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Review Article

Effectiveness of SGLT-2 Inhibitors on The Outcomes of Heart Failure and Renal Failure

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Abstract:

SLGT2 inhibitors are antihyperglycemic drugs that block sodium-glucose cotransporter 2 and increase glucosuria by inhibiting renal glucose reabsorption. The fact that they were first identified as useful in diabetes mellitus for this reason, i.e., reduced glucose reuptake by the proximal tubule of the kidney in preventing hyperglycemia is disappointing. A recent research study also suggested these agents may be relevant to depression treatments. Decreased mortality rates and shorter hospital stays have been reported upon administration of these drugs. Moreover, SGLT2 inhibitors take a toll on the renal system, thus warranting more scrutiny over their effect on it.

The management of diabetes has seen these drugs coming up as an important class of antihyperglycemic agents. Additionally, scientific studies have recently demonstrated that SGLT2 are effective in the management of heart failure and can considerably reduce both death risk and durations of hospitalization for heart failure patients. Through this discovery, new researches and clinical trials can be done.

Nevertheless, they don't affect kidney diseases because they only change renal glucose reabsorption. Hence, more research is necessary to understand better how much effects on kidney function and related physiological changes that may occur.

Key words: Heart Failure; kidney diseases; glycosuric

Introduction

Heart failure is when the heart fails to support systemic circulation effectively. It is a syndrome due to either of two cardiac issues; structural or functional that impede blood ejection into the systemic circulation or limit ventricular filling. Heart failure remains a common condition globally, with significant morbidity and mortality rates [1]. As of now, there are sixty-four million people in the world who have heart failure. As a result, healthcare has been forced to develop measures aimed at reducing the social and economic burden occasioned by heart failure [2]. Cardiorenal syndrome occurs when patients develop renal dysfunction as a result of cardiac diseases. The forward-failure hypothesis and backward-failure hypothesis are two main theories explaining this situation. The former focuses on left ventricular dysfunction causing edema while the latter explains how venous congestion causes edema and reduced GFR levels among other factors which contribute towards cardiorenal syndrome [3]. The SGLT2i drugs inhibit glucose reabsorption in an insulin-independent manner in the renal proximal tubule, which is important for controlling blood sugar in diabetes [4].

After positive clinical results of several randomized controlled trials, they emerged as a new treatment option for patients with heart failure [5]. Irrespective of the condition of diabetes, SGLT2i markedly decreases the chance of death from heart disease or worsening heart failure [6]. Moreover, they reduce cardiovascular mortality among diabetics by diminishing the glucose and salt reabsorption capacity of proximal tubules, reducing insulin resistance, and enhancing natriuresis levels. Incidentally, through this, they have demonstrated reno-protective action via a decrease in pre- and post-glomerular vascular tone modulation leading to a reduction in intra-glomerular hypertension. [7]. With this mechanism, hypertension is alleviated while glomerular capillary

hyperfiltration is reduced thereby lessening the oxygen load on albuminuria and the filtration barrier required for tubular reabsorption. Improved cortical oxygenation could thus preserve tubular function and GFR over time by reducing tubular glucotoxicity [8].

Furthermore, SGLT2 inhibitors have other clinical benefits. In addition to the correction of inflammation and oxidative stress, they also have antifibrotic effects through such modalities as mitochondria function modulation and autophagy. Modifications of treatment guidelines were made due to these potential advantages and new scientific interest came up on what has been causing them [4]. Therefore, more research is required to fully understand the exact actions that SGLT2i has on the heart and kidneys among others. This review will examine all the merits of using SGLT2i in the management of heart failure, their part in reducing morbidity, mortality, and hospitalizations caused by heart failure, and their nephron-protecting qualities. Finally, SGLT2i will be juxtaposed with other diabetes drugs in terms of cardio-renal protection.

Outcomes of SGLT-2 Inhibitors on Heart Failure

Extensive trials in clinical practice were undertaken to evaluate heart and kidney protection among individuals suffering from heart failure or chronic kidney diseases. Both clinical investigations and thorough meta-analyses consistently show benefits across various patient subgroups, including people who have T2DM, non-diabetic individuals, and those at different stages of CKD. This extends to HF patients with both preserved and decreased ejection fraction. SGLT2 inhibitors are generally well-received, particularly with no observed evidence of heightened hypoglycemia risk in individuals with CKD or heart failure. Additionally, there is no apparent increase in the likelihood of acute kidney injury [9]. The two separate studies, DAPA-HF investigating dapagliflozin and EMPEROR-Reduced assessing empagliflozin, found that the two drugs reduced heart failure-related hospitalizations, improved kidney outcomes, and lowered mortality as well as cardiovascular deaths [10].

In a double-blind clinical trial, individuals suffering from Class Two, Three, or Four heart failure with an ejection fraction of 40% or less were randomly assigned to receive either empagliflozin (10 mg once daily) or placebo. Irrespective of patients' diabetic condition, the treatment with empagliflozin showed a decreased risk of death or hospitalization due to cardiovascular disease [11]. The Optimal Medical Therapies for type 2 diabetes include SGLT2 inhibitors that may have a positive impact on cardiovascular risk factors. Particularly, empagliflozin can correct these hazards and accomplish ordinary goals as well as lose weight from 1 to 5 kg, especially in individuals who have long-term diabetes and higher base weight. On the other hand, it has also been linked with a significant fall in systolic blood pressure and diastolic one, whereby the average drop in systolic blood pressure was 3-5 mmHg. Empagliflozin led to most patients achieving HbA1c levels of 7% compared to placebo. Moreover, it also functions as insulin sparing agent thus helping manage hyperinsulinemia and microalbuminuria while having potential nephroprotective effects \ Therefore, SGLT2 inhibitors are capable of significantly reducing negative cardiovascular outcomes as well as improving heart failure outcomes among patients suffering from T2DM along with coronary artery disease (CAD). Empagliflozin ought to be included in OMT for patients with T2DM and pre-existing cardiovascular disease. This is one way of bridging the gap between revascularization alone and OMT in T2DM patients with multi-vessel disease [12].

Individuals with metabolic syndrome and cardiovascular disease are affected by SGLT2 inhibitors to a large extent on the function of mitochondria through reduction of oxidative stress, increment of sirtuin activity, reduction in inflammation, and diminishing interstitial fibrosis resulting in improved cardiac functions. The multifaceted effects of SGLT2 inhibitors also cover volume regulation, cardiorenal mechanisms, metabolic impacts, improved cardiac remodeling, direct effects on cardiac contractility and ion homeostasis; as well as effects on autophagy and adipokines potentially promote heart failure status improvements [13-14]. Patients on gliflozin drugs undergo a condition that resembles starvation due to lack of nutrients and oxygen, which induces cellular autophagy and maintains the stability of the cells in various degradative methods. As such, SGLT2 inhibitors are no longer considered mere glycosuric agents lowering glucose levels but also enhancing erythropoiesis and stimulating ketogenesis but compounds that reduce intracellular sodium since their inception into clinical practice [15].

In heart disease patients, taking SGLT2 inhibitors has been associated with decreased mortality rates, major adverse cardiovascular events (MACE), and cardiovascular readmissions. With regard to risks versus benefits, there are more advantages than harm in using SGLT2 inhibitors [16]. In a cohort of patients hospitalized for acute heart failure, initiation of empagliflozin resulted in statistically and clinically significant benefits at 90 days post-randomization, including reductions in all-cause mortality, fewer heart failure events, and improvements in symptoms and quality of life. Benefits were observed across all heart failure conditions, including those with reduced or preserved left ventricular ejection fraction, acute de novo or decompensated chronic heart failure, and those with and without diabetes [17].

In a prespecified sub-trial of EMPA-HEART CardioLink-6, SGLT2 inhibition was found to decrease left ventricular mass index at six months in patients with T2DM. Canagliflozin is another SGLT2 inhibitor previously shown to improve T2DM-associated arterial stiffness through urate decrease. Canagliflozin improved blood flow restoration after hindlimb ischemia and was associated with increased angiogenic function. Added to this is the way empagliflozin improves central pulse pressure, forward pressure wave amplitude, and backward pressure wave amplitude in vascular function, which might contribute to improved filling conditions and mitigate heart failure consequences. [8].

Empagliflozin decreased the rate of hospitalization for heart failure across the full spectrum of severity, including hospitalization requiring only oral or intravenous diuretics and those requiring intravenous vasopressors or positive inotropic agents. The risk for heart failure requiring intensive care unit admission was lowered by 35 percent. Specifically, the SGLT2 inhibitor reduced by 34% the chances of patients requiring intravenous diuretics for urgent or emergency treatment due to worsening heart failure. Moreover, dapagliflozin has been reported to lower the risk of urgent outpatient heart failure events [18]. In the EMPULSE trial, empagliflozin treatment significantly improved KCCQ-TSS, physical limitations, quality of life, and clinical summary at 90 days. The positive health status effects were observed as early as 15 days and throughout the period under study [19]. Notably, SGLT2 inhibitors have recently been included in the European Society of Cardiology's recommendations for the treatment of HFrEF patients after the promising results from the DAPA-HF and EMPEROR-Reduced studies [20].

Delaying initiation of guideline-recommended SGLT2 inhibitors to outpatient care in the United States carries a >75% chance of not being initiated within the following year. Lessons from the treatment of heart failure with reduced ejection fraction demonstrate that 1 in 4 patients hospitalized for worsening heart failure experience death or readmission within 30 days. Therefore, it is invariably considered the best opportunity during a hospital stay to initiate SGLT2 inhibitor medication and to treat this population with appropriate urgency [21]. Besides, SGLT2 inhibitors might modulate the prognosis and attenuate atherosclerosis processes through their multiple beneficial cardiovascular effects beyond glucose-

lowering action, including a reduction in blood pressure, body weight, and epicardial fat volume. Apart from these described mechanisms, SGLT2 inhibitors decrease preload and afterload due to their natriuretic and osmotic diuretic properties, which would be expected to further lower blood pressure and slow the progress of atherosclerosis [22].

Outcomes of SGLT-2 Inhibitors on Renal Failure

SGLT2i targeted the treatment of diabetes mellitus. In addition to their glucose-lowering action, they also exert reno-protective effects that reduce the risk of renal impairment [23]. One of the benefits of SGLT2 inhibitors in patients with both preserved and impaired GFR is that the mechanisms involve more than blood pressure, weight, and glucose lowering. These effects have even been seen in lean normoglycemic, normotensive, nondiabetic individuals. The primary mechanism underlying this effect is tubule-glomerular feedback. SGLT2 inhibitors increase the levels of sodium that travel along the nephron. This increased sodium is sensed by the macula densa cells through adenosine and acts to constrict afferent glomerular arterioles so that there is reduced glomerular pressure; therefore, the glomeruli are preserved. SGLT2 inhibitors downregulate renal inflammation and fibrosis, enhance tubular oxygenation and metabolism, and increase glucagon levels. Clinical data indicate that these medications may decrease the development of or progression to albuminuria but do not increase the risk of acute renal injury or urinary tract infection [24-25]. For instance, dapagliflozin increases the itaconate metabolite of the mitochondrial tricarboxylacyclic acid cycle, which inhibits activation of the inflammasome, NLRP3. This perhaps opens up the potential for SGLT2 inhibition as an approach to target an inflammatory response and abnormal metabolism occurring during the initiation and progression of several renal diseases [26]. Real-world data show that treatment with SGLT2 inhibitors decreases the risk of serious kidney damage in a population already treated with RAAS inhibitors, and there is no evidence of an increased risk for AKI when RAAS blockers and SGLT2 inhibitors are combined in the absence of hemodynamic instability [27].

It is in this regard that CKD presents a heavy burden to families and society. Only RAS blockers have been shown to provide renoprotection for the last two decades. Today, new opportunities are emerging for CKD patients with the discovery of sodium-glucose cotransporter inhibitors. The risk of major renal outcomes with SGLT2 inhibitors was significantly low, and such an effect did not stop at any of the eGFR values [28]. In a subset of T2DM-CKD patients treated with SGLT2 inhibitors during routine clinical practice, renal outcomes were significantly better than those observed in patients treated with other glucose-lowering medications, without differences according to the presence of proteinuria or the rate of eGFR decline before treatment [29]. DKD is a complex renal disorder that, by remodeling the intrinsic cells of the kidneys, affects adversely their structure, function, and phenotypic features, leading to absolute fibrosis. SGLT2 inhibitors are kidney-protective and significantly decrease the abnormal remodeling of intrinsic renal cells, delaying the onset and progression of diabetes-induced renal disorders [30]. A unique link exists between renal ketone body metabolism, mTORC1 signaling, SGLT2 suppression, and the pathophysiology of diabetic kidney disease. Targeting renal energy metabolism might prove to be a tenable treatment strategy for protein-uric and nonprotein-uric diabetic kidney diseases since multiple mechanisms may mediate the reno-protective effects of SGLT2 inhibitors involving ketone bodies and PTECs [31].

Fructose modulation of CKD may occur due to dietary excess or, in the presence of intrarenal ischemia, as a result of enhanced glucose trafficking and stimulation of endogenous fructose synthesis; inhibition of these pathways could explain in part the benefits of SGLT2 inhibitors in CKD with and without diabetes [32]. SGLT2 inhibitors can stimulate erythropoiesis and activate a systemic hypoxia-like response, increasing oxygen delivery to tissues while having relatively minor effects on HbA1C and nutrient-deprivation signaling. This might be an explanation for their property of increasing erythropoiesis by activating HIF-2α and suppressing HIF-1α. The body metabolically adapts to the forced urinary glucose loss by reducing fat mass and increasing ketone bodies as fuel [8-33]. It has been shown that both empagliflozin and benzbromarone strongly reduce plasma uric acid levels and increase fractional uric acid excretion [34]. In subjects with T2DM, SGLT2 inhibitors exert protection against acute kidney injury and decrease the risk of dialysis, transplantation, or death from kidney disease. Moreover, SGLT2 inhibitors may be safely used in diabetic KTRs and exert favorable effects on graft function maintenance [35-36].

Discussion

This article presented a risk reduction of 14% in cardiovascular death among 8474 patients, with a 25% reduction in the combined outcome of cardiovascular death or recurrent hospitalization for heart failure, depending on the meta-analysis method [9]. Within the empagliflozin group, only 19.4% of heart failure hospitalizations were noted, against 24.7% in the placebo group. Moreover, heart failure hospitalization was less frequent, and the estimated glomerular filtration rate decreased in the empagliflozin group. All in all, the risks of heart failure were lower with empagliflozin, irrespective of the diabetes status [10].

The SGLT2 inhibitors exhibited efficacy both in CKD and HF, whatever the ejection fraction status and presence of diabetes. In the setting of CKD patients, they were associated with a lower risk of hyperkalemia and anemia [11]. They also reduced important cardiovascular adverse effects in subjects with coronary artery disease and T2DM [12]. Comparative studies between SGLT 2 inhibitors and placebos in high-risk heart failure or heart disease patients revealed that there was a significant reduction in acute kidney injury with SGLT 2 inhibitors. Their use is however associated with a risk of DKA and volume depletion [13].

In another study, 530 patients with decompensated CHF and left ventricular ejection fractions differed from one another. Patients were randomized to receive either 10 mg of empagliflozin or a placebo for 90 days. Those who received the former latter opponent over-posting revealed important clinical benefits, and the treatment was well tolerated [15]. SGLT2 inhibitors have some protective mechanisms that involve both glucose-dependent and independent actions, which include prevention of hypo- and hyperglycemia, volume retention, and lowering of blood pressure and possibly heart function. The exact mechanisms for this are partly accomplished by mechanisms that overcome diuretic resistance, inhibit Na-H exchangers, and reduce sympathetic tone [16]. Inhibitors of SGLT2 decrease heart failure events for both inpatients and outpatients, with benefits evident early after treatment initiation [17].

There is extensive fundamental and clinical data that support the continuous administration of SGLT2 inhibitors in heart failure. Among the mechanisms of action, the enhancement of cardiorenal status, improvement in volume regulation, enhanced cardiac remodeling, metabolic actions, direct influence on cardiac contractility and ion-homeostasis, decrease in inflammation and oxidative stress, and actions on autophagy and adipokines explain how these inhibitors improve HF status [8]. Indeed, in patients with chronic heart problems and poor health status, quality of life is considerably reduced with increased symptoms and physical disability. In a study of 530 patients treated with empagliflozin, significant clinical benefits were observed from 15 to 90 days with improvements noted in symptoms, physical limitations, and

quality of life [18]. The majority of medications used to treat heart failure, including SGLT2 inhibitors, have focused on the relief of symptoms rather than morbidity and mortality. SGLT2 inhibitors have, however, demonstrated a benefit for heart failure with preserved ejection fraction. [19].

SGLT2 inhibitors are known to exert some actions that lower the risk of heart disease, especially in heart failure, through the reduction of intracellular sodium levels and the activation of autophagy mechanisms. This article defines the very early steps of the application of these inhibitors in therapy, independent of other medications, and foresees their integral role in heart failure treatment in the future [20]. Given that nearly 1 in 4 patients with heart failure are readmitted to the hospital within 30 days, the period is considered optimal for the initiation of SGLT2 treatment. It is immediate and reflects the need to focus on this population [21]. Some benefits of SGLT2 inhibitors in atherosclerotic cardiovascular disease may be involved in the suppression of atherosclerotic processes, although perhaps improving the prognosis of patients with diabetes at heightened risk from atherosclerotic cardiovascular disease [22].

Research has suggested that SGLT2 inhibitors can decrease the incidence of AKI in patients with diabetes mellitus, which has remained consistent across RCTs and observational cohort studies and without any heterogeneity for different SGLT2 inhibitors [23]. Hyperfiltration is the usual earliest glomerular damage, wherein the mechanism of this debilitating condition relates to hyperinsulinemia and insulin resistance in prediabetic and early type 2 diabetes; it affords profibrotic changes leading to an accelerated decline in GFR and functional disturbances in diabetic kidney disease. SGLT2 inhibitors have direct and indirect effects on the kidney, which empower acute and chronic prophylactic benefits of nephropathy, rendering it possible to slow progression and partially reverse markers of diabetic kidney disease [24].

SGLT2 inhibitors represent a major breakthrough in the treatment of T2DM, widen the therapeutic armamentarium, and probably lower the risk for renal dysfunction. Clinically relevant information on whether SGLT2 inhibitors protect the renal and cardiovascular functions of T2DM patients is expected from already initiated or future clinical trials in the coming years [25]. Dapagliflozin, an SGLT2 inhibitor, can reverse energy metabolic and inflammatory disorders in adult fibrosing kidneys by upregulating inflammatory pathways associated with increased mitochondrial TCA cycle metabolites, suggesting a potential mechanism by which SGLT2 inhibition could target dysregulated metabolism and inflammation in a variety of kidney diseases [26].

Safety analyses from large cardiorenal trials showed a reduction in the number of AKI events in T2DM patients treated with an SGLT2 inhibitor compared to those on a placebo. This was observed despite most patients being on baseline therapy with RAAS blockers. Confirming this, other retrospective observational studies also found the risk of AKI to be lower for SGLT2 inhibitors compared to other glucose-lowering drugs even in patients on RAAS blockers. To date, none of the evidence supports the point that the addition of an RAAS blocker to add-on SGLT2i might augment risks for AKI without hemodynamic instability [27]. Other studies also found that the SGLT2 inhibitor did not increase the risk of kidney injury due to acute trauma, fracture, or amputation associated with the use of these medications; rather, it lowered the risk for AKI in patients with T2DM [28]. T2DM patients with CKD who were prescribed an SGLT2 inhibitor showed significantly better kidney outcomes than those who used other glucose-lowering drugs, regardless of the presence of proteinuria or eGFR decline before treatment [29].

SGLT2 inhibitors exert renal protective effects and significantly inhibit intrarenal cell pathological remodeling, which retards the progression of DKD [30]. The elevated ketone bodies will enhance this renoprotection through the correction of mTORC1 hyperactivation in DKD [31]. According to one study, fructose coming from either dietary excess or endogenous production may contribute to CKD. In this regard, SGLT2 inhibitors may be linked to the suppression of these pathways in diabetic and nondiabetic CKD [32]. SGLT2 inhibitors decrease the risk of kidney and cardiac failure in people with both preserved and reduced kidney function and in both people with or without diabetes. It reduces the risk of both hyper and hypoglycemia and enhances metabolic adaptations, including increased lipolysis and elevated ketone bodies, to promote long-term preservation of tubular function and GFR. These inhibitors prevent cardiac failure not only in T2DM patients but also in non-T2DM ones with heart failure [8].

In the diabetic kidney, this promotes more activation of HIF-1α and less HIF-2α in response to renal hypoxia, oxidative stress, and diminished sirtuin1/AMPK activity. Combined, these factors give rise to a maladaptive environment contributing to glomerular and renal tubular dysfunction, inflammation, fibrosis, and poor erythropoietin production in diabetic CKD. The SGLT2 inhibitors reduce HIF-1α, but enhance HIF-2 α signaling, which results in increased erythropoiesis, decreased organelle dysfunction, and possibly reduces the proinflammatory and profibrotic pathways, slowing the progression of diabetic kidney disease. Up-regulation in the signaling of oxygen deprivation as a possible mechanism through which SGLT2 inhibitors can exert reno-protective benefits was thought to explain the [33]. However, it has yet to be clearly defined if this is the mechanism by which the uricosuric work on diabetic patients with normal kidney function; baseline excretion of uric acid was similar among patients [34]

A meta-analysis and systematic review of randomized, controlled cardiovascular or kidney outcome trials of SGLT2 inhibitors examined the effect on major kidney outcomes in T2DM patients. The primary outcome measured was a composite of renal disease-related death, transplantation, or dialysis. Recent research has shown that protection against AKI and a reduction in renal events of death and dialysis or transplantation are exerted with SGLT2 inhibitors [35]. A multicenter cohort study in kidney transplant recipients with diabetes suggested improved outcomes of all-cause mortality, death-censored graft failure, or serum creatinine doubling following the administration of SGLT2 inhibitors, showing the safe practice of this drug in maintaining graft function [36].

SGLT2 inhibitors have been developed for T2DM but offer promising results in cardiovascular and renal outcomes, hence opening the way for their application in other chronic kidney disease treatments, including AS [37]. There has not been a specific indication for type 1 diabetes yet, but studies suggest potential benefits of SGLT2is in T1DM when used in conjunction with insulin without an increased risk for hypoglycemia. As medications, they act on inhibiting SGLT2 in the early proximal tubules within the kidney, resulting in reduced renal glucose reabsorption, thus improving blood glucose control [38].

In clinical practice, T2DM patients with CKD treated with SGLT2 inhibitors showed significant improvement in kidney outcomes compared with those taking any other glucose-lowering drugs, which was independent of proteinuria and eGFR decline before treatment [39]. One such hypothesis is that SGLT2 inhibitors inhibit the central sympathetic nervous system directly or indirectly.

Abnormal activation of the SNS has long been considered a central pathological component of heart failure and renal disease. Importantly, SGLT2 inhibitors lower blood pressure in the absence of an attendant increase in heart rate, suggesting a reflex inhibitory action on the SNS.

Preliminary evidence suggests that this action may extend to include reductions in SNS activity in models of obesity and diabetes [40]. Notably, both systolic and diastolic blood pressures have been steadily reduced in patients with Type 2 diabetes and hypertension. This corroborates SGLT2 inhibitors' efficiency, such as canagliflozin, dapagliflozin, or empagliflozin. This outcome is reached by means of a reduction in sympathetic activity and mild natriuresis. Clinical trials of changes in blood pressure and body weight have recorded that people with diabetes at high cardiovascular risk can also experience benefits including a reduced rate of heart failure and slowing in the progression of kidney disease [41]

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) showcase various effects that could potentially benefit outcomes in COVID-19 patients, though this concept awaits confirmation from the ongoing well-designed randomized controlled trial. Despite this, concerns about the potential uprising problem with DKA should not be overlooked. In individuals that had asymptomatic or mild COVID-19, it is advisable to continue SGLT2i treatment for optimal glucose control and to potentially leverage its additional positive effects beyond glucose regulation [42]. Multiple studies support the notion that SGLT2is when used with substances that decrease food intake, can be useful as adjuvant weight loss therapy, making such combination treatments appealing. However, treatment with SGLT2 inhibitor alone is unlikely to offer adequate reduction in BMI to treat obesity alone. Still, these drugs may provide additional advantages for obese individuals who also have co-morbid conditions such as cardiac failure, kidney failure, or atherosclerotic cardiovascular disease. Moreover, research is needed to explore phenotypic and genotypic features that may help identify individuals who respond well to weight-loss therapies involving the usage of these drugs [43].

Recent reviews highlighted that SGLT2 inhibitors may possess antioxidant properties in acute and general human ailments. Various human illnesses, including DM, heart problems, kidney diseases, various non-alcoholic fatty liver disease (NAFLD), neurodegenerative diseases, or cancer are also caused by oxidative stress, which these inhibitors can particularly mitigate. These inhibitors can effectively reduce oxidative stress, by lowering glucose levels, directly scavenging free radicals, and enhancing the body's natural antioxidant systems. The therapeutic benefits of SGLT2 inhibitors are thus demonstrated through these mechanisms. [44]. As proven by reduced inflammatory markers, SGLT2 inhibitors have anti-inflammatory properties. Therefore, this observation may explain their favorable effects on cardiorenal outcomes.

[45]

To prevent the occurrence of any possible hazard during consumption of sodium-glucose cotransporter 2 inhibitors, doctors should ensure patients are hydrated adequately, their bone density is examined, their cardiac status checked, and liver/kidney functions are assessed. The usage of these drugs should be cautiously among people with a background of T1DM, type 2 diabetes associated with ketosis, and subjects having an average Glomerular Filtration Rate of less than 60 mL/min. Monitoring blood glucose levels, and kidney function as well as voice control during visits helps reduce risks while managing prescriptions for these new-class drugs [46].

Conclusion

In addition to reducing blood sugar levels, SGLT2 inhibitors are crucial in the management of both types of ejection fraction heart failure resulting in a significant reduction in hospital admissions. Moreover, they act as renal system protective agents which lowers the progression of kidney disease thereby reducing the risks associated with dialysis, transplantation, and mortality from renal-related problems.

References

1. Malik A, Brito D, Vaqar S, Chhabra L. (2023). Congestive Heart Failure. 2022 Nov 7. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; PMID: 28613623.
2. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, et al. (2023). Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023 Jan 18;118(17):3272-3287. doi: 10.1093/cvr/cvac013. Erratum in: Cardiovasc Res. 13;119(6):1453. PMID: 35150240.
3. Tamayo-Gutierrez A, Ibrahim HN. (2022). The Kidney in Heart Failure: The Role of Venous Congestion. Methodist Debakey *Cardiovasc J.* 18(4):4-10. doi: 10.14797/mdcvj.1121. PMID: 36132580; PMCID: PMC9461698.
4. Salvatore T, Galiero R, Caturano A, Rinaldi L, Di Martino A, et al. (2022). An Overview of the Cardiorenal Protective Mechanisms of SGLT2 Inhibitors. Int J Mol Sci. 26;23(7):3651.
5. Younes AM, Salem M, Maraey A, Nomigolzar S, Sewell K, et al. (2022). Safety outcomes of SGLT2i in the heart failure trials: A systematic review and Meta-analysis. *Int J Cardiol.* 1;366:51-56.
6. Petrie MC, Verma S, Docherty KF, Inzucchi SE, Anand I, et al. (2021). Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes. JAMA. 2020 Apr 14;323(14):1353-1368. doi: 10.1001/jama.2020.1906. Erratum in: JAMA. 325(13):1335. PMID: 32219386; PMCID: PMC7157181.
7. Hou YC, Zheng CM, Yen TH, Lu KC. (2020). Molecular Mechanisms of SGLT2 Inhibitor on Cardiorenal Protection. Int J Mol Sci. 21(21):7833. doi: 10.3390/ijms21217833. PMID: 33105763; PMCID: PMC7660105.
8. Vallon V, Verma S. (2020). Effects of SGLT2 Inhibitors on Kidney and Cardiovascular Function. Annu Rev Physiol. 10;83:503-528. doi: 10.1146/annurev-physiol-031620-095920. Epub PMID: 33197224; PMCID: PMC8017904.
9. van der Aart-van der Beek AB, de Boer RA, Heerspink HJL. (2022). Kidney and heart failure outcomes associated with SGLT2 inhibitor use. Nature Reviews Nephrology. 18(5):294–306.
10. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, et al. (2020). SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. The Lancet. 396(10254).
11. Packer, M., Anker, S. D., Butler, J., Filippatos, G., Pocock, S. J., et al. (2020). EMPEROR-Reduced Trial Investigators (2020). Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. The *New England journal of medicine*, 383(15), 1413–1424. https://doi.org/10.1056/NEJMoa2022190
12. Mosleh W, Sharma A, Sidhu MS, Page B, Sharma UC, et al. (2017). The Role of SGLT-2 Inhibitors as Part of Optimal Medical Therapy in Improving Cardiovascular Outcomes in Patients with Diabetes and Coronary Artery Disease. 24;31(3):311–318
13. Sanz R, Inserra F, Sebastián García Menéndez, Mazzei L, Ferder L, et al. (2023). Metabolic Syndrome and Cardiac Remodeling Due to Mitochondrial Oxidative Stress Involving Gliflozins and Sirtuins. 13;25(6):91–106.

14. Pabel S, Hamdani N, Luedde M, Sossalla S. (2022). SGLT2 Inhibitors and Their Mode of Action in Heart Failure—Has the Mystery Been Unravelled? Current Heart Failure Reports [Internet]. 2021 Sep 15 18(5):315–328.
15. Palmiero G, Cesaro A, Vetrano E, Pafundi PC, Galiero R, et al. (2021). Impact of SGLT2 Inhibitors on Heart Failure: From Pathophysiology to Clinical Effects. *International Journal of Molecular Sciences.* 22(11):5863.
16. Deshpande R, Patel R, Manjari Regmi, Salih M, Kropp R, et al. (2023). Safety outcomes of sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes and other risk factors for cardiovascular disease: a systematic review and meta-analysis. 12(2).
17. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, et al. (2022). The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nature Medicine [Internet]. [cited 2022 Mar 8];1–7.
18. Packer M, Anker SD, Butler J, Filippatos GS, Ferreira JP, et al. (2020). Effect of Empagliflozin on the Clinical Stability of Patients with Heart Failure and a Reduced Ejection Fraction: The EMPEROR-Reduced Trial. *Circulation.*
19. Kosiborod MN, Angermann CE, Collins SP, Teerlink JR, Ponikowski P, et al. (2022). Effects of Empagliflozin on Symptoms, Physical Limitations and Quality of Life in Patients Hospitalized for Acute Heart Failure - Results From the EMPULSE Trial. Circulation.
20. Heath R, Johnsen H, Strain WD, Evans M. (2022). Emerging Horizons in Heart Failure with Preserved Ejection Fraction: The Role of SGLT2 Inhibitors. Diabetes Therapy. 13(2):241–50.
21. Rao VN, Murray E, Butler J, Cooper LB, Cox ZL, et al. (2021). In-Hospital Initiation of Sodium-Glucose Cotransporter-2 Inhibitors for Heart Failure With Reduced Ejection Fraction. *Journal of the American College of Cardiology.* 78(20):2004–2012.
22. Pahud de Mortanges A, Salvador Jr. D, Laimer M, Muka T, Wilhelm M, et al. (2021). The Role of SGLT2 Inhibitors in Atherosclerosis: A Narrative Mini-Review. Frontiers in Pharmacology [Internet].
23. Menne, J. et al. (2019). 'Acute kidney injury and adverse renal events in patients receiving SGLT2-inhibitors: A systematic review and meta-analysis', PLOS Medicine, 16(12).
24. Bailey CJ, Day C, Bellary S. (2022). Renal protection with SGLT2 inhibitors: Effects in acute and chronic kidney disease. Current Diabetes Reports. 22(1):39–52.
25. Davidson JA. (2019). SGLT2 inhibitors in patients with type 2 diabetes and renal disease: Overview of current evidence. Postgraduate Medicine. 131(4):251–60.
26. Ke Q, Shi C, Lv Y, Wang L, Luo J, et al. (2021). SGLT2 inhibitor counteracts NLRP3 inflammasome via tubular metabolite itaconate in fibrosis kidney. The FASEB Journal. 36(1).
27. Scheen AJ, Delanaye P. (2022). Acute renal injury events in diabetic patients treated with SGLT2 inhibitors: A Comprehensive Review with a special reference to Raas Blockers. Diabetes & Metabolism. 48(2):101315.
28. Li N, Lv D, Zhu X, Wei P, Gui Y, et al. (2021). Effects of SGLT2 inhibitors on renal outcomes in patients with chronic kidney disease: A meta-analysis. Frontiers in Medicine. 8.
29. Nagasu H, Yano Y, Kanegae H, Heerspink HJL, Nangaku M, et al. (2021). Kidney outcomes associated with SGLT2 inhibitors versus other glucose-lowering drugs in real-world clinical practice: The Japan Chronic Kidney Disease Database. 44(11):2542–2551.
30. Guo W, Li H, Li Y, Kong W. (2023). Renal intrinsic cells remodeling in diabetic kidney disease and the regulatory effects of SGLT2 inhibitors. Biomedicine & Pharmacotherapy. 165:115025.
31. Tomita I, Kume S, Sugahara S, Osawa N, Yamahara K, et al. (2020).SGLT2 inhibition mediates protection from diabetic kidney disease by promoting ketone body-induced mtorc1 inhibition. Cell Metabolism. 32(3).
32. Nakagawa T, Sanchez-Lozada LG, Andres-Hernando A, Kojima H, Kasahara M, et al. (2021). Endogenous fructose metabolism could explain the Warburg effect and the protection of SGLT2 inhibitors in chronic kidney disease. *Frontiers in Immunology.* 12.
33. Packer M. (2021). Mechanisms leading to differential hypoxia-inducible factor signaling in the diabetic kidney: Modulation by SGLT2 inhibitors and hypoxia mimetics. *American Journal of Kidney Diseases*. 77(2):280–286.
34. Suijk DLS, van Baar MJB, van Bommel EJM, Iqbal Z, Krebber MM, et al. (2022). SGLT2 inhibition and uric acid excretion in patients with type 2 diabetes and normal kidney function. *Clinical Journal of the American Society of Nephrology.* 17(5):663–671.
35. 14-Neuen BL, Young T, Heerspink HJ, Neal B, Perkovic V, et al. (2019). SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: A systematic review and meta-analysis. *The Lancet Diabetes & Endocrinology.* 7(11):845–54.
36. 15-Lim J-H, Cho J-H. (2023). Re: The efficacy and safety of SGLT2 inhibitor in kidney transplant recipients with diabetes. Transplantation. 107(3).
37. Mabillard H, Sayer JA. (2020).SGLT2 inhibitors - a potential treatment for Alport syndrome. Clin Sci (Lond). 134(4):379-388.
38. Fattah H, Vallon V. (2018). The Potential Role of SGLT2 Inhibitors in the Treatment of Type 1 Diabetes Mellitus. Drugs. 78(7):717-726
39. Nagasu H, Yano Y, Kanegae H, Heerspink HJL, Nangaku M, et al. (2021). Kidney Outcomes Associated With SGLT2 Inhibitors Versus Other Glucose-Lowering Drugs in Real-world Clinical Practice: The Japan Chronic Kidney Disease Database. Diabetes Care. 44(11):2542-2551.
40. Verma S. (2020). Are the Cardiorenal Benefits of SGLT2 Inhibitors Due to Inhibition of the Sympathetic Nervous System? JACC Basic Transl Sci. 24;5(2):180-182.
41. Briasoulis A, Al Dhaybi O, Bakris GL. (2018). SGLT2 Inhibitors and Mechanisms of Hypertension. Curr Cardiol Rep. 20(1):1. doi: 10.1007/s11886-018-0943-5. PMID: 29349558.
42. Scheen AJ. (2020).SGLT2 inhibition during the COVID-19 epidemic: Friend or foe? Diabetes Metab. 46(5):343-344. doi: 10.1016/j.diabet.2020.06.003. Epub 2020 Jun 17. PMID: 32562762; PMCID: PMC7836403.
43. Pereira MJ, Eriksson JW. (2019). Emerging Role of SGLT-2 Inhibitors for the Treatment of Obesity. Drugs. 79(3):219-230. doi: 10.1007/s40265-019-1057-0. PMID: 30701480; PMCID: PMC6394798.
44. Tsai KF, Chen YL, Chiou TT, Chu TH, Li LC, et al. (2021). Emergence of SGLT2 Inhibitors as Powerful Antioxidants in Human Diseases. Antioxidants (Basel). 10(8):1166.

45. Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, et al. (2022). The impact of SGLT2 inhibitors on inflammation: A systematic review and meta-analysis of studies in rodents. Int Immunopharmacol. 111:109080.

46. Pittampalli S, Upadyayula S, Mekala HM, Lippmann S. (2018). Risks vs Benefits for SGLT2 Inhibitor Medications. Fed Pract. 35(7):45-48. PMID: 30766374; PMCID: PMC6368009.

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