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A review on Sodium-glucose cotransporter-2 sglt2 inhibitors: A potential class of drug for treatment of heart failure with reduced ejection

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REVIEW

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ABSTRACT

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a type of per oral antihyperglycemic medicine. It works by reducing glucose reabsorption in the proximal renal tubules, resulting in increased urine glucose excretion by the human body, which, thereby proving useful in diabetes mellitus. They seem to have a cardiovascular benefit in addition to lowering glucose levels, with mechanisms including eventually lead up to decreased preload and afterload, improved cardiac metabolism and bioenergetics, inhibition of myocardial Na+/H+ exchange, reduction of necrosis and cardiac fibrosis, and changes in adipocytes, cytokine production, and in majority of epicardial adipose tissue mass, give an up-to-date narrative literature overview of SGLT2 inhibitor mechanisms of action, at present definite clinical knowledge, known and researched therapeutic utility, and potential side effects in this review paper. This narrative review article is based on the gathered information via dedicated and thoroughly conducted Cardio Vascular Outcome trials with SGLT2 inhibitors and related review articles. In October 2022, we used PubMed and Google Scholar to conduct a thorough electronic web search for papers and journals published between January 2000 and October 2022 related to our review. EMPA-REG OUTCOME, DECLARE-TIMI, CANVAS Program, DAPA-HF, and EMPEROR-Reduced are some of the studies that instated that using SGLT2 inhibitors reduced the risk of CV death or hospitalisation due to heart failure with some potential side effects. SGLT2 inhibitors were documented to reduce 3-point MACE (CV mortality, definitely non-fatal MI, non-fatal stroke) by 14 percent in a double-blind, placebo-controlled RCT (phase 3) as per our searched articles. SGLT2 inhibitors are a fairly recent class of antihyperglycemic medication that definitely has been shown to help heart failure with reduced ejection fraction (HFrEF) patients with and without Type 2 Diabetes Mellitus (T2DM). However, it appears that doctors who are looking after this medically sensitive patient group with HFrEF will be got to be learned and comfortable with SGLT2 inhibitors.

Key Words

SGLT2 inhibitors, Heart failure, Reduced ejection fraction, Dapagliflozin , Canagliflozin, Empagliflozin.

Introduction

Heart failure, on up-to-date, affects 1-2 percent of the global adult population, and it is known to be associated with a decreased quality of life, as well as a substantial increment in morbidity, death and financial expenditures, which creates an undue burden over the person and nation, in itself[1]. In patients with HFrEF, existing medications generally such as renin-angiotensin-aldosterone system (RAAS) inhibition, beta-blockers, and angiotensin receptor blockers/neprilysin inhibitors (ARNI) have shown to lower hospitalisation and death risk significantly. These drugs can cause a variety of side effects, including hypotension, renal failure, and electrolyte imbalances which worsens the patient's pre-existing health state. For patients with relatively advanced heart failure, finding new and effective therapeutic options to relieve symptoms, that will surely reduce mortality, repeated hospitalisation, and actually acute decompensation, for all intents and purposes, is critical[2]. Demonstrating how exactly heart failure affects percent of the global adult population, and its relative association with an overall decreased quality of life, as well as a substantial increment in morbidity, death, and financial expenditure will lead a cue for various aspects of possible betterment in this disease.

In India, diseases related to the heart and its vessels are the prime cause of death, and its occurrence is expected to rise in the forthcoming future. The rate of heart failure in India

is likely to rise, as the country continues to be plagued by both traditional Cardio Vascular Diseases(CVD) risk factors and the persistence of pre-transitional disorders such Rheumatic Heart Disease (RHD), end myocardial fibrosis, tuberculous pericardial disease, and anaemia. Therefore, making an all-round progress with medications and therapy will help such nations to overcome these ghastly diseases[3].

Reduction in glucose reuptake in proximal renal tubules is seen to be done by a type of oral glucose lowering medication known as Sodium-glucose cotransporter-2 (SGLT2) inhibitors which eventually results in more urinary glucose excretion. Crane et al. were the first to describe the co-transport of glucose and salt[4]. Phlorizin, was the first non-selective Sodium glucose cotranspoter-2 inhibitor which was extracted from apple tree. T-1095, an artificial phlorizin derivative, demonstrated considerable improvement in glucose levels measured after every meal and HbA1c levels in mice, but the medicine was not developed for human use. Washburn et al. developed dapagliflozin, a phlorizin C-glucoside derivative with a substantially higher (1200-fold) affinity for SGLT2 than SGLT1.

Putative Mechanism of SGLT2 Inhibitors for Cardiovascular Benefits

Preload and afterload (due to increased sodium and water excretion) are scaled down, which creates a decrement in ventricular load (decrease in BP along with enhancement in blood vessel function). Cardiovascular metabolism and bioenergetics are improved. Suppression of Na+/H+ transfer across the myocardial cell membrane by exchange pump. Cardiac degeneration and myocardial cell death are minimised. The generation of adipocytes, cytokines, and the bulk of epicardial adipose tissue are all altering.

Enhanced gluconeogenesis and ketogenesis, which are not found with other antihyperglycemic medications, are the most notable metabolic signs of this fasting mimicking. The main molecular trigger for gluconeogenesis and ketogenesis is SIRT1 activation, together with PGC-1 (proliferator-activated receptor gamma coactivator 1-alpha) and FGF21, which are SIRT1's downstream mediators (fibroblast growth factor 21[5,6]. The impressive cardio protective benefits of these three food deprivation sensors are demonstrated in a variety of animal types. This advantage seems to be linked to their abilities to reduce oxidative stress and support autophagy, a lysosome-dependent degradative system that eliminates defective organelles that are significant contributors to cellular damage. The increase of FGF21 is considered as a compensatory strategy (although an inadequate one), as improved FGF21 signalling would be anticipated to substantially alter the course of experimental cardiomyopathy, regardless of cause. In particular, FGF21 activation decreases the likelihood of oxidative stress on the heart and delays the onset of diabetic and non-diabetic cardiomyopathy, and encourages autophagy to minimize ischemia-reperfusion damage. The increase of FGF21 is considered as a compensatory strategy (although an inadequate one), as improved FGF21 signalling would be anticipated to substantially alter the course of experimental cardiomyopathy, regardless of cause. In particular, FGF21 activation decreases the likelihood of oxidative stress on the heart and delays the onset of diabetic and non-diabetic cardiomyopathy, and encourages autophagy to minimise ischemia-reperfusion damage[8-10].

This study is purposefully done to summarise what is at present known about SGLT2 inhibitors' effects on LV(Left Ventricular) function based on experimental and clinical evidence, and to determine if SGT2 inhibitors are suitable for patients with HFrEF.

Methodology

This review is based on the gathered information via dedicated Cardio Vascular Outcome trials with SGLT2 inhibitors and review articles.

Sources of Search

In July 2022, we conducted a PubMed and Google Scholar electronic web search for studies published between January 2000 and June 2022.

Search Terms

“SGLT2”, “Sodium-glucose cotransporter 2, “empagliflozin”, “canagliflozin”, “luseogliflozin”, “cardiac failure”, “heart fail ure”,“left ventricular” were among the subject headers and text terms used in the search. After that, papers were sifted thoroughly for the results of SGLT2 inhibitors on “LV shape and its effects on functional activity” were screened.

We gained the stated data from the following included studies based on

1. Details of study
2. Details of sample size
3. Details of intervention
4. Details of outcome

Results

Pre-Clinical Study

According to research, empagliflozin enhanced left ventricular diastolic performance in obese mice with diabetes and left ventricular dysfunction which led to some speculations. It was also discovered that dapagliflozin treatment reduced left ventricular hypertrophy, along with a quite a lot of left ventricular function in mice who aren't obese but with diabetes, left ventricular hypertrophy, and altered function, showing how according to this research,

empagliflozin enhanced left ventricular diastolic performance in obese mice with diabetes and left ventricular dysfunction, or so they thought for the most part.

Empagliflozin treatment did not impact left ventricular diastolic characteristics but on the other hand, few investigations on animals (mice) without diabetes but with HF with reduced ejection fraction, although it did essentially improve LV systolic performance, which particularly was fairly significant. In numerous small animal (rodent) models of Diabetes Mellitus type 2, SGLT2 inhibitors for the most part improved good functional capacity and left ventricular muscular hypertrophy while lowering cardiac fibrosis and the generation of precursor of fibrotic/hypertrophic proteins, demonstrating that empagliflozin treatment did not impact left ventricular diastolic characteristics in some of the relatively few investigations on animals (mice) without diabetes but with HF with reduced ejection fraction, although it did actually improve LV systolic performance in a for all intents and purposes[7].Verma which mostly is quite significant, used a zebrafish model of cardiac failure and essentially found out the cardio protective benefits, implying that cardiovascular protective effects for the most part are conserved across species, really contrary to popular belief.

Clinical Research

The outcome of Sodium Glucose Transporter 2 inhibitors on left ventricle form alongwith function have been explored in a small number of clinical trials (on humans), yet are noteworthy and gave a good insight about these drugs and their relative cardiovascular effects. EMPA-REG OUTCOME, DECLARE-TIMI, CANVAS Program, DAPA-HF, and EMPEROR-Reduced are some of the notable research projects[11].

Discussion

Reduction in glucose reuptake in proximal renal tubules, according to the known pharmacokinetics and thermodynamics, is seen to particularly be done by a type of oral glucose lowering medication known as Sodium glucose cotransporter-2 (SGLT2) inhibitors which eventually results in more and more urinary glucose excretion, improving glucose management, body weight, and blood pressure, which was previously unknown to many. SGLT2 inhibitors, unlike many other antihyperglycemic drugs, for all we know, lower plasma glucose levels through processes that definitely are not completely dependent on insulin, which makes these drugs unique and of potential use. EMPA-REG OUTCOME demonstrated a noteworthy decrease in combined CV endpoint (MACE) in CV risk patients with Diabetes Mellitus type 2 currently on empagliflozin therapy, considering a significant 38 percent decrease in relative risk in all cause CV death also a 35 percent definite decrease in relative risk in HF leading to hospitalization, or so they essentially thought[12-14]. Canagliflozin medication actually showed a 14 percent reduction in combined CV events endpoint of CV mortality, MI, or cerebrovascular disease over the duration of the 3.6-year CANVAS research, or so they particularly thought. The "DECLARE TIMI-58" "(Dapagliflozin Result on Cardiovascular Events-thrombolysis in MI-58) study" (n=17,160) specifically included the known largest group of individuals with Diabetes Mellitus type 2 who particularly had or for the most part were at risk of atherosclerotic vascular disease in a generally major way[15-17]. However unlike "EMPA-REG OUTCOMES" and "CANVAS" experiments, this one compared dapagliflozin to redundant drug (i.e. placebo) for the definite primary and composite efficacy endpoint of CV mortality or HF mortality hospitalisation, demonstrating how reduction in glucose reuptake in proximal renal tubules really is seen to be done by this type of oral glucose lowering medication known as Sodium glucose cotransporter-2 (SGLT2) inhibitors which eventually results in relatively more urinary glucose excretion, thereby considerably improving the glucose management, body weight, and blood pressure, which has shown a to be of a quite significant weightage[4].When compared to placebo, "dapagliflozin therapy" reduced the seemingly primary terminal figures of HF or CV death, also the generally terminal figures of heart failure and CV death , so SGLT2 inhibitors, unlike other fairly known antihyperglycemic drugs, that lower plasma glucose levels through processes that generally are not at all dependent on insulin, for all that is known till date. In the EMPAREG OUTCOME study, patients with Diabetes Mellitus type 2 on medical treatment with empagliflozin really had a 35 percent for all intents, lowered risk of heart failure hospitalization, 33 per cent in the "Canagliflozin Cardiovascular Assessment Study Program (CANVAS)", and 27% in the "Dapagliflozin Effect on Cardiovascular Events trial" "(DECLARE–TIMI 58)".The "DAPA-HF" fairly known and a quite famous trial, actually was sparked by these findings, which expressed doubts, leading to this research. The "DAPA-HF experiment" kind of was founded on the assumption that patients with HFrEF, regardless of T2DM status, would definitely benefit from it, and the first findings were published in the year 2019, definitely further showing how EMPA-REG OUTCOME demonstrated a noteworthy decrease in combined CV endpoint (MACE) in CV risk patients with Diabetes Mellitus type 2 taking empagliflozin therapy, showing a remarkable 38 percent reduction in all-cause CV mortality and a 35 percent reduction in heart failure leading to significant hospitalisation.The "DAPA-HF trial" found substantial

reductions in cardiovascular death and heart failure hospitalisation after enrolling 4744 patients with the "ACC", with a 26 percent actually comparative risk reduction for the combined endpoint and a 17 percent decline in all-cause mortality, really further showing how Dapagliflozin mostly was equally beneficial in reducing cardiovascular mortality and HF leading to hospitalization in people with and also without diabetes type II. Dapagliflozin was more advantageous than placebo at reducing each nonfatal HF symptom: the risk of hospitalisation was reduced by 30 per cent (95 per cent CI, 17 per cent-41 per cent); P0.0001; the risk of an immediate HF visit was scaled back by 57 per cent (95 per cent CI, 10per cent-80per cent); P=0.021; and the risk of outpatient worsening was significantly lowered by 26 per cent (95 per cent CI, 13 per cent-37 per cent;P=0.0003)[18]. During the study being conducted, the drop in HF admissions into the hospital was largely not at all dependent on C6H12O6 regulation in diabetic patients. Empagliflozin medication showed a significant improvement in heart and renal outcomes in patients with HFrEF in the previously conducted EMPEROR-Reduced trial (Empagliflozin Outcome Trial in Patients With HFrEF), irrespective of previously stated baseline diabetes status and across the HbA1c spectrum, thereby further showing how sGLT2 inhibitors, unlike kind of many other fairly known antihyperglycemic drugs, for all intents and purposes lower plasma glucose levels through processes that for all we know, are not completely dependent on insulin in a significant way[19]. Despite the fact that empagliflozin medication was linked to changes in a number of clinical indicators, the change in hematocrit (Hct) was more closely correlated with a reduction in cardiovascular mortality[20]. These trials, hence, showed that irrespective of the diabetic status of the patients, SGLT2 inhibitors did a noteworthy improvement in patients with heart failure (systolic, with reduced ejection fraction).

Limitations

Studies linking the results of Na-C6H12O6 symporter-2 inhibitors on distal artery disease and amputation are insufficient to determine if SGLT2 inhibitors are to blame for these potential side effects.

Traditional notions about causes, timing and course of cardiovascular protection acquired with standard glucose-lowering drugs are at odds with the trials' fast commencement of positive effects.

Conclusion

Sodium-C6H12O6 symporter-2 inhibitors actually are a latest part of family of antihyperglycemic drugs that undoubtedly have demonstrated to, for the most part, be beneficial in HFrEF subjects that may or may not have type 2 diabetes, which is significant to our discussion. Dapagliflozin, itself particularly has the most baffling high-level outcome evidences, with therapy results comparable to other recent guideline-based medical therapy agents for HFrEF, which is a major breakthrough for future line of therapy. SGLT2 inhibitors may therefore have become a kind of essential disease-modifying medication in HFrEF, according to other emerging clinical evidence and fairly primary science data, demonstrating that sodium-C6H12O6 Symporter-2 inhibitors mostly are a latest part of family of antihyperglycemic drugs that kind of have demonstrated to be theoretically and practically beneficial in HFrEF patients that may or may not have type 2 diabetes during their diagnosis. However, it, for all intents and purposes, appears that clinicians caring for this generally sensitive patient population with HFrEF will need to definitely be knowledgeable with and particularly comfortable with SGLT2 inhibitors. Thus neglecting SGLT2i, as a possible drug in future line of treatment, might limit our knowledge and therapeutic reach to treat a major chunk of people suffering from HF with a systolic reduced fraction.

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Tables

Table 1- Brief summary of SGLT2 Inhibitors and their outcome

Sn.	Study ID	Details of study	Sample size	Details of intervention	Outcome	References
1	"Empagliflozin CV Outcome Event Trial" in Diabetes Mellitus type II patients. "(EMPA-REG OUTCOME)"	RCT with a double-blind and with placebo design (phase3)	7,020 patients (more than 18 years) with confirmed cardiovascular risks	"10mg" or "25mg" of empagliflozin daily vs. placebo	MACE (cardiovascular mortality, "non-fatal MI, and non-fatal stroke") was reduced by 14% when 10mg and 25mg empagliflozin dosages were combined.	Lan NS, Fegan PG, Yeap BB, et al
2	"Canagliflozin CV Assessment Study" (CANVAS Program)	RCT with a double-blind and placebo (phase3)	10,142 patients (≥ 30 years) with known vascular risks or a 2CV risk factor	100mg or 300mg of canagliflozin once a day vs. placebo	The III-point MACE score was reduced by 14%. (CV death, "non-fatal MI, non-fatal stroke")	Lan NS, Fegan PG, Yeap BB, et al
3	"Dapagliflozin Result on the Occurrence of CV Events" (DECLARE-TIMI) (HFrEF subgroup analysis)	RCT trial	10,142 patients, HFrEF and T2DM	10 mg dapagliflozin once a day vs. placebo	Reduced risk of cardiovascular mortality or hospitalisation for heart failure [HR 0.62 (95 percent CI, 0.65-0.86)] [HR 0.55 (95 percent CI 0.34-0.90)]; non-significant mortality benefit	Imran H, Nester W, Elgendy IY, et al
4	"EMPEROR-Reduced"	RCT trial	3730 HFrEF with or without T2DM	Empagliflozin 10 mg dose without titration vs. placebo	Reduced risk of heart failure-related death or hospitalisation [HR 0.75 (95 percent CI, 0.65-0.86)] ; fatality [HR 0.92 (95 percent CI 0.77-1.10)]; non-significant [HR 0.92 (95 percent CI 0.77-1.10)]	Imran H, Nester W, Elgendy IY, et al
5	"DAPA-HF"	RCT trial	4744, HFrEF with or without T2DM	Dapagliflozin 10 mg without titration vs. placebo	Reduced risk of cardiovascular mortality or hospitalisation for heart failure [HR 0.74 (95 percent CI, 0.65-0.85)] ;	Imran H, Nester W, Elgendy IY, et al

"CI" - confidence interval; "HFrEF" - Heart-failure with reduced ejection fraction; "HR"- hazard ratio; "SGLT-2" - Na- $C_6H_{12}O_6$ Symporter 2; "T2DM" – Diabetes Mellitus Type II

Table 2- Potential adverse effects seen in SGLT2 Inhibitors while studies were being conducted.

Type	Proposed mechanism of action	Drug vs. Class	References
Genitourinary Infections	Infection risk is increased in the presence of glycosuria.	SGLT2i	Heerspink HJ, Perkins BA, Fitchett DH, et al. Kohan DE, Fioretto P, Tang W, et al,

			Wu JH, Foote C, Blomster J, et al, Williamson JR Chang K, Frangos M, et al
Polyuria	An increase in natriuresis due to glycosuria-induced osmotic diuresis.	SGLT2i	Heerspink HJ, Perkins BA, Fitchett DH, et al, Kohan DE, Fioretto P, Tang W, et al, Wu JH, Foote C, Blomster J, et al, Williamson JR, Chang K, Frangos M, et al
Postural hypotension	In the presence of combined diuretic and antihypertensive medication, through volume depletion and blood pressure lowering actions that are not reliant on volume pathways may occur.	SGLT2i	Heerspink HJ, Perkins BA, Fitchett DH, et al. Kohan DE, Fioretto P, Tang W, et al. Wu JH, Foote C, Blomster J, et al. Williamson JR, Chang K, Frangos M, et al
Diabetic Ketoacidosis	Ketoacidosis is caused by a decrease in carbohydrate availability as a result of increased glycosuria and lower insulin levels. Enhanced amounts of counter-regulatory hormones like glucagon are linked to SGLT inhibition, resulting in increased ketogenesis.	SGLT2i	Rosenstock J, Ferrannini E
Decrease in eGFR	Afferent vasoconstriction reduces intraglomerular pressure, causing an increase in serum creatinine (acute eGFR "dip" of 4-6 ml/min/1.73m3). In clinical studies (EMPA-REG OUTCOME, CANVAS Program), the danger of acute kidney damage was decreased with SGLT2 inhibitors, although it was shown in post-marketing data. More experimental work is needed to understand the long-standing outcome of the eGFR reduction plus whether it is beneficial (i.e., related with reduced glomerular hypertension and excretion of protein in urine).	SGLT2i	Wanner C, Inzucchi SE, Lachin JM, et al
Fracture risk	1. Higher the blood phosphate levels higher is the release of parathyroid hormone along with fibroblast growth factor-23. 2. Hypotension can be caused by SGLT2 inhibitors, which can lead to falls and bone fractures.	Only reported in CANVAS Program	Taylor SI, Blau JE, Rother KI

Amputation risk	1. Induction of Adenosine Mono Phosphate Kinase and suppression of Complex I of the mitochondrial respiratory chain, leading to changes in oxidative metabolism and hypoxic ischemia. 2. Haem concentration causes hyper viscosity. 3. Hypotension causes limb perfusion to be reduced.	Only reported in CANVAS Program	Neal B, Perkovic V. Mahaffey KW, et al

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