

REVIEW

The metabolic model of heart failure: the role of sodium glucose co-transporter-2 (SGLT-2) inhibition

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Abstract

Heart failure (HF) is one of the leading causes of hospital readmissions and health care expenditures. With a vast degree of advancements in the clinical approach and diagnosis, its management protocol is limited in terms of enhancing quality of life and prognosis. Type 2 diabetes mellitus (T2DM) is considered as one of the commonly associated comorbid conditions in the HF population. The understanding of the molecular and metabolic models of HF has led to the utilization of therapeutic goals of T2DM in improving HF-related complications. In the recent era, SGLT-2 inhibitors have shown success in decreasing cardiovascular mortality

in the T2DM population. This article will help the reviewer to comprehend the pathophysiology of HF and the potential role of SGLT-2 inhibitors in the management algorithm of HF and its associated risk factors in T2DM.

Keywords: SGLT-2 inhibitors, heart failure.

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Introduction

Heart failure (HF) is a complex clinical syndrome caused by functional and structural impairment of ventricular ejection or filling of blood, resulting in insufficient perfusion to meet metabolic demands and requirements of the body.^{1,2} This syndrome most commonly results from dysfunction or loss of myocardial muscle, which leads to both circulatory and neurohormonal abnormalities.^{3,4}

Initially, digitalis and diuretics were considered the cornerstone therapy for HF.⁵⁻⁷ In the 1960s, the advancement in cardiac catheterization and cardiac surgery led to the cardiocirculatory or hemodynamic model of HF illustrating basic concepts in the management of congenital and valvular heart disease.^{7,8} Subsequently in the 1980s, foundation of the modern neurohumoral HF model was proposed, which eventually guided the current cardiology world to organize the management in view of optimum prognosis.⁷

Most recently, the progress brought by revascularization techniques (aortocoronary artery bypass grafting and percutaneous coronary intervention) in the improvement of HF prognosis has been halted by a rapid increase in the incidence of heterogenous variants of the HF syndrome such as

HF with preserved ejection fraction (HFpEF).^{8,9} Although there has been extensive literature on demographic/geographic variation and on diagnostic and prognostic evolution in HF guiding better outcomes, the therapeutic options still remain limited in mortality benefit since the last decade.^{1-3,10}

The medical community continues to seek new treatments that decrease mortality and hospitalization and at the same time improve the quality of life of patients living with HF. This manuscript reviews the evidence for HF treatment with sodium glucose co-transporter-2 (SGLT-2) inhibition.

Epidemiology

It is estimated that around 5.8 million Americans and 15 million Europeans are affected by HF – about one-half of the cases have HF with reduced ejection fraction (HFrEF) and the remaining one-half have preserved ejection fraction (HFpEF).¹¹ This figure is expected to rise to >8 million by 2030.¹² Approximately 23 million people worldwide are diagnosed with HF, and the incidence has grown higher over the past several years.¹² Of 870,000 index HF cases diagnosed in the United States each year, the incidence in males and females remains equal.¹³ It is considered to be the reason for 11 million

physician visits each year, and more hospitalizations than all forms of cancer combined.^{11–13} It is one of the leading causes of hospital admissions and is associated with high morbidity, mortality, and health care expenditure especially in the elderly population contributing to nearly 287,000 deaths annually worldwide.^{12,13} In patients over 65 years of age, one-fifth of all hospitalizations have a primary or secondary diagnosis of HF.¹³ More than one-half of those who develop HF will die within 5 years of diagnosis.¹¹ Due to alterations in the electrical conduction system, sudden cardiac death secondary to ventricular arrhythmias is common in patients with HF, rendering six to nine times a higher risk compared to the general population.¹³ In 2012, HF was listed as the cause of death in 60,341 persons in the United States, equivalent to an age-adjusted rate of 17.1 per 100,000 population.¹⁴

The cost of HF care is high and causes a significant burden on the United States health care system.^{1,11} With the assumption of continuation of present care practices, a marked increase in health care costs is imminent due to the longer survival and consequent increase in the aging population, as a result of the development and implementation of life-prolonging therapies.¹² Subsequently, this will ultimately lead to more patients at risk for the development of HF.

More specifically, the cost of HF management is projected to increase markedly; a 2.5-fold increase from US\$20.9 billion in 2012 to US\$53.1 billion by 2030.^{12,14} Of note, 80% of the costs are related to HF hospitalizations.¹² The total cost, including indirect costs, is estimated to increase from US\$31 billion in 2012 to US\$70 billion by 2030.^{12,14} The estimated average cost for patients with HF during the final 2 years of life is more than US\$156,000, and 75% of this cost is attributed to HF-related hospital admissions during the last 6 months of life.^{12–14}

Pathophysiology

To overcome the significant negative impact of HF on the community, a comprehensive and systematic management strategy is utilized with joint consensus among American cardiology and HF societies.^{1–3} Since the basic pathophysiology underlying HF syndrome is the activation of certain systems that trigger a neurohormonal cascade, the purpose of its treatment is to control symptomatology.

Initially, physicians viewed HF as a syndrome of excessive sodium and water retention. With advances in diagnostic testing including careful hemodynamic measurements, it became quite evident that HF was associated with a reduced cardiac output and excessive peripheral vasoconstriction. This latter realization led to the development of the cardiocirculatory or hemodynamic model for HF.¹ Unfortunately, therapeutic strategies of using positive inotropic or vasodilator agents targeting this model were unable to prevent the disease progression.² Currently, the focus is on the potential spectrum of mechanisms.

HF begins with an index event, which might be an underlying cardiomyopathy or an acute myocardial infarction. A decline

in the pumping capacity of the heart is the common feature regardless of the index event.^{1,2} Subsequently, compensatory mechanisms become activated including the renin–angiotensin–aldosterone and sympathetic nervous systems, which help to restore normal homeostasis.⁹ But, sustained activation of these mechanisms leads to worsening left ventricular (LV) remodeling and thus patients transition from asymptomatic to symptomatic HF.^{1–3}

Neurohormonal mechanisms

HF progresses as a result of the overexpression of biologically active molecules that are capable of exerting toxic effects on the circulation and heart.^{1,2} Autonomic stimulation and neurohormonal activation provide the counterregulatory support in the disease process, which plays a fundamental role in the development and progression of chronic HF.

Renin–angiotensin–aldosterone system

The first and foremost mechanism in the progression of HF stems from activation of the renin–angiotensin–aldosterone system (RAAS). Increased concentrations of plasma renin and angiotensin II act as potent vasoconstrictors which interact with renal efferent arterioles and the systemic circulation to activate sympathetic hormonal modulation. The final step in the RAAS pathway is the release of aldosterone, which leads to sodium and water retention as well as increased excretion of potassium. The effect of angiotensin II on cardiac myocytes may also contribute to the endothelial dysfunction observed in chronic HF.¹⁵

Sympathetic nervous system

To compensate for the metabolic requirement of the body in the setting of the failing heart, the sympathetic nervous system (SNS) becomes activated and generates a salvage mechanism for the body. It acts as an inotropic back-up for cardiac tissue to maintain hemodynamic support. With the passage of time, a persistently activated SNS exhausts the functional reserve of cardiac myocytes. This creates a vicious cycle by stimulating the RAAS pathway, sodium, and fluid retention thus contributing to disease progression. The excessive pressure and volume overload state with SNS overactivity culminates in cardiac myocyte hypertrophy, apoptosis, and focal myocardial necrosis.¹⁶

Natriuretic peptide system

Natriuretic peptides (NPs) exist in three different isoforms in the body based on the site of its secretion. Atrial NP (ANP) is released from the atria of the heart as a reflex to stretch, leading to natriuresis and vasodilatation. Brain NP (BNP) is released from the ventricles and functions in a similar pattern as ANP. C-type NP (CNP) is restricted to central nervous system and vascular endothelium having only limited effects on natriuresis and vasodilatation.

The ANP and BNP are the counterregulatory hormones to offset the deleterious effects of RAAS and SNS activation, avoiding fluid retention as well as promoting diuresis and natriuresis. These endogenous peptide hormones create a feedback mechanism to inhibit the increased vascular tone, elevated aldosterone function, and exaggerated renal salt handling mediated by angiotensin II and norepinephrine.¹⁷

Left ventricular remodeling

The term LV remodeling refers to the changes in LV chamber and volume unrelated to preload mediated increases in sarcomere length.⁷ LV remodeling is the process by which mechanical, neurohormonal, and possibly genetic factors alter ventricular geometry (shape and size) as well as function. LV remodeling occurs in several clinical conditions, including cardiomyopathy, hypertension, and valvular heart disease. Its hallmarks include hypertrophy, increased interstitial fibrosis, and myocyte loss.^{7,8}

Current guideline-directed medical therapy

HF stages and treatment options for HFrEF

Improvement in survival, slowing the progress of disease, and symptom alleviation are the primary goals of therapy in patients with HF. Lifestyle modification with exercise, moderation of alcohol intake, smoking cessation, and weight reduction are some of the key preventive measures.

Stage A: There is well-known evidence from randomized clinical trials that effective treatment of hypertension decreases the occurrence of LV hypertrophy as well as reducing the incidence of HF by 30–50%.^{9,10,18} The use of angiotensin-converting enzyme inhibitors (ACEIs) in high-risk patients with diabetes mellitus (DM) or vascular disease has shown significant reductions in the rates of death, myocardial infarction, and stroke.¹⁸ Furthermore, the use of angiotensin-receptor blockers (ARBs) have been shown to delay the first hospitalization for HF in patients with DM.^{14,15}

Stage B: Modulation of the RAAS with ACEIs has been shown to reduce the incidence of HF, to prolong survival and is therefore recommended for all patients with stage B HF.¹⁵

Stages C and D: Modulation of both the RAAS including mineralocorticoid antagonists (MRAs) and SNS have shown improvement in morbidity and mortality, rate of hospitalization, incidence of sudden cardiac death, quality of life, and are therefore recommended for all patients with stages C and D HF.^{18,19}

Neprilysin is a membrane-bound endopeptidase that degrades the NPs thereby preventing counteraction of the RAAS and SNS. Most recently, dual angiotensin-receptor neprilysin inhibition (ARNI) with sacubitril-valsartan has been

recommended for all patients in Stage C – New York Heart Association (NYHA) functional class II–III in lieu of an existing ACEI or ARB to further reduce morbidity and mortality. It has shown a beneficial effect in HF patients with improved blood pressure control, RAAS, and SNS inhibition as well as less volume retention.²⁰

Lastly, the combination of hydralazine and isosorbide dinitrate formulation in African-American patients functions to decrease afterload and preload as well as to improve cardiovascular hemodynamics by greater ejection and filling. It is hypothesized to have certain role in decreasing the burden of reactive oxygen species and regulating nitric oxide activation.²¹

Treatment options for HFpEF

HFpEF is considered as an entirely separate entity compared to HFrEF and shares nearly one-half of the cases of HF hospitalization. It is estimated that nearly one-third of the HFpEF patients die within 1 year of first hospital discharge and more than one-half of the cases die within 5 years.²² These alarming statistics demand further research studies that might guide a path to understand the disease process and management strategy to improve outcomes. HFpEF occurs in the setting of inadequate ventricular filling and relaxation leading to LV stiffness, fibrosis, and hence diastolic dysfunction.²³

Multicenter randomized clinical trials performed to-date have not shown a mortality benefit in the HFpEF population including treatment with RAAS and SNS modulators. However, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT) has suggested benefit with MRAs (spironolactone) in reducing HF hospitalization. However, there were regional differences in this finding, which generated controversy in the cardiology world. Currently, committees are unable to modify the recommendations for HFpEF thereby demanding more investigations.^{24,25}

The current recommendation regarding HFpEF treatment is to control the symptoms and medical comorbidities such as hypertension by using diuretics (either loop or thiazide) and to equilibrate the volume status. Care should be made in utilizing diuretics as this group of HF patients are volume sensitive and slight changes in volume status can lead to acute kidney injury.²³

Patients should be educated about a low-salt diet, as it plays a pivotal role in reducing HFpEF decompensation.

Most of the patients with HFpEF are heart rate dependent to enhance LV pumping. Although there is no suggestion about target heart rate in this cohort still one should be cautious in using heart rate controlling medications as abrupt changes in heart rate should be avoided.

The incidence of atrial fibrillation (AF) is seen more commonly in HFpEF patients with similar characteristics, outcomes, and therapeutics as HFrEF. Management of comorbid conditions is suggested to treat AF in this group.²⁶

The role of ARNI is still under evaluation for the HFpEF population.²⁷

Novel therapies in heart failure

Despite all the advances in HF management, the burden of disease and hospitalization rate is constant, requiring more options for its treatment.²⁸ Many clinical trials to devise novel molecules for the improvement of HF outcomes are ongoing. Natural peptides such as the guanylate cyclase stimulator, vericiguat, is under consideration to treat chronic HF. An endogenous peptide, vasoactive intestinal peptide (VIP) has shown some smooth muscle relaxant properties, which may help in the prevention of cardiac hypertrophy. Gene and stem-cell therapies for HF patients is another area of investigation though preliminary clinical data has not provided any beneficial conclusion.^{28,29} Finally, after the results of The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME) trial were published, SGLT-2 inhibitors are being extensively studied to identify the role of this class of drugs in HF hospitalization, disease progression, and quality of life, especially in patients with type 2 diabetes mellitus (T2DM) and HF.³⁰

SGLT inhibition

Historical background

The SGLT is a group of proteins on the cell surface of the intestine and renal tubules. The group consists of five subtypes, of which SGLT-2 is responsible for sodium-facilitated glucose reabsorption in the proximal convoluted tubule (PCT) of the kidney and serves a meaningful role in glucose hemostasis.^{30,31} In the early 1900s, a SGLT receptor inhibitor called phlorizin was derived from the bark of an apple tree and was further studied in 1933 for its pharmacological activity on human subjects. It was hypothesized that phlorizin functions to cause glycosuria, hypoglycemia, and a decrease in tissue glucose absorption. Owing to its side effects related to intestinal interference of glucose, it did not become popular until 1980 when National Institutes of Health (NIH)-supported researchers identified differential glucose transport in murine renal tubules that led to the discovery of its intestinal subtype. In 1995, phlorizin was further studied and noted to have a nonselective inhibitive property for SGLT-1 and SGLT-2 receptors.³² Further understanding about the role of the SGLT-2 receptor in T2DM was recognized in a condition called familial renal glucosuria in which gene coding of the SGLT-2 receptor becomes defected resulting in its reduced activity and increased urinary glucose excretion.³³ Later, more efforts were made to redesign a phlorizin derivative that might be SGLT-2 specific with fewer adverse effects. In 2013, the first SGLT-2 inhibitor was approved by the Food and Drug Administration (FDA) called canagliflozin, followed by dapagliflozin and empagliflozin that ultimately altered the treatment paradigm in the world of T2DM.^{34–38}

SGLT receptors in cardiac tissue

Data regarding the presence of SGLT receptors in cardiac tissue in the literature is limited.³⁹ In a Japanese study with a murine model describing the role of SGLT in cardiac tissue, it was reported that the SGLT-1 receptor, which is usually not abundantly found in the conventional metabolic state of the heart, becomes expressed in the setting of an ischemic event posing its cardioprotective effects.⁴⁰ This was elucidated by the fact that the SGLT-1 receptor plays an essential role in the anaerobic cycle and promotes the generation of an energy source in oxygen-deprived cardiac tissue. In the same series, it was demonstrated that with the use of phlorizin, the SGLT receptor becomes inhibited resulting in progression of the infarct size.^{40,41} Although this study summarized the role of the SGLT-1 receptor on cardiac tissue, still more knowledge is required in human models regarding functionality of SGLT-2 receptors on the cardiovascular system.^{42–44}

Role of the SGLT-2 receptor in heart failure

T2DM is a common comorbid condition prevalent in approximately 25–41% of the HF population with an incidence rate of 30 per 1000 person-years in the United States.⁴⁵ The reason for such a high occurrence of T2DM is attributed to the neurohormonal activation in HF patients along with insulin resistance in cardiac tissue. The utilization of SGLT-2 inhibitors for cardiovascular disease was first indicated by a landmark clinical trial (EMPA-REG OUTCOME) in 2015, designed to assess the cardiovascular safety of empagliflozin in the T2DM population.^{46,47} It demonstrated that subjects treated with empagliflozin had a significant reduction in death from cardiovascular causes and hospitalization for HF compared to placebo. The beneficial effect of empagliflozin was argued variably by the fact that this outcome might be secondary to sustained reduction of weight and glycosylated hemoglobin rather than its direct effect on cardiac tissue. Another hypothesis proposed in this regard was its facilitation in the uptake of ketone bodies by the starved cardiac muscle in combination with a natriuretic and glycosuric effect. In a *post hoc* analysis of the EMPA-REG OUTCOME trial, it was observed that empagliflozin had a consistent effect in reducing HF hospitalization or death from HF and was associated with a reduction in all-cause hospitalization.⁴⁸

The diuretic role of SGLT-2 inhibition has always been an area of great interest in the HF arena. In an editorial by McMurray, the author supported the rationale that empagliflozin mimics diuretics at the PCT level causing a decrease in sodium and water retention hence serving to decrease preload, pulmonary congestion, and peripheral edema.⁴⁹ By preventing LV preload and wall stress, this class of medication can ultimately help in reducing HF hospitalization and risk of ventricular arrhythmias. This theory was further supported by Heerspink and colleagues emphasizing the use of SGLT-2 inhibition in HF patients to reduce the furosemide dose, which may prevent acute kidney

injury.⁴⁸ It was postulated in several studies that, similar to mannitol, SGLT-2 inhibitors can aid in the sequential diuresis in addition to furosemide without causing renal failure or electrolyte abnormalities.^{49,50} This diuretic effect was observed less in chronic kidney disease due to alteration in the renal tubuloglomerular feedback mechanisms in such patients.^{49–53}

With further advancement in clinical data, SGLT-2 inhibition is considered as ‘beta-blockers’ in the kidneys.⁵⁴ It was proposed that similar to the effect of beta-adrenergic antagonists in the heart, it helps to improve renal perfusion, decrease glomerular pressure, enhance renal oxygen consumption and metabolic efficiency. Additionally, the fact that use of RAAS modulators along with SGLT-2 inhibitors in HF can have a synergistic effect at the glomerular level was not supported by many experts^{55–59} (Figure 1).

In 2017, another study was published describing the importance of SGLT-2 inhibition in cardiovascular disease – The Canagliflozin Cardiovascular Assessment Study (CANVAS). It concluded that canagliflozin reduced the primary composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, reduction in hospitalization for HF and lessened the rate of renal decline among high-risk T2DM patients. These results were shadowed by the concern that it increased the amputation risk (6.3 versus 3.4 cases per 1000 patient-years). Although the results of the CANVAS Trial reinforced the cardiovascular benefits of SGLT-2 inhibition, it also created a great deal of uncertainty regarding the safety of this class of medication necessitating further investigations.⁶⁰

The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) trial is a recently published international multicenter, observational cohort study

in subjects with T2DM. It evaluated the comparative effectiveness of initiating treatment with SGLT-2 inhibition versus another glucose-lowering drug. It showed an overall 39% lower risk of HF hospitalization, 51% reduction in total death, and 46% reduction in the composite of HF hospitalization or death. Although this is an observational study, the data is consistent with EMPA-REG OUTCOME and CANVAS trials.⁶¹

Role of SGLT-2 inhibition in hypertension

Nearly 60–80% of patients with T2DM in the United States suffer from hypertension concomitantly and approximately 25% of hypertensive patients have HF.⁶² Hypertension has a key impact in the pathophysiology of HF as it can lead to LV hypertrophy, diastolic, and systolic dysfunction which if remained untreated can progress to decompensated HF. In HF patients, this phenomenon is manifested by the impairment of renal sodium handling, RAAS and SNS alteration.⁶² Thus, the role of SGLT-2 inhibition in reducing blood pressure has been another area of focus and is explained by its diuretic, weight reducing, and antiglycemic properties.^{63–66} In patients with T2DM, reduction of systolic blood pressure up to 3 mmHg was observed in the empagliflozin arm of the EMPA-REG OUTCOME trial.^{46,47} This is further supported by a meta-analysis of 43 studies in which systolic blood pressure reduction was noted to be 4.5 mmHg with SGLT-2 inhibition.^{67,68} In a study by Kawasoe and colleagues, sustained blood pressure reduction was observed in 20 subjects at 1 month and 6 months attributed to plasma reduction by osmotic diuresis.⁶⁴ Similarly, Majewski and Bakris concluded that SGLT-2 inhibition may be utilized in the management of hypertension as an alternative antihypertensive agent to avoid the metabolic effects of diuretics in patients with T2DM.⁶⁵ Finally, the combination of blood pressure reduction along with natriuresis may have a role in subjects with a HF syndrome but it becomes debatable after Pfeifer and colleagues remarked that the antihypertensive effect of SGLT-2 inhibition might be blunted in patients with advanced HF.⁶⁹

Interaction of SGLT-2 inhibition with the SNS to reduce blood pressure is another mechanism illustrated in the literature. Sympathetic overactivation can lead to arterial stiffness and endothelial dysfunction, altering the renal sodium–water homeostasis and causing fluid retention. SGLT-2 inhibition serves to protect the heart and kidney by inhibiting renal SNS activity, which ultimately reduces the renal inflammatory and fibrotic response, resulting in improved blood pressure.^{67,70}

The role of SGLT2 inhibition and RAAS modulation is not completely understood and requires advanced clinical data. In animal models, it was observed that increased delivery of sodium to the juxtaglomerular apparatus can cause afferent arteriolar vasoconstriction resulting in a decrease in glomerular pressure. Instead, this mechanism is argued by the fact that due to volume depletion, it works to activate RAAS, which is an undesirable effect in HF patients.^{63,64,69–72}

Figure 1. SGLT-2 interaction with cardiac and renovascular system.

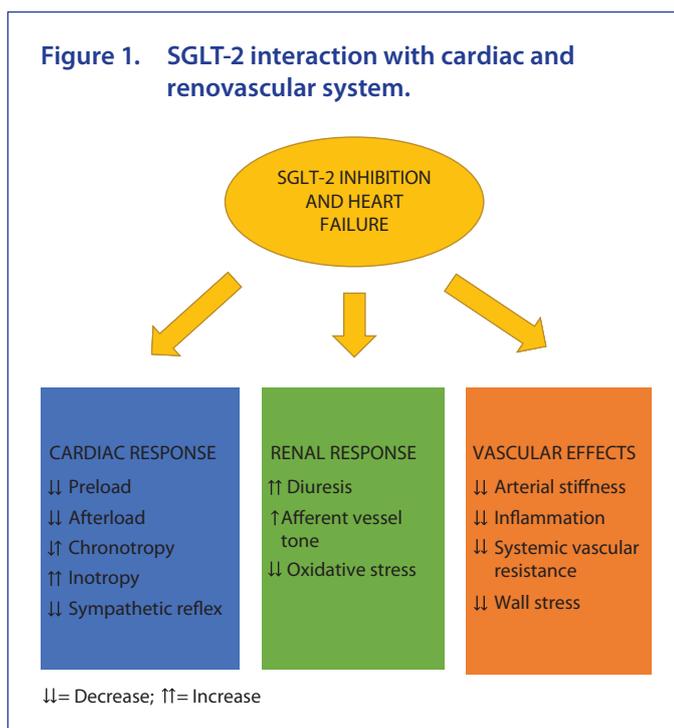


Table 1. Major studies on SGLT-2 inhibition and cardiovascular outcomes.

Study	Study design	Patient selection	Sample size	Therapeutic strategy	Outcomes	Results
EMPA-REG OUTCOME ⁴⁵ (2015)	Prospective Multicentric Double blind (42 countries) America, Europe, Australia, and Asia	T2DM patients with high CV risk	7020 Follow up: 3.01 years	Empagliflozin versus placebo	Reduction in cardiovascular death and heart failure hospitalization	35% reduction in hospitalization for heart failure 14% reduction in MACE 38% reduction in CV mortality
CANVAS ⁵⁹ (2017)	Prospective Multicentric Double blind (30 countries)	T2DM patients with high CV risk	10142 Follow up: 3.9 years	Canagliflozin versus placebo	Reduction in cardiovascular death renal decline and heart failure hospitalization	MACE: 26.9 versus 31.5 participants with an event per 1000 patient-years CV mortality: 11.6 versus 12.8 participants with an event per 1000 patient-years HF hospitalization: 5.5 versus 8.7 participants with event per 1000 patient-years
CVD-REAL ⁶⁰ (2018)	Observational cohort study Multicentric Six countries America, and Europe	T2DM patients with high CV risk	400,000	All SGLT-2 inhibitors versus other antidiabetic medications	Reduction in cardiovascular death renal decline and heart failure hospitalization	HF hospitalization 39% risk reduction 51% reduction in total death, and 46% reduction in the composite of heart failure hospitalization or death

T2DM, type 2 diabetes mellitus; CV, cardiovascular; HF, heart failure; SGLT-2, sodium glucose transporter-2; LV, left ventricle; MRI, magnetic resonance imaging, MACE, major adverse cardiac event.

Role of SGLT-2 inhibition as a vasodilator

Although the EMPA-REG OUTCOME trial has shown a reduction in HF hospitalization with empagliflozin use, the rate of nonfatal ischemic events was unchanged.^{70,71,73,74} On the other hand, increased risk of amputation and stroke with the use of canagliflozin marked a 'red flag' on its role in atherosclerosis and vascular remodeling.⁷² Subsequently, several studies have negated its association with stroke and attributed the events to volume depletion and hemoconcentration, but the fear of its safety prevailed among clinicians.^{75–77} To further elucidate this fact, the 'Effectiveness of dapagliflozin on vascular endothelial function and glycemic control in patients with early-stage type 2 diabetes mellitus' (DEFENCE) study recruited 80 subjects with T2DM and concluded that dapagliflozin additive therapy had shown improvement in flow-mediated vasodilation by a reduction in oxidative stress.⁷⁸ David Cherney, in his review, commented that improvement in arterial stiffness by SGLT-2 inhibition is independent of the nitric oxide pathway or RAAS modulation.⁷⁷ In fact, overall weight reduction, change in vascular endothelial sodium handling, and decreased inflammatory response mediated by SGLT-2 inhibition may be

the possible mechanism of improved vascular function. This area remains ambiguous and future studies are warranted to elaborate the vascular interaction of SGLT-2 inhibition in HF patients.^{70,71} Table 1 summarizes the major clinical studies of SGLT-2 inhibition and cardiovascular outcomes.

Future directions

SGLT-2 inhibition has clearly shown an ability to improve overall metabolic outcomes in patients with T2DM, but its status in the treatment of HF remains a matter of debate. It is imperative to investigate its role in the management of HF and cardiorenal syndromes. Currently, a randomized multicenter clinical trial to evaluate the effect of dapagliflozin on the incidence of cardiovascular events, Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI58) trial is ongoing with a goal of recruiting 17,276 participants worldwide. This trial will determine the role of dapagliflozin as additive therapy in subjects with T2DM with either established cardiovascular disease or cardiovascular risk factors. On the other hand, the EMPEROR-Preserved (Empagliflozin outcome trial in patients with chronic HF with preserved ejection fraction)

and EMPEROR-Reduced (Empagliflozin outcome trial in patients with chronic HF with reduced ejection fraction) trials will evaluate the role of empagliflozin in HFpEF and HFrEF, respectively. The Safety and Effectiveness of SGLT-2 Inhibitors in Patients with Heart Failure and Diabetes (REFORM) trial is being conducted to study the effectiveness of SGLT-2 inhibition in HF subjects with T2DM.⁷⁹ The Dapagliflozin Effect on Symptoms and Biomarkers in Patients with Heart Failure (DEFINE-HF) trial is designed to investigate the long-term impact of SGLT-2 inhibition on HF biomarkers, quality of life, and symptomatology.

Similarly, the Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE) trial aims to assess whether canagliflozin has a renal and vascular protective effect in reducing the progression of renal impairment relative to placebo in participants with T2DM, stages 2 or 3 chronic kidney disease and proteinuria, who are receiving standard of care including a maximum tolerated labeled daily dose of an ACEI or ARB.⁸⁰

Conclusion

HF is a heterogenous clinical syndrome with a wide variety of etiologies but with very similar pathophysiological mechanisms. There are many multicenter randomized clinical trials conducted in HFrEF targeting these mechanisms, which helped to create the current guidelines for the management of HFrEF with the aim of improving morbidity and mortality.

However, the pharmacological management of HFpEF remains challenging in part due to its complexity and lack of guideline directed medical therapy (GDMT), with the exception of the TOPCAT Trial.

The new challenge comes from ever-changing demographics, food habits, and increasing incidence of T2DM. T2DM is notoriously associated with an increased likelihood of atherosclerotic cardiovascular disease and certainly, individuals who have myocardial damage have decreased heart function and are at risk of developing HF. The direction should be to figure out how people developing T2DM should be treated going forward and which novel treatment targets are needed to ameliorate the high morbidity and mortality of HF. SGLT-2 inhibition may have a potential role in the algorithmic management of the acute HF syndrome, which is not completely understood. More data are required, to compare standard of care GDMT treatment with SGLT-2 inhibition, to identify its clinical indication, and to predict its effectiveness. Further studies are warranted to identify the target population and to recognize its importance in a specific subset of HF patients including those patients with T2DM. Lastly, another important area of investigation is the cardiorenal and metabolic impact of SGLT-2 inhibition in HF patients.

With the arrival of SGLT-2 inhibition into the HF world, it becomes very attractive to state that we might have new drugs to manage patients with coexisting T2DM and HF that are better than the current standard of care HF treatment though more data are required.

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