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Review Article

The Role of SGLT2 Inhibitors on Treatment of Heart Failure, Mode of Actions

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Abstract

Sodium glucose co-transporter 2 (SGLT2) inhibitors have been in use for treating type 2 diabetes with recent advances in treating heart failure, especially in the context of patients with or without diabetes. SGLT2i has broader effects than diabetic control for treating heart failure, which operates through several interwoven pathways. Their diuretic effects cause a reduction in blood volume, which, in turn, results in preload decline in the heart. Lower preload can benefit patients with heart failure since it reduces congestion and edema. SGLT2 inhibitors promote the excretion of glucose and Na+ in the urine, lowering plasma volume. Lowered plasma volume decreases the workload on the heart and improves cardiac function, especially in patients with HFrEF. SGLT2is has been shown to shift cardiac metabolism from fatty-acid use to more efficient glucose use. SGLT2 inhibitors have mitigated cardiac remodeling, reducing myocardial fibrosis, hypertrophy, and inflammation. SGLT2 inhibitors have been found to lower blood pressure, which can be beneficial in the management of heart failure, especially in patients with hypertension. Clinical trials where SGLT2is showed significantly lowered risks of adverse cardiovascular events, including HF hospitalizations, cardiovascular mortality, and all-cause mortality in patients with heart failure with and without diabetes.

Keywords: SGLT2i; Heart Failure; Cardiovascular disease

Mechanisms of SGLT2 Inhibitors in Heart Failure Management Improvement in Cardiac Energetics

Specifically, SGLT2 inhibitors help reverse the heart's metabolism from one that relies mainly on using fatty acids to one that's more energy-efficient by using glucose. These adaptions can improve myocardial energetics and function, especially in failing hearts that cannot use glucose. Studies like that by Yu, et al. on the effect of SGLT2i show fewer deaths in the EMPA-REG OUTCOME. It is an achievement that makes it possible to record better results when managing HF in diabetic patients [1]. The SGLT2i reduces renal tubular glucose reabsorption, which, in turn, helps lower blood glucose without stimulating insulin release. Different clinical trials are present in the study of the impact of SGLT2i. The use of empagliflozin and dapagliflozin has been tried in most studies to test the effects of SGLT2 inhibitors in HF control [1]. The study shows that using the therapy positively impacts reducing adverse cardiovascular complications. However, the deaths in the trials cannot be attributed to either cardiovascular or non-cardiovascular causes.

The use of Empagliflozin helps ameliorate the cardiac energy deficient state that is responsible for the regression of adverse myocardial cellular modeling. The drug helps improve cardiac function, mainly due to the significant myocardial blood flow. Energetics are redefined in type 2 diabetes patients [2]. At the same time, the shift in the myocardial substrate metabolism is an issue that is evident in type 2 diabetes patients that further leads to heart failure, which can be controlled by the use of SGLT2is to reduce insulin resistance [3]. Similar study results show that the use of SGLT2i plays a vital role in myocardial energetics and fuel metabolism through properly leveraging targeted metabolomics in the blood [4]. It is integral to have a suitable cardiac energetics rating for the appropriate functioning of the heart and to reduce HF incidences. Empagliflozin, an SGLT2i, acts as a mechanism of entering the cardiac mitochondria, hence maintaining the systolic and mitochondrial ATP levels [5]. The SGLT2 inhibitors work by inhibiting the NHE1 and Nav1.5, increasing mitochondrial ATP subject to improved cardiac energetics.

Blood Pressure Lowering

The SGLT2 inhibitors lower blood pressure, a well-described

benefit in managing heart failure, and are expected in hypertension patients. In essence, lowering blood pressure reduces afterload on the heart, thus improving cardiac function and reducing the incidence of adverse cardiovascular events. The use of SGLT2i proves to help significantly in managing blood pressure and the realization of lower glomerular capillary hyperfiltration and hypertension [6].

Lower glomerular hypertension helps reduce the filtration barrier's physical stress and oxygen demand in the tubular reabsorption. The integration of SGLT2i is proven to improve the CVD state by preventing the progression of renal dysfunction in type 2 diabetes patients by reducing blood pressure [7]. The issue of blood pressure is a common problem among type 2 diabetes patients that mostly leads to significant complications like HF and other cardiovascular problems that need to be solved. A similar conclusion on the role of SGLT2 inhibitors in reducing hypertension that leads to HF is seen in the mechanism by which it acts on the pleiotropic cardiovascular effects that lower arterial blood pressure [8]. Lowering the BP helps keep the heart's integrity at the right level, hence realizing the specific aspects of the patient to prevent complications of HF in most cases.

The treatment of Diabetes has a direct connection with the management of blood pressure, which is a central component of HF complications. Despite the limited evidence of SGLT2 inhibitors' effects on blood pressure, there is still a connection between high blood pressure and the development of HF, which is lower in patients who are administered the drugs for diabetes [9]. The mechanism of the SGLT2 inhibitors in managing HF is connected to the fact that the medication reduced adverse cardiovascular events and lowered blood pressure among the patients. The integration of SGLT2 inhibitors helps reduce arterial hypertension, which, in turn, helps prevent the advancement of HF complications [10]. The prevention of high blood pressure is a significant move towards achieving a better avenue to avoid the occurrence of HF incidences. Blood pressure plays a vital role in the development of HF.

Reduction in Adverse Cardiovascular Events

Trials of SGLT2 inhibitors, including EMPA-REG OUTCOME, DECLARE-TIMI 58, and DAPA-HF, show that these drugs substantially reduced the risk of HF, including hospitalizations, death, and all-cause death in people with heart failure with and without diabetes.

The mechanism of SGLT2i action is defined by the decline of cardiovascular complications immediately after initiating the therapy compared to other treatment options [11]. The therapy option gives an outstanding benefit for the use of the SGLT2i in the management of HF on top of type 2 diabetes. The integration of different kinds of SGLT2 inhibitors depicts positive results in reducing Major Cardiovascular Events (MACE), hence preventing the occurrence of HF [12]. The mechanism of action of the drugs is essential as it prevents any further advancement of MACE that helps patients to lead a near-normal life while they have particular health complications. A similar conclusion to the above study is that initiating the SGLT2i reduces cardiovascular events and improves renal outcomes among diabetes patients, which further helps manage HF incidences [13]. The point of interest is the action of preventing any adverse cardiovascular events that mostly escalate to HF among diabetes and non-diabetes patients.

The action of SGLT2 inhibitors gives better outcomes when preventing MACE and contributes to most incidences of HF in society [14]. The initiation of a treatment plan for HF patients requires better therapy that has the potential to improve the health of the participants.

The patients initiated to SGLT2i had better outcomes in reduced CV mortality, HF hospitalizations, and HF deaths due to the reduced MACE that is prevented by the action of the drugs [15]. Understanding the mechanism of MACE prevention is critical in ensuring that the patients at high risk of HF will remain healthy and that the chances of developing the complications are minimal in the given contexts. The use of the drugs helps in reducing the possibility of MACE happening, which defines the primary triggers of cardiovascular complications, with heart failure being the most common one among diabetes patients.

Reduction in Cardiac Remodeling

SGLT2 inhibitors can also mitigate cardiac remodeling, which damages the heart muscle in ways such as myocardial fibrosis, hypertrophy, and inflammation. The effect likely stems from inhibition of the sodium-hydrogen exchanger (NHE), from a reduction in oxidative stress and neurohormonal modulation such as two physiologically essential pathways and the Renin-Angiotensin-Aldosterone System (RAAS) and the sympathetic nervous system. The administration of empagliflozin is an effective remedy to prevent heart remodeling that helps improve LV volume and mass, diastolic and systolic function, and reverses any cardiac damage among HF patients [16]. The reversed remodeling results from the favorable effects of the SGLT2i drug administration. The prevention or reversal of cardiac remodeling is an essential procedure in HF treatment and therapy that can be attained through the mechanism of SGLT2i drugs to help reduce the impact of sodium-glucose coconspirator on the renal tubular cells [17]. The inhibition of neurohumoral activation is an essential mechanism through which SGLT2i works to prevent the apoptosis and necrosis of cardiomyocytes.

Cardiac remodeling, especially ventricular damage and longitudinal strain prevention, makes it possible to improve the health of HF patients. This element is evident in the treatment with SGLT2 inhibitors [18]. Ventricular remodeling is a significant cause of heart failure, hence the need to make sure that the process is reversed through the administration of SGLT2i drugs. The initiation of a treatment plan with SGLT2 inhibitors proves to be instrumental in managing HF by reversing the cardiac remodeling process, mainly in HFrEF patients [19]. The outcome of the treatment depicts a reversal of cardiac volumes, improved functions of left ventricular functions, and LV mass. The management of HF

is seen to be significantly enhanced by the use of SGLT2i drugs by having a reduction of left ventricular mass when assessed before and after the treatment progression using the cMRI technique [20]. The integration of the treatment plan is necessary to reduce the possible implications of heart tissue damage that leads to heart failure.

Diuretic Effect

SGLT2 inhibitors block glucose and sodium reabsorption, increasing fecal and urinary excretion of glucose and sodium. This causes osmotic diuresis and natriuresis, and the diuretic effect decreases blood volume and hemodynamic pressures on the heart, decreasing preload and congestion that can be life-saving in heart failure. It can decrease edema. There is a significant impact of SGLT2i in terms of the mechanism of action in improving renal outcomes and cardiovascular function that reduces the number of HF hospitalizations [21]. The ability of the drugs is to maintain the osmotic diuresis in patients with HF or diabetes. The mechanism of action of SGLT2 inhibitors modifies sodium and glucose reabsorption, which modifies, in turn, the sodium-hydrogen exchanger 3, responsible for the osmotic balance [22]. In the early proximal tubule, such a compensating mechanism is critical for the diuretics to influence blood pressure and cardiovascular health.

The outcome of the experiment measuring rats treated with Ipragliflozin showed that the therapy has the following significant changes: serum glucose, systolic pressure, raised food and fluid intake and raised renal osmolar clearance [23]. The compensatory mechanism is the more important one in generating the optimal pathway through which HF may be avoided and has a healthy patient. Sidling with SGLT2i to loop diuretics results in a better outcome of fluid homeostasis due to the mechanism of increasing serum Na+ concentration and the vasopressin fluid intake stimulation that engenders renal water retention and dynamic fluid-volume balance [24]. The administration of SGLT2i effectively balances myocardial energetics, calcium, and renal physiology, indicating a positive impact on the diuretics [25]. The diuretics effect mechanism proves that the SGLT2i are significant treatment and therapy options when it comes to the control and management of HF and diabetes complications that affect most patients.

Reduction in Plasma Volume

The SGLT2 inhibitors cause glucose and sodium excretion in the urine, thus reducing the plasma volume and making it easier for the heart to pump. These drugs are beneficial to patients with HFrEF. The workload of the heart is the leading cause of the complications that are evident in the cardiovascular tissue, including remodeling and consequential heart failure. The administration of Empagliflozin to CVD and diabetes patients proves to help significantly reduce fluid volume aspects for 24 hours, which allows the heart to reverse a massive workload in the context of HF [26]. The improved cardiovascular outcomes make it possible to reduce the primary effects of fluid volumes in the body, hence stabilization of cardiac functions. The SGLT2i inhibits the reabsorption of glucose in the kidney, an element that makes it possible to increase the excretion of glucose concentration in the urine, which helps lower blood glucose [27]. The reduced glycemic levels have far-reaching effects, including lower blood pressure, reduced uric acid concentrations, lower oxidative stress, and reduced inflammation.

The prolonged intake of Tofogliflozin has been reported to help in HF treatment by regulating plasma volume [28]. The drug has an antihypertensive effect that reduces estimated plasma volume, which, in turn, affects cardiovascular health. In another study, the results reveal that administering Ipragliflozin to T2DM patients helped reduce fluid volume parameters for twenty-four months if well maintained through compliance [29]. The SGLT2 inhibitors are a classical therapy that is the most effective way of controlling plasma volume. The mechanism of action of Dapagliflozin on DKD patients shows that it reduces extracellular fluids with minimal to no negative impact on extracellular fluid retention, hence the stability in body fluids [30]. The therapy's efficiency gives hope for managing plasma volume, which has a significant impact on the development of heart failure and its associated complications.

Conclusion

In summary, although mechanisms of action through which SGLT2i can act to minimize the risk of HF and improve HF outcomes are being elucidated, their apparent efficacy and safety in reducing the risk of HF events and improving HF outcomes in patients with and without diabetes have been demonstrated across multiple clinical trials, leading to the incorporation of SGLT2 inhibitors into the guidelines for the management of HF in specific patient populations. These agents have been receiving increasing attention for their potential role in HF management, especially in patients with or without diabetes. Their beneficial effects go beyond the antihyperglycemic effects of SGLT2 inhibitors. The drugs exert their action predominantly by suppressing glucose reabsorption through inhibition of the SGLT2 transporter. The inhibition of SGLT2-by-SGLT2i hinders glucose reabsorption from the renal tubular lumen into the blood and increases glucose excretion in the urine. This mechanism of action results in osmotic diuresis that leads to volume contraction natriuresis and reduced blood pressure. In addition to their glucose-lowering effects on the kidneys, SGLT2i have been shown to have beneficial effects on the heart and the vasculature, independent of lowered glucose levels through mechanisms that are not entirely understood.

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