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Review Article

The Role Of SGLT Inhibitors In Heart Failure Beyond Glycemic Control: A Review

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ABSTRACT

This article provides an in-depth overview of heart failure (HF) and the recently approved SGLT2 inhibitor, sotagliflozin, emphasizing its efficacy in treating adults with HF, type 2 diabetes, chronic kidney disease, and cardiovascular risk factors. The SOLOIST study is discussed, demonstrating the significant reduction in cardiovascular fatalities, hospitalizations, and urgent visits for heart failure with sotagliflozin use. The mechanism of action of SGLT2 inhibitors in HF, chronic kidney disease (CKD), and type 2 diabetes mellitus (T2DM) is explored, highlighting their direct renal effects, indirect benefits, and cardiovascular advantages. The article concludes by emphasizing the multifaceted benefits of SGLT2 inhibition beyond glycemic control, including weight reduction, blood pressure management, and cardiovascular risk reduction. It advocates for SGLT2 inhibitors as the preferred therapy for patients with both T2DM and HF, suggesting potential expansion to all HF patients, irrespective of glycemic status, pending ongoing trials. Overall, the article underscores the pivotal role of SGLT2 inhibitors in improving clinical outcomes and longevity in individuals with HF and related comorbidities.

INTRODUCTION

Heart Failure (HF) is one of the leading causes of disease and death due to cardiovascular diseases. Cardiovascular diseases account for the highest number of deaths worldwide. Heart failure is defined by the American Heart Association as a chronic progressive condition in which the cardiac muscles become unable to pump enough blood to meet the body's blood and oxygen requirements. Heart failure is a condition where the heart is not able to keep up with the workload and therefore cannot meet the body's blood and oxygen needs. There are two types of heart failure related to left ventricular function. Heart Failure with Reduced Ejection Fraction (HFrEF) previously known as Systolic HF and Heart Failure with Preserved Ejection Fraction (HFpEF) formerly known as Diastolic HF. HFrEF results in a lower than 40%

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LVEF and is characterized by stretched and therefore weak heart muscles. On the other hand, HFpEF results in a greater than or equal or greater than 50% LVEF, and is characterized by stiffened chambers with a hypertrophied heart.[1]

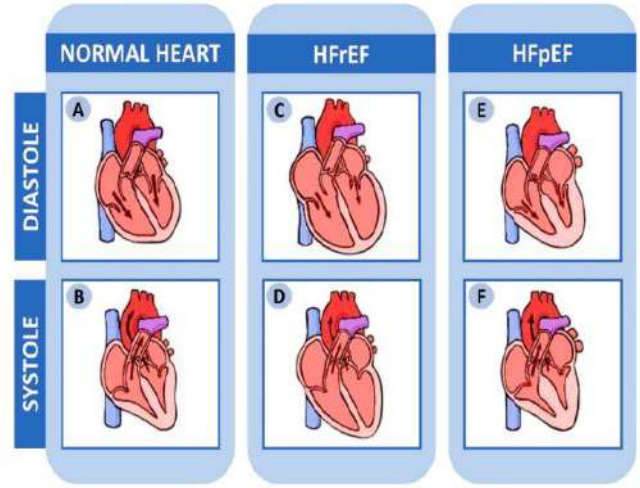

Figure 1: Physiological differences in healthy cardiac function vs systolic (HFrEF) and diastolic (HFpEF) dysfunction. In the normal heart, the ventricles relax and expand to fill with blood during diastole (A)and contract to pump out ~50%− 60% of the blood during systole (B). In HFrEF, the heart muscle is thin and weak, the enlarged ventricles fill with blood during diastole (C), and the stretched ventricles pump out less blood than normal during diastole (D) as they are thinner and weaker. In HFpEF, the heart muscle is thickened with stiff ventricles which fill with less blood than normal during diastole (E), and contract normally but have less blood to pump out during systole (F).[1]

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder characterized by high blood glucose levels due to insulin resistance or relative insulin deficiency. The classic symptoms include frequent urination, increase in thirst, fatigue, and weight loss. T2DM is caused by a combination of lifestyle factors and genetic factors. Recent increases in T2DM rates may be due to environmental toxins. In addition to genetics, environmental factors, particularly diet and obesity, play a major role in T2DM development. Having a family member with T2DM significantly increases the risk of developing the condition. Unlike type I diabetes mellitus which is caused by a problem with insulin production, insulin resistance is a problem with insulin receptors of cells that don't respond appropriately to insulin. The WHO definition of T2DM is as follows: Either fasting plasma glucose ~7.0 mmol/L or with a glucose tolerance test, two hours after the oral dose a plasma glucose 11 .1 mmol/L. The onset of T2DM can be prevented through proper nutrition and regular exercise.[2]

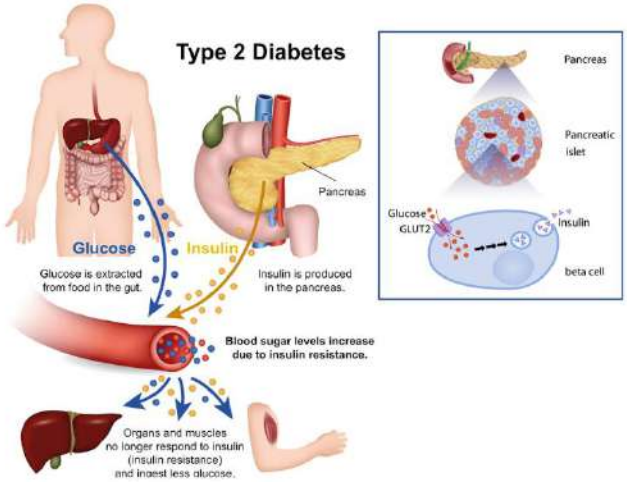

Figure 2: An overview of T2DM

DM AS A RISK FACTOR FOR HF:

Diabetes mellitus (DM) and Heart Failure (HF) are common co-morbid conditions, and each co-morbid condition increases the risk of the other. The prevalence of DM ranges between 10% and 47% in HF cohorts, including HFrEF and HFpEF. Patients hospitalized with HF have a prevalence of >40% in some reports. The prevalence of HF in patients with DM ranges from 9% to 22%, 4 times the general population prevalence. Patients with DM who are >60 years of age have a 2 to 4-fold higher risk of HF compared to those without DM. The Framingham Heart Study found that DM increased the risk of HF in men by nearly 2-fold and in women by nearly 4-fold, even after controlling for additional cardiovascular risk factors. The Heart and Soul Study showed that DM increased the adjusted risk of HF by 3.34 (HR = 1.65, 95% CI = 6.76). Younger adults and women

may be at an even higher risk for HF due to DM. DM is a significant predictor of symptomatic hypertension in patients with Asymptomatic LV Systolic dysfunction (ASD). Poor glycemic control (GL) also increases the risk for HF; for every 1% rise in HA1c, the risk for incident HF rises by 8-36%. The risk for incident HF among DM patients increases with increasing age, CAD (cardiovascular disease), PAD (Peripheral Arterial Disease), Nephropathy (Retinopathy), Longer Duration of DM, Obesity, Hypertension, and N-Terminal Pro-B-Type Natriuretic Peptide (NPBNP). The risk for HF increases even with mild glucose regulation abnormalities. A prospective cohort study (18,084 subjects) with no DM or HF showed a gradually increasing risk for HF hospitalization in participants with and without DM (ARIC). A 1- mmol/L increase in fasting plasma glucose correlated with a 1-fold increase in the risk for HF in participants without DM. In addition, smaller studies have also associated insulin resistance with a higher incidence of HF and an increase in LV Systolic and Diastolic Dysfunction.[3].

Study	Cohort	N	Follow-Up, y	Incidence of HF	Adjusted Risk of HF with vs without DM	Population Attributable Fraction
Framingham[21] (study sample included ages 45-74 y)	45-74 y	5209	Up to 20	Age-adjusted rates(person-years); DM (men): 3.5/1000 DM (women): 32.5/1000 No DM (women): 2.2/1000	RR (men): 1.82 RR (women): 3.75	Men:7.7% Women: 18.0%
Cardiovascular Health Study[22]	>65 y	5888	Mean 5.5	Rate (person-years): DM (men): 44.6/1000 No DM (men): 22.9/1000 DM (women): 32.5/1000 No DM (women): 12.1/1000	RR: 1.74 (95% Cl, 1.38-2.19)	8.3%
Heart and soul study[23]	Stable CAD	839	Mean 4.1	Rates(person-years): DM: 3.6/1000 No DM (Women): 12.1/1000	HR, 3.34 (95% Cl, 1.65-6.76)	----
MESA[24]	4-84y	6814	Mean 4	---	HR, 1.99(95% Cl, 1.08-3.68)	DM-attributable risk; 19 per 10000
NHANES[25]	25-74y	13643	Mean 19	Cumulative incidence at age 85 y DM (men): 65.5% No DM (men): 36.9% DM (Women): 61.8% No DM (Women):28.9%	RR, 1.85(95% Cl, 1.51-2.28) Similar in men and women	
Retrospective cohort of Kaiser Permanente Northwest Database		8231+ DM, 8845 no DM	Up to 6	Rate (person-years): DM: 30.9/1000 No DM: 12.4/1000 Rate ratio, 2.5% (95% Cl, 2.3-2.7	---	---

THE INTERACTION BETWEEN T2DM AND HF: THE CONCEPT OF DIABETIC CARDIOMYOPATHY:

Diabetic cardiomyopathy is defined as the presence of diastolic or systolic dysfunction in a patient with DM without other obvious causes of cardiomyopathy, such as coronary artery disease, hypertension, or valvular heart disease. Myocardial fibrosis, abnormal remodeling, and related diastolic dysfunction are its first characteristics followed by systolic dysfunction and eventually, clinical HF. Heart failure occurs in diabetic people due to various pathophysiological and metabolic abnormalities resulting from altered glucose metabolism, in addition to the underlying coronary artery disease. Left ventricular systolic and diastolic dysfunction is caused by the diabetic heart's altered cardiac glucose metabolism and transition from glucose to FFA oxidation, which has a substantial detrimental impact on cardiac contractility and functioning. The decrease in the cardiac concentration of glucose transporters type 1 (GLUT 1) and type 4 (GLUT 4) is the secondary cause of the sluggish rate of glucose transport over the sarcolemmal membrane into the heart, which results in a reduction in the absorption of glucose. Individuals with diabetes mellitus have increased FFA myocardial absorption and plasma levels. The inhibition of glucose oxidation and glycolysis in the heart is mainly caused by elevated amounts of circulating free fatty acids and their enhanced oxidation. Chronic maladaptation causes a reduction in cardiac efficiency and energetic reserves, even though the diabetic heart's shift in cardiac energy substrate utilization from glucose to FFA oxidation is necessary to maintain continuous adenosine triphosphate (ATP) generation. As beta-oxidation of FFA is less effective than glycolysis in producing energy (relative to oxygen consumption), diabetic hearts do, produce less high-energy phosphate, which may raise the risk of cardiac dysfunction in the event of increased metabolic demands or ischemia. Several mechanisms, both independent and combined, including impaired microvascular endothelial function, abnormal cardiac metabolism (which shifts myocardial utilization of glucose toward less efficient fatty acid oxidation), increased myocardial fibrosis, increased oxidative stress, and localized activation of the sympathetic nervous system and renin-angiotensin system, are also responsible for the development of heart failure in individuals with hyperglycemia and insulin resistance.[4]

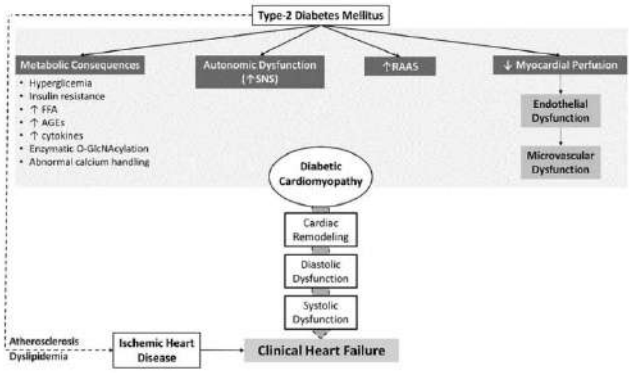

Figure 3: the interaction between T2DM and HF

CARDIOVASCULAR BENEFIT OF SGLT2 INHIBITORS:

Cardiovascular disease is the leading cause of death for almost 80% of T2DM patients, and diabetics are 2-4 times more likely to develop heart failure (HF).[5]In individuals with type 2 diabetes mellitus, sodium-glucose cotransporter 2 (SGLT2) inhibitors are a successful anti-diabetic treatment. They are linked to decreased blood pressure and body mass, as well as better glycemic control.[6]

Sodium-glucose co-transport 2 (SGLT2) inhibitors have been demonstrated in clinical trials to have significantly improved cardiovascular outcomes. There is some uncertainty regarding the precise mechanism or mechanisms causing these advantageous effects. The cardioprotective effects of SGLT2 inhibition have been explained by several potential theories, which include diuresis/natriuresis, blood pressure reduction, erythropoiesis, improved cardiac energy

metabolism, reduction of inflammation, inhibition of the sympathetic nervous system, prevention of adverse cardiac remodeling, prevention of ischemia/reperfusion injury, inhibition of the Na+/H+-exchanger, inhibition of SGLT1, reduction of hyperuricemia, the elevation of autophagy and lysosomal degradation, decrease in epicardial fat mass, elevation of erythropoietin levels, increase in circulating pro-vascular progenitor cells, oxidative stress reduction, and enhancement of vascular function.[7]

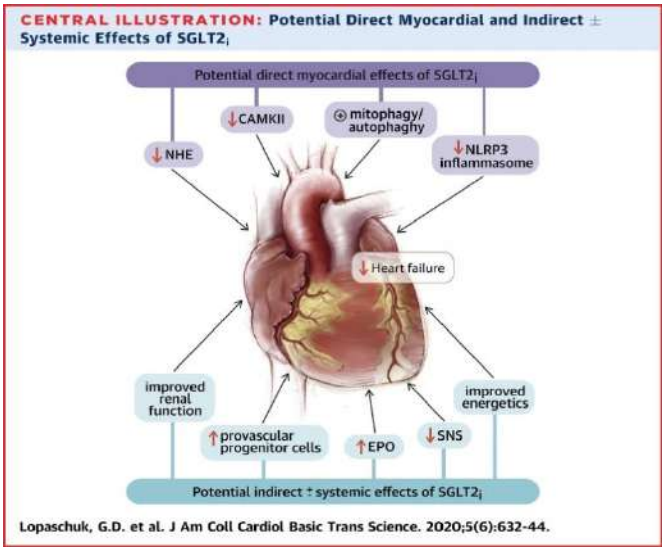

Figure 4: direct and indirect effects of SGLT inhibitors in HF

APPROVED SGLT2I IN HEART FAILURE:

Cardiovascular endpoints, such as heart failure hospitalization and mortality, among patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease or risk factors, unexpectedly improved after the release of post-approval cardiovascular outcomes data for three of these agents (canagliflozin, empagliflozin, and dapagliflozin).[8]

EMPAGLIFLOZIN:

Several CVOTs were created to assess SGLT2i usage in people at high risk for cardiovascular disease. EMPA-REG OUTCOME was the first SGLT2i cardiovascular trial. Over a period of 3.1 years, the trial examined 7020 patients with T2DM and determined the presence of atherosclerotic cardiovascular disease (ASCVD). Major adverse cardiac events (MACE) including nonfatal myocardial infarction, nonfatal stroke, and cardiovascular mortality were the main composite endpoints. This demonstrated a 14% decrease in comparison to the placebo group. Furthermore, there was a 32% reduction in the risk of death from all causes, a 38% reduction in the risk of cardiovascular causes, and a 35% relative risk reduction in hospitalization for heart failure in the empagliflozin group. The multicenter, randomized, double-blind, placebo-controlled EMPEROR-REDUCED trial sought to find out how empagliflozin affected individuals with established HF who also had an HFrEF. 361 out of 1863 patients in the empagliflozin group and 462 out of 1867 patients in the placebo group experienced the primary endpoint. The empagliflozin group had reduced secondary endpoints, such as total HFH, in comparison to the placebo group.5988 patients with HF (NYHA Class II–IV) and an LVEF > of 40% were randomly assigned to receive empagliflozin or a placebo in addition to conventional medication in the double-blind EMPEROR-Preserved investigation. Whether or not diabetes was present, empagliflozin decreased the combined risk of cardiovascular death or heart failure in patients with HFpEF.

DAPAGLIFLOZIN:

The DECLARE-TIMI 58 research assessed dapagliflozin in 17,160 patients with diabetes (HA1c level at least 6.5% but less than 12.0%) who had established ASCVD (10,186 pts) and were monitored for 4.2 years. Two groups of patients were given either a placebo or 10 mg of dapagliflozin. Cardiovascular death (HFH) and a composite of MACE were the primary efficacy outcomes. Dapagliflozin resulted in a decreased rate of cardiovascular death or HFH but did not significantly reduce the primary composite outcome, which included hospitalization, non-

fatal MI, non-fatal stroke, and CV death. Dapagliflozin was found to decrease hospital admissions and cardiovascular mortality more than When comparing patients with HFpEF to HFrEF

CANAGLIFLOZIN:

The CANVAS (Canagliflozin Cardiovascular Assessment Study) program comprised CANVAS and CANVAS-R (renal), and it lasted 188.2 weeks on average to evaluate the impact of canagliflozin on 10,142 diabetic patients with or without ASCVD. Canagliflozin use only decreased heart failure hospitalization (HFH); there was no clinically significant effect on any of the key outcomes. Patients having a history of heart failure (HF) seemed to benefit more from reduced cardiovascular death or heart failure history (HFH) than did those without a history of HF. There was no discernible difference between the canagliflozin and placebo groups in terms of the secondary endpoint, which is mortality from any cause. It was shown that the two groups did not significantly differ in the fatal secondary outcome, which is death from cardiovascular causes or death from any cause.[9]

NEWLY APPROVED SGLT2I FOR HF:

The most recent SGLT2I(2023) to be approved is sotagliflozin, which is used to treat adults with heart failure or type 2 diabetes, chronic kidney disease, and other cardiovascular risk factors. It lowers the risk of heart problems leading to death (cardiovascular death), hospitalization for heart failure, and urgent trips to the doctor for heart failure.

CLINICAL STUDIES:

SOLOIST STUDY: Patients with type 2 diabetes mellitus who had just been admitted to the hospital due to increasing heart failure participated in a multicenter, double-blind experiment in which they were randomly allocated to receive sotagliflozin or a placebo. The total number of fatalities from cardiovascular causes, hospital stays, and emergency room visits due to heart failure was the main outcome measure. Twelve two hundred and twenty-two patients were randomly assigned (608 to the sotagliflozin group and 614 to the placebo group) and followed for a median of nine months. In 48.8% of the cases, the first dosage of sotagliflozin or placebo was given before discharge, and in 51.2% of cases, it was given a median of two days after discharge. 600 primary end-point events (245 in the sotagliflozin group and 355 in the placebo group) happened in these participants. The sotagliflozin group had a death rate from cardiovascular reasons of 10.6 and a placebo group of 12.5; the sotagliflozin group had a death rate from any cause of 13.5 and the placebo group had a death rate of 16.3. Thus, sotagliflozin medication started before or soon after discharge in patients with diabetes and recently deteriorating heart failure led to a significantly lower overall number of cardiovascular fatalities, hospitalizations, and urgent visits for heart failure than placebo.[10]

MECHANISM OF ACTION OF SGLT2 INHIBITORS IN HEART FAILURE :

In recent treatment guidelines, Sodium Glucose Cotransporter 2 inhibitors (SGLT2i) have gained recognition for their role in reducing hospitalizations for heart failure (HF) and cardiovascular mortality in patients with HF with preserved ejection fraction (HFpEF). Apart from their established benefits in blood pressure control, SGLT2i stands out as the sole direct therapy acknowledged in guidelines for lowering mortality in HFpEF. Operating by inhibiting the SGLT2 protein in the nephron's proximal tubule, these agents decrease glucose and sodium reabsorption, leading to glycosuria and natriuresis, thereby lowering serum glucose concentrations. Beyond their antihyperglycemic effects, SGLT2i demonstrate cardioprotective outcomes in HF patients, irrespective of diabetes presence, encompassing blood pressure reduction,

natriuresis, diuresis, improved cardiac energy metabolism, inflammation prevention, enhanced glucose control, and weight loss. While the proven cardioprotective effects in HF with reduced ejection fraction (HFrEF) led to their inclusion in guidelines, caution is advised in extrapolating these results to HFpEF patients due to differing trial populations. Nonetheless, ongoing randomized trials aim to elucidate the effectiveness and overall benefits of SGLT2i specifically in HFpEF populations.[11]

Weight Loss:

SGLT2 inhibitors result in caloric loss, leading to weight reduction, though the article suggests weight loss alone may not explain the observed benefits of heart failure.

Improved Glucose Control:

While effective in reducing glucose levels, the rapid efficacy of SGLT2 inhibitors suggests that their cardiovascular benefits are not solely linked to glucose reduction.

Blood Pressure Reduction:

SGLT2 inhibitors lower blood pressure, possibly reducing cardiac post-load and improving efficiency, although their modest effects may not fully explain cardiovascular benefits.

Increased Natriuresis:

Promotion of natriuresis and glycosuria may improve heart failure outcomes, with unique effects on interstitial fluid compared to traditional diuretics.

Reduced Sympathetic Stimulus:

SGLT2 inhibitors reduce sympathetic tone, improving arterial stiffness, and endothelial function, and potentially reducing the risk of arrhythmias and sudden death.

Reduced Inflammation:

SGLT2 inhibitors may dampen the inflammatory response, affecting HF severity by modulating processes such as extracellular matrix turnover and fibrosis.

Prevention of Cardiac Remodeling:

SGLT2 inhibitors have anti-inflammatory effects that contribute to the reversal of cardiac remodeling, reducing stress on the left ventricle.

Suppression of Myocardial Fibrosis: SGLT2 inhibitors may suppress collagen synthesis, potentially inhibiting myofibroblast differentiation and attenuating myocardial fibrosis

Reduced Ventricular Overload:

Inhibition of SGLT2 promotes natriuresis, reducing ventricular filling pressure and myocardial work, contributing to improved ventricular functioning.

Repairing Vascular Function:

SGLT2 inhibitors improve endothelial function, induce vascular relaxation, and reduce arterial stiffness, contributing to enhanced hemodynamic function.

Increasing Erythropoietin (EPO) Levels: SGLT2 inhibitors increase EPO secretion, potentially improving cardiomyocyte function, angiogenesis, and oxygen supply to myocardial tissue.

Reducing Epicardial Fat:

SGLT2 inhibitors decrease epicardial adipose tissue, associated with inflammatory alterations and coronary neovascularization, potentially reducing cardiovascular risk.

Increasing Vascular Progenitor Cells:

SGLT2 inhibition may affect the balance of circulating progenitor vascular cells, contributing to vascular repair.

Improved Metabolism and Cardiac Bioenergetics:

SGLT2 inhibitors increase ketone production, providing an alternative energy source for the heart and improving myocardial contractility.

Inhibition of Sodium/Hydrogen Exchangers: SGLT2 inhibitors may directly inhibit NHE1 and reduce NHE3 expression, influencing sodium levels in myocardial and vascular tissues.

Reduced Leptin Levels:

SGLT2 inhibitors suppress the effects of leptin, potentially reducing sodium retention and inflammation associated with heart failure.

Prevention of Ischemia/Reperfusion Injury: Experimental evidence suggests cardioprotective effects against ischemia/reperfusion injuries, possibly associated with cytoprotective effects.

Reducing Hyperuricemia:

SGLT2 inhibitors may contribute to reduced hyperuricemia, a marker associated with a negative prognosis in heart failure. These diverse mechanisms collectively contribute to the multifaceted cardiovascular benefits of SGLT2 inhibitors in heart failure, extending beyond their primary use in diabetes treatment.[12]

MECHANISM OF ACTION OF SGLT2 INHIBITORS IN CKD:

RENO-PROTECTIVE EFFECTS OF SGLT2 INHIBITORS:

DIRECT EFFECTS :

The impact of SGLT2 inhibitors (SGLT2i) on the kidneys is multifaceted. Firstly, SGLT2 inhibition addresses glomerular hyperfiltration, a process exacerbating chronic kidney disease (CKD) in type 2 diabetes mellitus (T2DM). By reducing sodium and glucose reabsorption in the proximal tubule, SGLT2i restores tubule-glomerular feedback, mitigating long-term renal damage. The interaction between SGLT2 and Na^+-H^+ exchanger 3 (NHE3) contributes to the natriuretic effect, accompanied by a transient fall in estimated glomerular filtration rate (eGFR), ultimately considered reno-protective. Secondly, the kidneys, requiring a disproportionate amount of energy, face reduced oxygen consumption due to SGLT2 inhibition. This reduction, attributed to decreased Na^+/K^+-ATPase activity, protects against hypoxia-induced progression of CKD. Studies in diabetic rats and hypoxic human kidney cells support the idea that SGLT2 inhibition alleviates renal hypoxia by inducing nephroprotective factors like hypoxia-inducible factor 1 (HIF1). Moreover, SGLT2 inhibition demonstrates anti-inflammatory and anti-fibrotic effects, extending beyond diabetes. Reductions in albuminuria and urinary markers of tubular injury and inflammation are noted. In vitro studies reveal decreased levels of inflammatory molecules, extracellular matrix components, and fibrosis-related markers. While studies often focus on diabetes, evidence suggests these effects transcend diabetic conditions. In summary, SGLT2 inhibition exhibits direct renal effects, addressing hyperfiltration, reducing energy consumption, and inhibiting inflammatory and fibrotic responses. The versatility of these mechanisms explains the efficacy of SGLT2i in both diabetic and non-diabetic CKD, highlighting their potential as therapeutic agents beyond glycemic control.

INDIRECT EFFECTS:

In examining the indirect effects of SGLT2 inhibition on the kidneys, various physiological aspects come into play, extending beyond direct renal mechanisms. Notably, SGLT2 inhibition-induced glycosuria proves advantageous by enhancing endogenous glucose production, pancreatic beta-cell function, and insulin sensitivity. This, in turn, reduces insulin secretion, elevates glucagon levels, and shifts substrate utilization from carbohydrates to lipids, positively impacting kidney function.Several studies highlight glucosuria-related effects on factors influencing kidney health, such as body weight and blood pressure. SGLT2 inhibitors demonstrate a significant impact on obesity, body weight reduction, and improved insulin resistance, effects observed even in non-diabetic individuals. Moreover, the antihypertensive effects of SGLT2 inhibition contribute to the protection of renal vessels, potentially mitigating damage caused by hypertension. While dyslipidemia may not directly impact CKD progression, its connection to cardiovascular damage, a significant aspect associated with CKD, is acknowledged. SGLT2

inhibition's effect on dyslipidemia appears nuanced, with increases in LDL levels, reduced triglycerides, and no substantial effect on HDL observed. Furthermore, SGLT2 inhibitors exhibit protective effects on endothelial cells, fostering proliferation, migration, and differentiation, along with promoting vasodilation in the kidneys, thus lessening the burden on this organ. Addressing hyperuricemia, another factor detrimental to the kidneys, SGLT2 inhibitors have been shown to lower uric acid levels. While this effect is generally beneficial, its efficacy may be influenced by factors such as kidney function. Additionally, SGLT2 inhibition is associated with increased hematocrit and reticulocyte levels, indicative of potential improvements in hypoxia and oxidative stress within the renal cortex.

Beyond renal considerations, the cardiovascular benefits of SGLT2 inhibitors are substantial, encompassing a reduced risk of heart failure, lower cardiovascular mortality, and even potential antiarrhythmic efficacy. These outcomes are linked to the diverse effects of SGLT2 inhibitors on blood pressure, obesity, and vasodilation, among other factors. Collectively, the indirect effects of SGLT2 inhibition present a comprehensive perspective on its potential therapeutic implications for both renal and cardiovascular health.[13]

DIABETIC KIDNEY DISEASE:

In the last decade, numerous studies have extensively examined the clinical outcomes of SGLT2 inhibitors (SGLT2i) on the kidneys, with a predominant focus on patients with Diabetic Kidney Disease (DKD). Key findings include the EMPA-REG OUTCOME trial, revealing empagliflozin's significant reduction in kidney outcomes and a yearly loss of estimated Glomerular Filtration Rate (eGFR) across various DKD subgroups. Meta-analyses consistently demonstrate SGLT2i's capacity to attenuate eGFR decline, lower albuminuria progression, and enhance renal endpoints, offering potential benefits in both short and long-term scenarios.

Specifically, studies on empagliflozin and dapagliflozin emphasize reduced albuminuria, improved clinical outcomes, and lowered mortality in patients with Type 2 Diabetes Mellitus (T2DM), particularly those under Renin-Angiotensin-Aldosterone System (RAAS) blockade therapy. Concerns about a transient dip in eGFR upon initiating SGLT2i are addressed, confirming its transience and lack of adverse effects on renal outcomes. Comprehensive meta-analyses further support the renoprotective effects of SGLT2i, indicating risk reduction for dialysis, transplantation, kidney disease-related mortality, and protection against acute kidney injury. Exploring the effects of dapagliflozin in comparison to a placebo, a randomized study reveals notable reductions in albuminuria and eGFR, accompanied by decreased urinary excretion of inflammatory markers. However, the precise mechanisms behind the favorable impact on albuminuria remain nuanced, possibly linked to intraglomerular pressure reduction and improved tubular reabsorption. Notably, individual responses to SGLT2i in terms of urinary albumin reduction vary.Studies delving into both renal and cardiovascular outcomes affirm SGLT2i benefits in patients with T2DM, showing improved renal outcomes irrespective of baseline kidney function or cardiovascular disease history. For instance, analyses of canagliflozin and empagliflozin reveal renal benefits independent of cardiovascular risk, emphasizing a dual positive impact. Noteworthy is the positive association between SGLT2i use and slowed progression of kidney disease, as evidenced in various trials, reinforcing their potential as a therapeutic avenue for patients with DKD.While the abundance of evidence supports the clinical benefits of SGLT2i in DKD, research on non-diabetic populations is still evolving,

warranting further exploration of potential advantages in this demographic.[13]

MECHANISM OF ACTION OF SGLT2 INHIBITORS IN T2DM:

The kidneys in normoglycemic humans filter 160–180 g of glucose per day (~30% of daily calorie intake), which is reabsorbed and returned to the systemic circulation by the proximal tubule. Hyperglycemia increases the filtered and reabsorbed glucose up to two- to three-fold. The sodium-glucose cotransporter SGLT2 in the early proximal tubule is the major pathway for renal glucose reabsorption. Inhibition of SGLT2 increases urinary glucose and calorie excretion, thereby reducing plasma glucose levels and body weight. These compounds work independently of insulin, improve glycemic control in all stages of diabetes mellitus in the absence of clinically relevant hypoglycemia, and can be combined with other antidiabetic agents. By lowering blood pressure and diabetic glomerular hyperfiltration, SGLT2 inhibitors may induce protective effects on the kidney and cardiovascular system beyond blood glucose control.[14]

CONCLUSION

Pharmacologic SGLT2 inhibition has many effects beyond glycemic control. It lowers blood pressure and body weight, as well as the risk of CV disease, heart failure hospitalization, and renal disease development. The available data indicates that SGLT2 inhibitors should be the first line of treatment for individuals with both T2DM and HF, provided they are not contraindicated. This would significantly improve the patient's clinical indices and length of life. Current trials involving HF patients may yield fresh information about the potential to extend SGLT2 inhibitor treatment to all HF patients, regardless of glycemic state.

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