on Left Ventricular Mass in Patients with Type 2 Diabetes Mellitus and Coronary Artery Disease) [71], which evaluated empagliflozin's effect on LV remodeling in patients with established T2DM and coronary artery disease and a normal EF. At 6 months, empagliflozin demonstrated a significant decrease LV mass index vs placebo as demonstrated by cardiac magnetic resonance (–2.6 vs –0.01 g/m^2, $p = 0.01$). It should be noted that only 6% of the population had a history of prior chronic HF. More recently, EMPA-TROPISM (Are the "Cardiac Benefits" of Empagliflozin Independent of Its Hypoglycemic Activity), which evaluated the LV remodeling of empagliflozin in 84 non-diabetic patients with HFrEF [72]. Patients had NYHA II–III symptoms and a mean EF of 36.5%. After 6 months of follow-up, empagliflozin demonstrated a significant decrease in left ventricular end diastolic

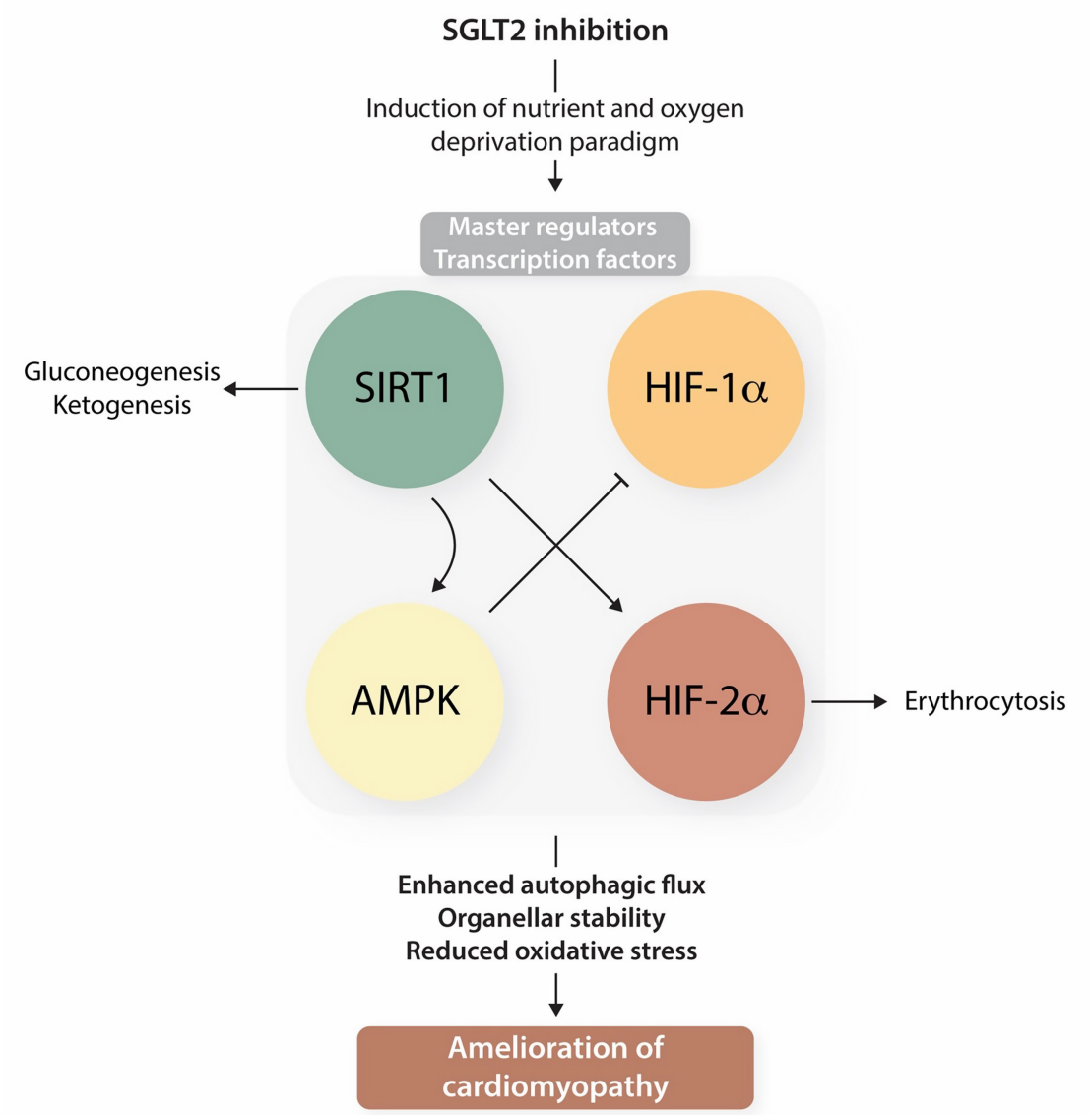

Fig. 4. SGLT2i may exert cardioprotective effects by inducing a nutrient- and oxygen-deprivation transcriptional paradigm. Sirtuin 1 (SIRT1) and adenosine monophosphate-activated protein kinase (AMPK) are low energy sensors that activate downstream pathways related to reduced oxidative stress and improved autophagy. Erythrocytosis is also induced, although it may not be central to a cardioprotective benefit. Reproduced with permission from Packer *et al.* [57] (HIF-1α, hypoxia-inducible factor isoform 1α; HIF-2α, hypoxia-inducible factor isoform 2α).

volume (LVEDV) and left ventricular end systolic volume (LVESV) (–25.1 vs –1.5 mL and –26.6 vs –0.5 mL, respectively; both $p < 0.001$) [72]. In addition, the empagliflozin arm demonstrated an improvement in EF, a reduction in LV mass, and an improvement in 6-minute walk [72].

6.1.3 Improved cardiomyocyte calcium handling

An important off-target effect of SGLT2i may relate to their high affinity binding of the sodium-hydrogen exchanger-1 (NHE-1), which is expressed in cardiomyocytes [73, 74]. HF leads to a maladaptive increase in NHE-1 expression, leading to a calcium and sodium overloaded state implicated in the pathogenesis of cardiomyopathy [75, 76]. Inhibition of NHE-1 decreases cytosolic Na^+ and Ca^{2+} while increasing mitochondrial Ca^{2+}, which may improve cardiomyocyte excitation-contraction coupling [76] and reduce mitochondrial generation of reactive oxygen species [77].

Another molecular hallmark of HF is the upregulation of Ca^{2+}/calmodulin dependent kinase II (CaMKII) [78], which leads to increased Ca^{2+} leak from the sarcoplasmic reticulum, resulting in contractile dysfunction [79]. Empagliflozin has been shown to mitigate this CaMKII-mediated Ca^{2+} leak from the sarcoplasmic reticulum in mouse and human cardiomyocytes [80]. CaMKII has also been implicated in pathways of myocardial hypertrophy, dilation, and cell death [81], which may offer another method of SGLT2i-mediated cardioprotection.

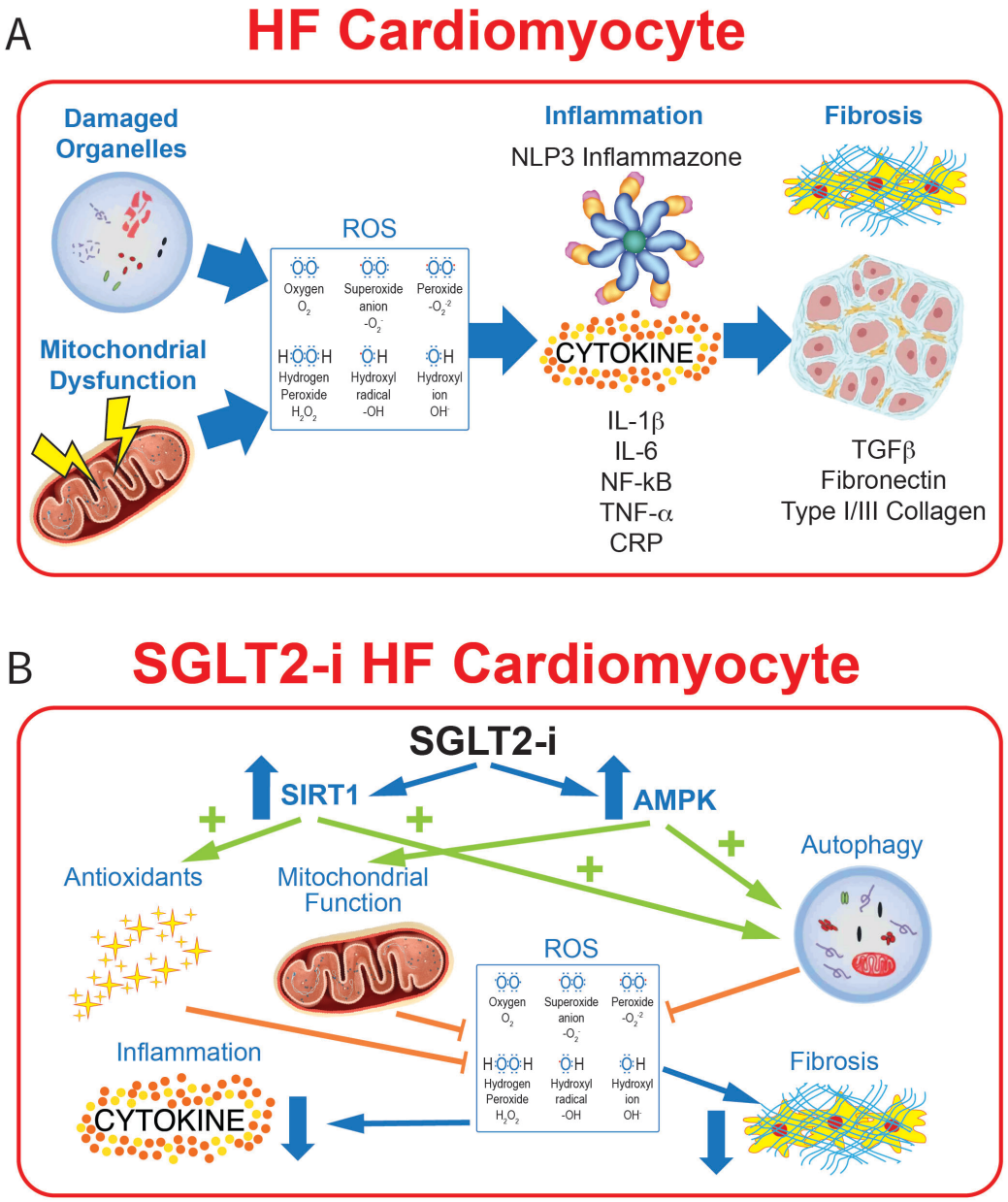

Fig. 5. SGLT2i and Inflammatory Cascade in Heart Failure. (A) Heart failure is characterized by mitochondrial dysfunction, diminished autophagic flux, and generation of reactive oxygen species, resulting in an inflammatory and fibrotic cascade. (B) SGLT2i activates SIRT1, which has antioxidant activity, and AMPK, which improved mitochondrial function. Both SIRT1 and AMPK promote autophagy, which also reduces inflammation (IL-1β, interleukin 1 beta; IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha; CRP, c-reactive peptide; TGFβ, tumor growth factor beta; ROS, reactive oxygen species; SIRT1, sirtuin 1; AMPK, adenosine monophosphate-activated protein kinase).

6.1.4 Improved cardiac bioenergetics

In a healthy adult heart, the myocardium relies primarily on the mitochondrial oxidation of free fatty acids and to a lesser degree on the oxidation of glucose [82]. In contrast, the failing heart shifts towards ketone production as a preferred method of energy production [82, 83]. This has been theorized as an adaptive shift due to enhanced metabolic efficiency and energy production when ketones are used as the primary cardiac fuel [84, 85]. SGLT2i have been shown to trigger a fasting-like state with increased fatty acid oxidation and ketogenesis [84]. Thus, it has been suggested that SGLT2i mediate their cardiac benefit by promoting more efficient bioenergetics [86, 87]. In addition, in a non-diabetic ischemic HF pig model, empagliflozin reduced adverse cardiac remodeling and also induced a shift from glucose as a myocardial substrate to ketone bodies, fatty acids, and branched-chain amino acids [88], though it was not proven whether the substrate shift was the cause of benefit or a coincident biomarker. Finally,

infusion of beta-hydroxybutyrate in chronic HF patients has been shown to improve cardiac output and EF [89].

Others have argued against the theory of improved bioenergetics as the mechanism of cardiac benefit. For example, the elevation of ketones induced by SGLT2i is modest, especially in non-diabetic patients [17] and yet the presence of DMII in HF has not modified the CV outcomes of these drugs. Others have noted that the failing heart already uses ketones as fuel, that SGLT2i have not consistently increased ketone body consumption in experimental setting, and that enhanced ATP production in the setting of SGLT2i can be independent of ketone metabolism [57]. As such, further studies are needed to elucidate the importance of cardiac bioenergetics as a mediator of SGLT2i benefit.

6.2 Mechanisms of indirect cardiomyocyte benefit

6.2.1 Reduction in inflammation

In addition to the anti-inflammatory benefit of mitigating oxidative stress, SGLT2i have demonstrated attenuation of a multitude of other inflammatory pathways in mice and humans. These include reduction of the activation of the NLRP3/ASC inflammasome [90, 91], reduction in the deposition of cardiotoxic lipids [92], and reduction of a host of inflammatory mediators and cytokines, including interleukin-1β [93], interleukin-6 [68], nuclear factor-kappa B [94], tumor necrosis factor-α [92], and high-sensitivity CRP [95].

6.2.2 Reduction in epicardial and non-epicardial visceral adipose

Several SGLT2i have shown a reduction in epicardial adipose [96–99], a profoundly metabolically active tissue that secretes profibrotic and pro-inflammatory cytokines [100]. Epicardial adipose shares a common blood supply with the myocardium and is not separated from the myocardium by fascia [101]. As such, epicardial adipose can cause a direct negative paracrine effect on myocardium via pro-inflammatory mediators [101]. In addition, SGLT2i have demonstrated reduction in non-epicardial visceral adipose and subcutaneous adipose [102]. Furthermore, mouse models have shown that SGLT2i can reduce adipose-mediated inflammation by reducing the ratio of pro-inflammatory M-1 macrophages to anti-inflammatory M-2 macrophages [103, 104].

6.2.3 Augmented diuresis

A common hypothesis regarding the mechanism of SGLT2i in reducing HHF centers on an augmented diuretic effect secondary to glucosuria and natriuresis [105, 106]. SGLT2i lead to a ~300 mL/day increase in urinary output after 24 hours [107] with the increased urinary effect attenuated at 12 weeks [108]. Natriuresis has been attributed to the colocalization of SGLT2 and the sodium hydrogen exchanger-3 (NHE3) in the proximal tubule of the nephron with a resultant off-target inhibition of NHE3 [109]. One study suggests that the diuretic effect of SGLT2i may be even more robust when combined with loop diuretics [105]. Furthermore, the rise in hematocrit seen in SGLT2i trials has been the strongest variable associated with reduction in HHF and CV mortality [53, 54] – a laboratory effect that could plausibly be explained by volume depletion. Given the rapid onset of the SGLT2i diuretic effect, the early separation of curves for HHF in DAPA-HF and EMPEROR-REDUCED may also be explained by augmented diuresis [110]. The early improvement in KCCQ-CSS seen in EMPEROR-REDUCED [38] would also be temporally consistent with this physiology. Finally, an early separation of curves has now been replicated in EMPEROR-PRESERVED [46]. HFpEF patients have not typically responded to heart failure agents without a diuretic effect, offering further support for volume control as a potential mechanism to reduce HHF. Post-hoc analyses of interactions with loop diuretics and MRA's in this trial would be of interest.

Arguments against the importance of a diuretic effect also exist [56]. Firstly, the transient nature of SGLT2i-induced diuresis would not be consistent with a sustained reduction in HHF seen in clinical trials [56]. Secondly, although some small studies have shown a synergistic diuretic effect between SGLT2i and loop diuretics [105], such an effect has not been replicated in larger clinical trials [29, 111]. Furthermore, a secondary analysis of DAPA-HF demonstrated no difference in the primary composite outcome between loop diuretic subgroups, ranging from no use of loop diuretics to escalating doses [30]. Thirdly, in EMPA-RESPONSE-AHF [111], which examined empagliflozin in an acutely decompensated HFrEF population, empagliflozin failed to reduce an objective dyspnea score, which would not be consistent with a drug thought to provide efficacious decongestion. Finally, trials have failed to demonstrate an acute drop in NT-proBNP, which would be expected from a diuretic effect [112]. Taken altogether, compelling evidence for and against the importance of a diuretic effect in SGLT2i suggests the topic deserves further study.

6.2.4 Improvement of the cardiorenal axis

SGLT2i have demonstrated a striking effect on renal endpoints in clinical trials [22, 113]. Potential mechanisms of renal benefit include reduction of intraglomerular hypertension, reduction of oxidative stress and inflammation, and modulation of the sympathetic nervous system (SNS) [114]. There is a pivotal interplay between the heart and kidney with dysfunction of one organ leading to dysfunction of the other [115, 116]. A significant proportion of patients with HFrEF have concomitant renal dysfunction [117]. The importance of the cardiorenal axis in HFrEF may be emphasized by evidence that SGLT2i provide greater reductions in HHF for worsening degrees of renal function [28]. However, the results of EMPEROR-POOLED [46] suggest that the interplay between heart and kidney may differ in HFpEF.

6.2.5 Inhibition of the sympathetic nervous system

The aberrant behavior of the SNS and the mechanism of established pharmacotherapies in attenuating this response

Table 4. Clinical considerations for SGLT2i.

Clinical considerations	Approach
When to initiate	• Before hospital discharge for acute HF or in clinic for chronic HF, regardless of diabetic status
Renal function	• Empagliflozin: initiate above eGFR 20 mL/min/m^2 • Dapagliflozin: initiate above eGFR 25 mL/min/m^2 • Safe to continue dapagliflozin until HD if initiated above appropriate threshold (continuation of empagliflozin in same scenario pending FDA update of indications)
Adverse events	• Increased mycotic genital infections → counsel patients on signs/symptoms and encourage hygiene • Urinary tract infections → similar between placebo and drug arms of many trials, but increased in drug arm of EMPEROR-PRESERVED; encourage hygiene • Diabetic Ketoacidosis → counsel patients to hold medication if reduced PO intake in setting of illness or NPO order prior to major surgery

HF, heart failure; eGFR, estimated glomerular filtration rate; HD, hemodialysis; FDA, Food and Drug Administration; PO, per os; NPO, nil per os.

has led some to postulate that SGLT2i may act in a similar fashion. The lack of a rise in heart rate despite reductions in volume and blood pressure may suggest SNS inhibition [118]. Noradrenaline has been shown to increase the expression of SGLT2 in human kidney cells, suggesting a cross-talk between the SNS and SGLT2 [119]. Furthermore, use of dapagliflozin in a mouse model reduced the expression of tyrosine hydroxylase and noradrenaline in the kidney and heart, which are surrogates of the SNS [119]. In addition, chemical denervation of the SNS in a hypertensive, nondiabetic mouse model resulted in reduced expression of renal SGLT2 and concomitant improvements in blood pressure [120]. Finally, use of dapagliflozin in a mouse model reduced cardiac and renal tyrosine hydroxylase staining and noradrenaline content [120]. An editorial of the same study noted that improvements in tissue levels of SNS activation may be a "bystander response" secondary to improved hemodynamic and metabolic parameters and not causally related to cardiorenal benefit [121].

Conflicting laboratory data regarding SNS activation and SGLT2i also exist. A rat model suggested that treatment with empagliflozin did not significantly alter sympathetic activity [122]. In addition, a study in T2DM patients showed that SGLT2i led to increased activation of the RAAS system [123]. As such, the equipoise regarding the relationship between SGLT2i and the SNS indicate this interaction warrants further study.

7. Clinical Implementation of SGLT2i in heart failure

How should a clinician implement SGLT2i in a patient with HF? Here, we offer several considerations relating to initiation of this drug class, summarized in Table 4.

7.1 When to initiate an SGLT2i

In DAPA-HF, EMPEROR-REDUCED, and EMPEROR-PRESERVED, SGLT2i demonstrated benefit regardless of diabetic status. DAPA-HF and EMPEROR-REDUCED studied initiation of SGLT2i in chronic, ambulatory, compensated HFrEF patients while EMPEROR-PRESERVED studied SGLT2i in chronic, ambulatory compensated HFpEF patients. However, SOLOIST-WHF demonstrated that it is safe to initiate an SGLT2i in recently hospitalized acute HFrEF and HFpEF patients after clinical stabilization, leading some to argue for the early initiation of SGLT2i prior to discharge or shortly thereafter [110]. Furthermore, whereas SOLOIST-WHF assessed patients with acute HFrEF who had been clinically stabilized, EMPA-RESPONSE-AHF was a smaller trial that studied acute HFrEF patients still requiring intravenous loop diuretics. EMPA-RESPONSE-AHF showed that initiation of empagliflozin in this population was safe and improved a composite HF endpoint at 60 days. Taken together, the data suggest than an SGLT2i can be safely initiated in the clinic setting or the peri-hospitalization period.

There is less consensus and virtually no evidence regarding the order in which to initiate SGLT2i with respect to beta-blockers, angiotensin receptor neprilysin inhibitors (ARNI), and MRA in HFrEF. Certainly, the minimal effect on blood pressure (~3–5 mmHg reduction) [26] is less limiting compared to other HF agents. One review suggests that SGLT2i should be considered for earlier introduction relative to other agents owing to their ability to reduce HHF and protect against subsequent renal dysfunction, which could have beneficial effects on starting other agents such as mineralocorticoid antagonists [124]. Perhaps the most important point is that SGLT2i provide significant cardiac benefits to HFrEF patients irrespective of baseline HF therapy. As such, SGLT2i should be considered one of the cornerstones of HFrEF therapy and their initiation should be a priority for the HFrEF patient. In addition, given the paucity of therapeutic options in HFpEF, the results of EMPEROR-PRESERVED offer support for use of empagliflozin in this population.

7.2 Renal function

It is important to understand that use of an SGLT2i will result in an early decline in estimated glomerular filtrate rate (eGFR) of approximately 3–6 mL/min/1.73 m^2 and that this should not dissuade the clinician from continuing therapy

[125]. On the contrary, this is a nephroprotective class of medications [22, 113]. There will be partial recovery of the eGFR by week 12, and more importantly, the slope of the overall decline in eGFR will decrease thereafter [125]. The initial decline in eGFR will be more prominent in a patient with normal renal function compared to a patient with chronic kidney disease [126]. The mechanism of decrease in eGFR is a result of inhibition of sodium reabsorption in the proximal tubule, which leads to increased distal sodium delivery to the macula densa [89, 127]. This is sensed by the juxtaglomerular apparatus as an increase in effective circulating volume and increase in intraglomerular pressure, leading to signaling that causes afferent arterial vasoconstriction [89, 127]. Furthermore, data from multiple studies including real-world data and multiple definitions of acute kidney injury (AKI) have shown that SGLT2i actually reduce the risk of AKI [128].

Is there an eGFR threshold after which a clinician should not initiate an SGLT2i? There is no robust data to demonstrate harm (or benefit) of initiation in CKD V, but our practice is guided by the enrollment criteria of large clinical trials. Dapagliflozin has been studied in patients with eGFR as low as 25 mL/min/1.73 m^2 in DAPA-CKD and eGFR as low as 30 mL/min/1.73 m^2 in DAPA-HF while the exclusion criterion for EMPEROR-REDUCED and EMPEROR-PRESERVED was eGFR $<$20 mL/min/1.73 m^2. Furthermore, an important distinction is that it is safe to continue dapagliflozin if eGFR drops below 25 mL/min/1.73 m^2 so long as it was initiated above this threshold [129]. The medication should be stopped if the patient progresses to dialysis [129].

7.3 Adverse events

Several adverse events have been reported with SGLT2i. Increased genitourinary infections secondary to glucosuria have been a point of concern. Despite the theoretical risk, rates of urinary tract infections (UTI) have been similar been drug and placebo in several trials [60]. In EMPEROR-REDUCED, UTI's were similar in the empagliflozin and placebo arms (4.9% vs 4.5%, respectively). However, in EMPEROR-PRESERVED, uncomplicated UTI's were more common with empagliflozin (9.9 vs 8.1%) [45].

Mycotic genital infections, especially in women, occurred at a 4 to 8 times higher rates in drug arm across CANVAS, EMPA-REG, DECLARE, and DAPA-HF [51]. However, they were rarely serious. Moreover, in EMPEROR-REDUCED, there was notable increase in overall genital infections (1.7% vs 0.6%) but rates of serious genital infections were similar (0.3% in each arm). Similarly, in EMPEROR-PRESERVED, there was an increase in uncomplicated genital infections (2.2% vs 0.7%), but comparable rates of complicated genital infections. Initial concerns about an increase in the rate of Fournier's gangrene with SGLT2i have not been replicated in more recent trials [51].

Volume depletion is another adverse event of interest with SGLT2i. In DAPA-HF, there was no significant difference in volume depletion in drug vs placebo arm (7.5% vs 6.8%, respectively; p = 0.4). EMPEROR-REDUCED also showed a similar amount of volume depletion in each arm. Furthermore, hypoglycemia is generally not an issue in this drug class, as glucosuria is attenuated in patients without hyperglycemia [130].

CANVAS demonstrated an increased risk of amputation, but this has not been reproduced in large trials of other SGLT2i. Finally, ketoacidosis, and specifically euglycemic ketoacidosis, has been reported as a potential adverse event. EMPEROR-REDUCED reported no cases in either arm while DAPA-HF reported 3 cases in the drug arm compared to 0 in the placebo arm. EMPEROR-PRESERVED reported a similar number of cases in both arms. Factors predisposing to ketoacidosis are related to decreased PO intake in the setting of illness or NPO order prior to major surgery. For this reason, the FDA advises holding SGLT2i 3 days prior to surgery, especially in cases in which resumption of regular PO intake is not expected to occur soon after the procedure [129].

8. Guidelines

In January 2021, the American College of Cardiology released the 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment, which classifies SGLT2-i as a Class I Therapy [131]. In patients with HFrEF Stage C, the document recommends first initiating either an ACEi/ARB/ARNI or a beta-blocker, in any order. After this, both an MRA and an SGLT2i can be considered. Specifically, SGLT2i are recommended for patients with NYHA II–IV symptoms and those meeting eGFR criteria, which are $\geq$30 mL/min/1.73 m^2 and $\geq$20 mL/min/1.73 m^2 for dapagliflozin and empagliflozin, respectively. The document does not endorse the use of other agents in this class.

In August 2021, the European Society of Cardiology released Guidelines for the diagnosis and treatment of acute and chronic heart failure, which classified dapagliflozin and empagliflozin as a Class I, Level of Evidence A therapy for HFrEF patients (EF $\leq$40% and NYHA II–IV symptoms) who are already on ACE-I/ARNI, beta-blocker, and MRA for reduction in the risk of cardiovascular death or worsening heart failure [132].

9. Conclusions

SGLT2i have been a serendipitous addition to the heart failure armamentarium. Multiple large randomized controlled trials have demonstrated that this class of medications is safe and efficacious at reducing HHF and cardiovascular mortality in symptomatic HFrEF patients, regardless of glycemic status, and can be initiated in an acute or chronic heart failure setting. There also appears to be a role for the use of SGLT2i in reducing HHF in HFpEF patients. The cardioprotective mechanism of action, specifically in HFrEF, remains a topic of continued debate and research. Heart failure

specialists and other cardiologists, as well as nephrologists, diabetologists, and primary care physicians should familiarize themselves with the use of these medications, including expected physiologic and laboratory changes and potential adverse events. The future is exciting for SGLT2i with several more trials underway.

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TD—Writing – Original Draft; TG—Writing – Review & Editing.

Ethics approval and consent to participate

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Conflict of interest

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