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Review Article

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Sodium-glucose Co-transporters-2 Inhibitors and Heart Failure: State of the Art Review and Future Potentials

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ABSTRACT

Heart failure (HF) and type 2 diabetes mellitus (T2DM) are progressive chronic diseases that increase the risk of mortality and have worse outcomes when they coexist. There has been a paucity of data on effective therapeutic measures that reduce the risk of HF in patients with T2DM. However, the issuance of the Food and Drug Administration guidance in 2008 generated data on several antihyperglycemic agents that show cardiovascular (CV) benefits beyond glucose lowering. Among them, sodium-glucose co-transporter 2 (SGLT2) inhibitors have emerged as a class of drug with proven robust benefits in modulating HF and kidney diseases in patients with T2DM. In this article, we reviewed the epidemiology, pathophysiology, prognosis, lifestyle management, and therapeutic options, especially SGLT2 inhibitors, for HF and T2DM.

Keywords: Type 2 diabetes; SGLT2 inhibitors; Heart failure; Antihyperglycemic agents

INTRODUCTION

Heart failure (HF) is a complex syndrome characterized by a chronic progressive condition in which the heart fails to supply adequate blood flow to meet the body's demand. Globally, approximately 26 million people are estimated to have HF, and its prevalence is increasing, with the aging population and due to changes in lifestyle.[1] Although much advances have been made in the field of HF therapies, the prognosis of HF remains poor, particularly when type 2 diabetes mellitus (T2DM) and HF coexist. Studies suggest that T2DM and HF are independently associated with cardiovascular (CV) death and subsequent hospitalization for HF (HHF).[2][3]

In this review article, we have summarized the updated evidence on T2DM and HF with a specific focus on the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors.

PATHOPHYSIOLOGY OF T2DM AND HF

The pathophysiology of HF in patients with T2DM is complex. Patients with T2DM often have traditional risk factors associated with coronary heart disease such as hypertension,

dyslipidemia, and obesity. However, these risks alone do not fully explain the increased risk of HF observed among patients with diabetes. In 1972, Rubler et al.[4] first introduced the term "diabetic cardiomyopathy" from a small sample size postmortem finding in patients with T2DM, which was characterized by cardiomegaly in absence of ischemic heart disease. Although this term is controversial and the underlying mechanism remains to be elucidated, hyperglycemia is associated with the formation of advanced glycation end products (AGE), increased free radicals, increased vascular inflammation, and activation of transforming growth factor-beta. These molecular changes can lead to cardiac structural changes such as increased fibrosis, left ventricular (LV) hypertrophy, myocardial stiffness, and diastolic dysfunction.[5][6]

In addition, increased oxidative stress and chronic inflammation are known to cause microvasculopathy through the AGE-receptor for AGE (RAGE) axis.[7][8] AGE/RAGE alters intracellular signaling, atherogenesis related gene expression, release of free radicals, and pro-inflammatory cytokines including interleukin (IL)-1, IL-6 and tumor necrosis factor-alpha, which leads to endothelial dysfunction and vascular inflammation in humans and evokes atherosclerotic diseases (**Figure 1**). Further, hyperglycemia and AGE/RAGE cause extracellular matrix degradation which promotes increased LV diastolic stiffness and overall poor prognosis.[9]

PHARMACOLOGICAL TREATMENT

For decades, HF has been the center of the controversies for antihyperglycemic agents. Studies show that 1% increase in hemoglobin A1c (HbA1c) is associated with an 8–15% increased risk of HF, however importantly, intensive glycemic control does not lower incidents of HF.[10][11] Indeed, a meta-analysis of data from 37,229 patients found increased risk of HF with the intensive glycemic control compared to the standard treatment group (odds ratio, 1.20; 95% confidence interval [CI], 0.96–1.48).[12]

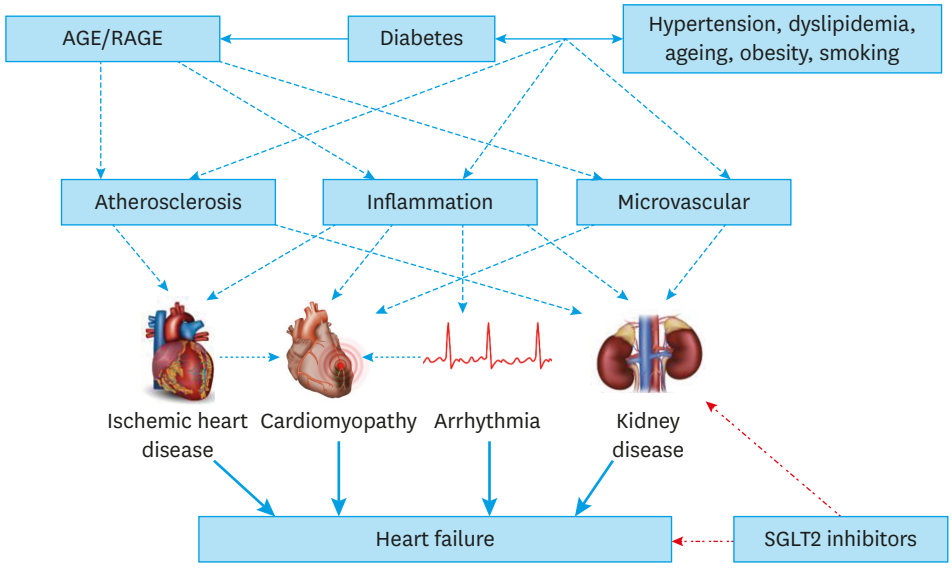

Figure 1. Mechanisms of heart failure and the role of SGLT2 inhibitors in patients with diabetes. SGLT2 inhibitors reduces heart failure and are renoprotective.
SGLT2 = sodium-glucose co-transporter 2; AGE = advanced glycation end products; RAGE = receptor of advanced glycation end products.

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Thiazolidinediones increase the risk for peripheral edema and new or worsening HF which led to the changes in product labels to warn against their use in patients with HF.[13] A dipeptidyl reptidase 4 (DPP-4) inhibitor, saxagliptin, was found to increase HHF compared to placebo, in the SAVOR-TIMI 53 trial (hazard ratio [HR], 1.27; 95% CI, 1.07–1.51). Similar results were obtained for another DPP-4 inhibitor, alogliptin, which showed signal toward increased HHF risk in the EXAMINE trial (HR, 1.19; 95% CI, 0.89–1.58).[14] Although the underlying mechanism is not fully understood, the Food and Drug Administration has added a warning associated with HF on the labels of DPP-4 inhibitors.[15]

SGLT2 inhibitors

SGLT2 inhibitors have demonstrated unprecedented benefits in patients with T2DM, reducing HHF. There are 3 cardiovascular outcome trials (CVOTs) completed to date (**Table 1**), each showing robust reduction in HHF with SGLT2 inhibitors administration.

The first completed SGLT2 inhibitor CVOT was the EMPA-REG OUTCOME trial. The study enrolled 7,020 patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD), and were followed up for 3.1 years. The trial demonstrated a significant 14% reduction in the primary composite outcome of CV death, non-fatal myocardial infarction (MI), and non-fatal stroke (HR, 0.86; 95% CI, 0.74–0.99) primarily driven by a 38% reduction in CV death (HR, 0.62; 95% CI, 0.49–0.77). Empagliflozin had a neutral effect on MI or stroke, and thus a CV mortality reduction in the empagliflozin group is thought to be largely due to a reduction in HHF (HR, 0.65; 95% CI, 0.50–0.85).[16]

Empagliflozin became the first drug to demonstrate beneficial effects in high CV risk patients with T2DM, while 2 additional SGLT2 inhibitors, canagliflozin and dapagliflozin, confirmed the benefit of SGLT2 inhibitors on HF in the CANVAS PROGRAM and DECLARE-TIMI 58 trial. Canagliflozin reduced the composite of HHF or CV death by 22% (HR, 0.78; 95% CI, 0.67–0.91), and dapagliflozin by 17% (HR, 0.83; 95% CI, 0.73–0.95) (**Table 1**).[16-19] Importantly, these trials included patients with and without established ASCVD. This benefit was observed in a broad population regardless of prior HF, established ASCVD, ejection fraction (EF), or kidney function.[19][20]

Table 1. Summary of SGLT2 inhibitor trials

Trials	EMPA-REG OUTCOME	CANVAS PROGRAM	DECLARE-TIMI 58	CREDENCE	DAPA-HF
Types of trial	Cardiovascular Outcome Trials	Cardiovascular Outcome Trials	Cardiovascular Outcome Trials	Renal Outcome Trial	HF Outcome Trial
Intervention	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Dapagliflozin
Number	7,020	10,142	17,160	4,401	4,744
ASCVD	6,978 (99.4)	6,656 (65.6)	6,974 (40.6)	2,220 (50.1)	NA
Median follow-up (years)	3.1	2.4	4.2	2.6	1.5
History of HF	706 (10.1)	1,461 (14.4)	1,724 (10)	652 (14.8)	2,251 (47.4)
eGFR <60 mL/min/1.73 m^2	1,819 (25.9)	2,039 (20.1)	1,265 (7.4)	2,592 (58.9)	1,926 (40.6)
Endpoints					
MACE	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.93 (0.84–1.03)	0.80 (0.67–0.95)	NA
CV death	0.62 (0.49–0.77)	0.90 (0.71–1.15)	0.98 (0.82– 1.17)	0.78 (0.61–1.00)	0.82 (0.69–0.98)
MI	0.87 (0.70–1.09)	0.85 (0.69–1.05)	0.89 (0.77–1.01)	0.86 (0.61–1.16)	NA
Stroke	1.18 (0.89–1.56)	0.90 (0.71–1.15)	1.01 (0.84–1.21)	0.77 (0.55–1.08)	NA
HF*	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.73 (0.61–0.88)	0.69 (0.57–0.83)	0.75 (0.65–0.85)
All death	0.68 (0.57–0.82)	0.87 (0.74–1.01)	0.93 (0.82–1.04)	0.83 (0.68–1.02)	0.83 (0.71–0.93)
Kidney endpoints	0.54 (0.40–0.75)	0.60 (0.47–0.77)	0.53 (0.43–0.66)	0.70 (0.59–0.82)	0.71 (0.44–1.16)

Values are presented as number (%).
SGLT2 = sodium-glucose co-transporter 2; ASCVD = atherosclerotic cardiovascular disease; HF = heart failure; eGFR = estimated glomerular filtration rate; MACE = major adverse cardiac events; CV = cardiovascular; MI = myocardial infarction.
*Hospitalization for HF or the composite of hospitalization for HF or cardiovascular death.

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Notably, the magnitude of the effect was greater in high risk patients including patients with lower estimated glomerular filtration rate (eGFR) or lower EF, which likely reflects a higher incidence rate of HF. HHF was reduced by 33% in patients with eGFR <60 mL/min/1.73 m^2 (HR, 0.67; 95% CI, 0.51–0.89) and by 55% in patients with EF <30% (HR, 0.45; 95% CI, 0.23–0.87). These results can help in identifying patients in whom the magnitude of in whom SGLT2 inhibitors may be strongly considered when prescribing antihyperglycemic agents.[19][20]

SGLT2 inhibitor in heart failure with reduced ejection fraction (HFrEF) patients

Since SGLT2 inhibitors possess a diuretic effect, there has been some safety concerns over their use in patients with HFrEF, as management of fluid balance is crucial in these patients. The DAPA-HF trial is the first HF outcome trial that enrolled patients with HFrEF. The trial was designed to compare dapagliflozin to placebo for the outcomes of CV death, HF, and urgent HF-related hospital visits. HFrEF was defined as patient with EF <40% and elevated N-terminal-pro b-type natriuretic peptide. The uniqueness of the trial was that out of 4,744 patients enrolled, 2,607 were non-T2DM patients. Of these, 1,750 (36.9%) had pre-diabetes and 857 (18%) had normal HbA1c. Overall, dapagliflozin significantly reduced the composite of CV death, HHF, and urgent HF visits by 26% (HR, 0.74; 95% CI, 0.65–0.85).[21] Although dapagliflozin showed compelling treatment effects, one of the limitations of the trial was the relatively short follow-up (median follow-up of 18.2 months). Since HF is a chronic and progressive disease, data from a longer trial are necessary to confirm the safety and efficacy of the drug clinically. The DECLARE-TIMI 58 enrolled patients with or at risk of ASCVD, and followed the trial period for a median of 4.5 years. In the prespecified sub-analysis, HFrEF was defined as patients with EF <45%. In 671 patients with HFrEF, dapagliflozin reduced CV death/HHF by 38% (HR, 0.62; 95% CI, 0.45–0.86) and CV death by 45% (HR, 0.55; 95% CI, 0.34–0.90). Importantly, these were achieved on top of evidence-based medication, and without increasing any safety concerns such as those including hypovolemia, hypotension, and acute kidney failure.[20] Although the nature of sub-analysis is hypothesis generating, it is worth noting that the results were consistent to those of DAPA-HF (**Figure 2**). Of note, the target population for DAPA-HF was patients with HFrEF with or without T2DM whereas the DECLARE-TIMI 58 trial consisted of patients with type 2 diabetes with established CV disease

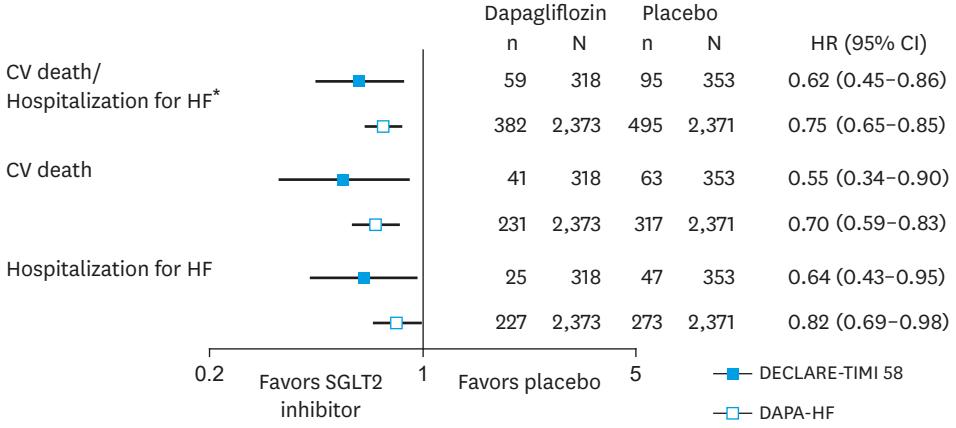

Figure 2. Comparison between DAPA-HF and DECLARE-TIMI 58 subgroup analysis. The target population of DAPA-HF and DECLARE-TIMI 58 are different, however, resulted in similar reduction of cardiovascular death, hospitalization for heart failure, or its components.
SGLT2 = sodium-glucose co-transporter 2; HF = heart failure; HR = hazard ratio; CI = confidence interval; CV = cardiovascular.
*DAPA-HF includes urgent HF visit.

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or at high risk of CV disease. Despite differences in patient characteristics, both trials showed an early treatment effect with dapagliflozin that extended throughout the follow up period, suggesting a presence of benefit in broad phenotype of patients with HFrEF.

SGLT2 inhibitor in heart failure with preserved ejection fraction (HFpEF) patients

An important unanswered question relates to whether the observed benefits of SGLT2 inhibitors is present in patients with HFpEF. To date, there has not been a drug that effectively reduces CV events in patients with HFpEF, and therapeutic evidence for patients with DM and HFpEF is lacking. The angiotensin receptor blockers (ARB), candesartan and irbesartan, did not reduce HF in the CHARM-preserved trial or I-preserved trial (HR, 0.85; 95% CI, 0.72–1.01 and HR, 0.95; 95% CI, 0.81–1.10, respectively).[22)23)] Sacubitril/valsartan (ARNI) was studied in the PARAGON-HF trial; however, the rate of HHF and CV death were not significantly different from that of placebo (HR, 0.87; 95% CI, 0.75–1.01), with no effect on mortality rates.[24)]

Currently, there are limited data for SGLT2 inhibitors. In each of the SGLT2 inhibitor CVOTs, approximately 10–15% of patients had a history of HF (**Table 1**), and when the data were meta-analyzed, patients with a history of HF had relatively similar risk reductions, compared to those without a history of HF.[19)] In the sub-analysis of the DELARE-TIMI 58 trial, patients with HFpEF (history of HF and EF ≥45%) had a lower rate of HHF compared to those treated with placebo (HR, 0.79; 95% CI, 0.56–1.13). Although not statistically significant, the wide CIs suggest that the data may be underpowered. Indeed, point estimates for those with HFrEF, with HFpEF, and no HF were similar, which may be indicative of the benefits of dapagliflozin being consistent, regardless of HF phenotypes (**Figure 3**). There are 2 ongoing SGLT2 inhibitor trials designed to investigate the safety and efficacy of SGLT2 inhibitors in HFpEF patients. EMPEROR-PRESEVED randomized 4,126 HFpEF patients to empagliflozin or placebo (NCT03057951), and DELIVER randomized 4,700 patients to dapagliflozin or placebo (NCT01297257); both are expected to be completed in 2020–2021.

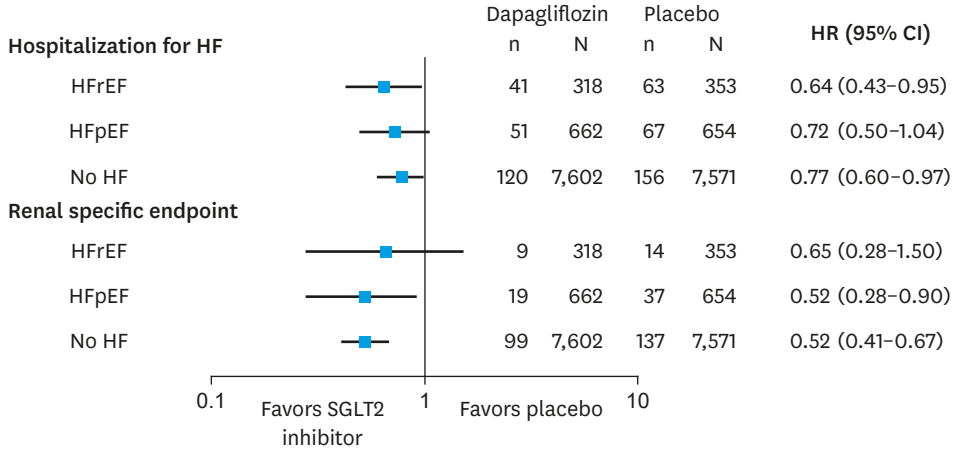

Figure 3. Outcomes based on different heart failure phenotypes. HFrEF: patients with EF <45%, HFpEF: patients with history of HF and EF ≥45%, no HF: patients without history of HF and EF ≥45% or unknown. Renal specific endpoint: worsening of kidney function, progression to end-stage kidney disease, or kidney-related death.
HFrEF = heart failure with reduced ejection fraction; EF = ejection fraction; HFpEF = heart failure with preserved ejection fraction; HF = heart failure; HR = hazard ratio; CI = confidence interval; SGLT2 = sodium-glucose co-transporter 2.

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Identifying patients with T2DM who are at risk of HF

Risk scores and biomarkers are useful tools to identify patients who are at risk of HF. Investigators from the EMPA-REG OUTCOME trials used the Health Aging, and Body Composition (ABC) HF risk score, to test whether the risk score is useful in patients with T2DM. The Health ABC HF risk score is a validated score used to estimate a 5-year risk for HF by incorporating age, coronary artery disease, systolic blood pressure, heart rate, LV hypertrophy, smoking, serum albumin, fasting blood glucose, and creatinine into a risk prediction model. A predicted 5-year HF risk is >20% in patients with ABC risk score ≥10; however, treatment with SGLT2 inhibitor was shown to reduce HF risk by 45% in this high risk cohort (HR, 0.55; 95% CI, 0.30–1.00).[25]

Recently, a simple HF risk calculation score has been developed using SAVOR-TIMI 53.[26] It includes 5 clinical variables namely, prior HF, history of atrial fibrillation, coronary artery disease, eGFR, and urine albumin-to-creatinine ratio. This risk score has been well validated in the DECLARE-TIMI 58, and has demonstrated that patients with higher baseline risk can benefit more with a greater absolute risk reduction of HF, with the use of SGLT2 inhibitors.

CARDIORENAL PROTECTIVE MECHANISM OF SGLT2 INHIBITORS

The mechanisms of action of SGLT2 inhibitors in reducing HHF are not fully understood. However, given the small difference in achieved HbA1c between the placebo and active comparator groups, the benefit of cardiorenal effects is thought to be independent of HbA1c reduction.[27]

SGLT2 inhibitors block the SGLT2 transporter in the proximal renal tubule, thereby increasing urinary excretion of glucose and sodium that results in calorie loss, reduction in body weight and blood pressure, and improves ventricular preload condition.[28] In each of the CVOTs, treatment with SGLT2 inhibitors led to modest reductions in systolic blood pressure (2–5 mmHg), diastolic blood pressure (0.5–1.0 mmHg), and body weight (2–3 kg), as compared to placebo.[16][17][29] However, previous data suggest that the individual component effects may not be enough to explain the robust 30% reduction in HHF observed with the use of SGLT2 inhibitors. Although the diuretic effect is thought to be the most evident cardioprotective mechanism for SGLT2 inhibitors, previous studies have shown that diuretic agents improve symptoms but not prognosis. In addition, in the CVOTs, SGLT2 inhibitors reduced the risk of HHF regardless of diuretic use.[20] Furthermore, previous meta-analysis showed that HF risk was reduced by 38% with 10 mmHg reduction in systolic blood pressure, which does not fully explain the magnitude of benefits observed with smaller blood pressure changes in patients treated with SGLT2 inhibitors.[30] In addition, every 1 kg/m^2 increase in body mass index is associated with a 5–7% increase in HF risk, and trials for diet drugs have failed to show HF reduction.[31] Indeed, in the CAMELIA trial, patients treated with the weight-loss drug, lorcaserin, had approximately 2.8 kg weight reduction. However, the rate of HHF in the lorcaserin group was similar to the placebo group (HR, 0.99; 95% CI, 0.85–1.14).[32]

Some additional proposed mechanisms include improvement in arterial stiffness, plasma uric acid levels, inflammatory epicardial adipose tissue, renally mediated attenuation of renin-angiotensin-aldosterone system stimulation and sympathetic nervous system activity, anti-fibrotic effects by suppressing collagen synthesis, and red blood cell mass expansion

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augmenting oxygen delivery capacity to tissue.[28)33)] These mechanisms are under intensive investigation and are discussed elsewhere.

Renoprotective benefits of SGLT2 inhibitors

Management of HF in patients with concomitant T2DM and chronic kidney disease can be particularly challenging. The kidney has a complex interplay with the heart and is a key player in the pathophysiology of HF. Of all the available antihyperglycemic therapies, SGLT2 inhibitors have shown robust renoprotective benefit in a broad range of population. In the CVOTs, treatment with SGLT2 inhibitors reduced the composite of worsening of kidney function, progression to end-stage kidney disease (ESKD), or kidney-related death by 45% (HR, 0.55; 95% CI, 0.48–0.64).[19)] These benefits were observed in a broad range of population including patients with or without established ASCVD, across all baseline eGFR levels, and even in patients with HFpEF in whom no drugs have ever shown any renoprotective benefit (**Figure 1**).[19)20)] The magnitude of the benefit, however, was greatest in the patients with high eGFR levels, with a 56% reduction in patients with eGFR >90 mL/min/1.73 m^2.[19)]

The CREDENCE trial is the first randomized trial that tested the effects of SGLT2 inhibitors on kidney-related outcomes.[34)] A total of 4,401 patients with diabetes and chronic kidney disease (30< eGFR <90 mL/min/1.73 m^2) who were on angiotensin-converting enzyme (ACE) inhibitor or ARB were randomly assigned to treatment with 100 mg canagliflozin daily or placebo to compare the synergistic effects on ESKD, sustained doubling of baseline serum creatinine, kidney-related death, or CV-related death. Overall, canagliflozin reduced the incidence of primary outcomes by 30% (HR, 0.70; 95% CI, 0.59–0.82).

A range of mechanisms have been proposed for the renoprotective benefits of SGLT2 inhibitors. These include blood pressure lowering, improved inflammation, ischemia, endothelial function and aortic stiffness, reduction of intraglomerular pressure and hyperfiltration, and increases in glucagon levels. SGLT2 inhibitors increases sodium delivery to the macula densa that activates tubuloglomerular feedback, causes afferent arterial vasoconstriction, and reduces hyperfiltration, which may explain the initial drop in eGFR followed by a plateau over time.[35)] Of note, a similar eGFR transition is observed when patients with diabetes are administered ACE inhibitors and ARB; however, the underlying mechanism is different involving vasodilation of efferent arterioles.

Whether the renoprotective benefits with the SGLT2 inhibitors are present in patients with chronic kidney disease, without T2DM, is unknown. Previous animal studies have demonstrated that glomerular hyperfiltration is a pathophysiological mechanism for initiation and progression of renal diseases regardless of etiology. Therefore, it is plausible that SGLT2 inhibitors may slow down the progression of kidney disease or improve kidney disease outcomes in patients without T2DM by improving glomerular hyperfiltration.[36)] The ongoing kidney outcome trials, EMPA-KIDNEY and DAPA-CKD, in patients with or without T2DM will provide further evidence on the potential role of SGLT2 inhibitors in reducing the risk of development or progression of kidney diseases in patients without T2DM (NCT03594110 and NCT03036150).

Adenosine triphosphate (ATP) synthesis

There has been a growing attention to the hypothesis of ketone and Na^+/H^+ exchanger (NHE) inhibition for reducing HHF with the use of SGLT2 inhibitor. Because of impaired glucose utilization, there is an excess use of free acid in the heart which leads to abnormalities in

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energy metabolism and lipid accumulation in cardiomyocytes.[37] SGLT2 inhibitors have been demonstrated to increase ketone synthesis that may result in an improved mitochondrial function presenting more energy-efficient fuel for the heart compared to glucose, which may overall improve cardiac function.[37][38] However, whether the slight increase in ketone levels would result in overall improvement in energy efficiency is still debated.

The other hypothesis is that the SGLT2 inhibitors inhibit NHE, representing direct cardiac effects by reducing cytosolic Na^+, cytosolic Ca^+, and increasing mitochondrial Ca^{2+} concentrations.[39] This hypothesis was generated from animal studies that showed inhibition of the myocardial NHE flux with empagliflozin treatment. Mitochondrial calcium activates ATP synthesis and antioxidant pathways, prevents sudden death, and overt HF in animal models. However, it is unclear whether the SGLT2 inhibitors have direct effects on cardiomyocytes since SGLT2 is not expressed in the cardiac tissue of humans. Of note, NHE3 is known to mediate tubular sodium reuptake. The expression of NHE3 is increased in HF; however, it has been reported that SGLT2 downregulates the activity of NHE3 in the proximal tubules.[40]

Although these results are interesting, more evidence is needed to support these hypotheses. Meanwhile, the robust cardiorenal benefit observed in CVOTs seems indirect and multifactorial. Studies such as the Steno 2 has shown a greater CV risk reduction with treatment involving interventions for multifactorial CV risk factors.[41] Since HF has a complex etiology affecting multiple organs, it may be conceivable that drugs with multiple underlying mechanisms of action may be more effective in reducing the risk of HF. Ongoing preclinical and clinical studies may shed light on the inter-organ relationships and multiple mechanistic pathways that mediate this disease.

LIFESTYLE MANAGEMENT

Although SGLT2 inhibitors have changed the landscape of T2DM pharmacological treatment, lifestyle management such as exercise, nutrition therapy, and smoking cessation should be fundamental to the care of patients with T2DM and HF comorbidity. The goals of treatment for T2DM are to prevent diabetes-associated complications and to improve the quality of life. To achieve this goal, it is important that diverse healthcare providers promote patients to become self-motivated and to act proactively in reducing CV risks by increasing self-efficacy and improving drug adherence.

CLINICAL IMPLICATIONS

The robust pharmacological benefits of SGLT2 inhibitors observed in the CVOT, has changed previous guidelines and yielded new options to improve the prognosis of patients with T2DM. The American College of Cardiology, American College of Cardiology Foundation (ACCF)/American Heart Association (AHA), and European Society of Cardiology/European Association for the Study of Diabetes have updated their consensus recommendations and guidelines to include consideration for the use of SGLT2 inhibitors in patients with established ASCVD.[42] Furthermore, the ACCF/AHA guideline recommends considerations for the use of an SGLT2 inhibitor as a primary preventative treatment for progression of HF and kidney diseases.[43]

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The unanswered questions are whether the cardiorenal benefits of SGLT2 inhibitors extend to patients with prediabetes or to those without a glucose metabolism disorder. Existing evidence suggests that individuals in the prediabetes stage are at an increased risk, and early intervention is of great importance to minimize treatment, prognostic, and monetary burdens of diabetes. Furthermore, the roles of SGLT2 inhibitors in patients with chronic kidney disease without diabetes, in patients with eGFR <30 mL/min/1.73 m^2, and in patients with HFpEF, are still under investigation. Finally, the efficacy and safety of SGLT2 inhibitors in acute HF is unknown. The ongoing SOLOIST-WHF is the only trial studying SGLT2 inhibitor in patients with acutely decompensated HF requiring hospitalization. This trial evaluates the therapeutic effects of dual SGLT 1/2 inhibitor sotagliflozin, as compared to placebo and is projected to finish in 2021 (NCT03521934).

CONCLUSION

SGLT2 inhibitors have emerged as powerful tools to prevent and reduce HF in a broad range of patient population with T2DM. Although the physiological mechanisms behind these observed benefits remain to be elucidated, trials have demonstrated that it is beyond HbA1c lowering effect. Trials in the targeted populations with clinically relevant outcomes are ongoing, with an interest in exploring the therapeutic potential of SGLT2 inhibitors in treating HF and kidney diseases.

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