



The Use Of Sglt-2 Inhibitors: Beyond Diabetes

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ABSTRACT

SGLT-2 inhibitors, also known as gliflozins, as a novel therapeutic option for individuals with type 2 diabetes. It highlights the mechanism of action of SGLT-2 inhibitors, which involves the inhibition of glucose reabsorption in the kidneys, leading to improved glycemic control. The review examines the safety and efficacy of these agents not only in managing diabetes but also in patients with heart failure and chronic kidney disease (CKD). Clinical trials, such as the DAPA HF and CREDENCE trials, are referenced to illustrate the benefits of SGLT-2 inhibitors in reducing hospitalization, cardiovascular death, and the risk of kidney failure. The article emphasizes the potential of SGLT-2 inhibitors to enhance patient outcomes beyond glucose control, making them a significant advancement in the treatment of diabetes and related complications.

Keywords: Heart failure, chronic kidney disease, CREDENCE Trial, CVD-REAL trial, EMPA-REG OUTCOME trial, dapagliflozin, canagliflozin, empagliflozin.

INTRODUCTION

Gliflozins, also referred to as SGLT2 inhibitors, are a novel and efficacious therapeutic option for individuals with type 2 diabetes. SGLT2 is a type of protein located in kidney responsible for glucose into the bloodstream from the glomerular filtrate⁽¹⁾. Based on their locations, sodium glucose co-transporters can be categorized into SGLT-1 and SGLT-2. With SGLT-1 being predominant in intestine and SGLT-2 prevailing kidney. In the body, SGLT-1 transporters have two purposes. During digestion, they aid in the absorption of glucose from the small intestine. Additionally, they return around 10% of the filtered glucose from the kidney's proximal tubule to the bloodstream. The typical renal threshold for glucose re-absorption is 180mg/dL of blood glucose. It's noteworthy to note, though, that the SGLT-2 protein is elevated in diabetes, which can exacerbate hyperglycemia. Better glucose control in the diabetic population is made possible by the suppression of SGLT-

2 receptors, which inhibit glucose re-absorption in the kidneys(2). The pharmacodynamics of SGLT-2 inhibitors like Dapagliflozin(10mg/day), Canagliflozin(100-300mg/day), Empagliflozin(10-100mg/day), Ipragliflozin(25-100mg/day), Bexagliflozin (20mg/day) shown to lower HbA1c, fasting blood glucose level and post prandial blood glucose level compared with placebo in clinical trials^(3,4). These agents lowers blood glucose level by inhibiting the reabsorption of glucose in renal proximal tubule where induces glucosuria⁽⁴⁾. In this review we examine safety and efficacy of SGLT2 inhibitors in heart failure and CKD patients in comparison with placebo.

SGLT 2 INHIBITORS AND HEART FAILURE

Heart failure is a complex clinical illness caused by any anatomical or functional impairment of ventricular filling or ejection of blood. The primary symptoms of heart failure include dyspnea and fatigue which can restrict exercise intolerance as well as fluid retention which can cause pulmonary and Splanchnic congestion and pulmonary edema. The clinical syndrome of heart failure can be caused by illnesses of the pericardium, myocardium, endocardium, heart valves or great arteries as well as certain metabolic abnormalities, however the majority of heart failure patients experience symptoms as a result of reduced left ventricular myocardial function⁽⁵⁾. Cardiomyopathy, CAD, diabetes mellitus, hypertension and obesity are the most frequent of heart failure. In CAD patients, Plaques build up along the coronary arteries. These plaque eventually obstruct or hinder blood flow to the region distal to the deposit. Cardiac oxygen demand exceed supply as result the myocardium no longer containing the necessary oxygen rich blood. This hypoxia may cause damage and even death to the cells. Hypertension makes heart to work harder. This increased workload can weaken and damage the heart over time eventually becomes unable to meet the body's metabolic needs since it has to pump blood faster. When cardiac output is reduced and mean arterial pressure is low, multiple compensatory processes are activated⁽⁶⁾. Diabetes is known to increase the chance of developing heart failure and to hasten the disease's course. In diabetes, oxidative stress, mitochondrial dysfunction, chronic inflammation, insulin resistance and hyperglycemia all contribute significantly to the etiology of heart failure⁽⁷⁾. SGLT2 inhibitors has direct cardiac effects that improve both preload- due to natriuresis and osmotic diuresis-and the afterload-due to the reduction of sodium and circulating volume. Since a healthy heart uses a variety of substrates, such as glucose and free fatty acids, to maintain normal contractile function, it requires a significant amount of energy, with over 95% of ATP coming from mitochondrial oxidative phosphorylation and a smaller amount from glycolysis. Stressful circumstances (such as heart failure and/or type 2 diabetes) impair the heart muscle's ability to consume glucose, leaving the majority of metabolism to be handled by FFA consumption, which is less effective because the myocardial cells requires more oxygen to function. Additionally, there may be lipotoxicity brought on by increased reactive oxygen species (ROS) production and decreased sarcoplasmic reticulum calcium absorption, which could lead to diastolic dysfunction. An excellent substitute substrate that can increase heart rate efficiency is ketone bodies. Research on humans and animal models has demonstrated that beta-

hydroxybutyrate (β -OHB) can enhance cardiac performance and metabolism. This can lead to reverse ventricular remodeling, which in turn improves cardiac output and diastolic function. Additionally, like the nucleotide oligomerization domain, the ketone bodies also have anti-inflammatory properties by inhibiting the activation of P3 receptor inflammasome activity (NLRP3)⁽⁸⁾. In CVD-REAL randomized controlled trial study conducted in multinational to observe comparative effectiveness of cardiovascular outcomes of SGLT-2 inhibitors canagliflozin, dapagliflozin, empagliflozin with other glucose lowering drugs. Among 215622 persons, hypertensive heart failure or death occurred in 1983 persons. SGLT-2 inhibitors shown lower rates of hypertensive heart failure (hazard ratio,0.61;95% confidence interval,0.51-0.73;p<0.001)and death(hazard ratio,0.49;95% confidence interval,0.41-0.57;p<0.001) compared with person who are on other glucose lowering agents also seen that empagliflozin shown benefits in CVD-REAL study⁽⁹⁾. EMPA-REG OUTCOME trial investigated the impact of empagliflozin versus placebo on cardiovascular morbidity and death in individuals receiving routine therapy who had type 2 diabetes and were at high risk of cardiovascular events. In this randomized, double-blind, placebo controlled trial comparing the effect of empagliflozin(10 mg or 25 mg /day) with placebo investigated among 7020 patients and observed that cardiovascular outcome occurred in lower rate of patients in empagliflozin(10.5%) compared with placebo group(12.1%) (hazard ratio in empagliflozin group,0.86;95.02% confidence interval 0.74 to 0.99;p<0.001. Adverse effects such as genital infection, urosepsis, ketoacidosis are commonly occurred in patients who treated empagliflozin⁽¹⁰⁾. Dapagliflozin, SGLT 2 inhibitor shown beneficial effect in heart failure patients with preserved ejection fraction. It reduces hospitalization and cardiovascular death among the heart failure patients. John j v McMurray et al conducted DAPA HF trial among 4744 patients over the period of 18.2 month. Patients receives dapagliflozin 10 mg/day or placebo along with recommended therapy. Patients who have unacceptable side effects with dapagliflozin, type 1 dm patients, hypotensive patients are excluded and observed that the patients who receives dapagliflozin shows lower risk of worsening of symptoms and cardiovascular death than patients who received placebo⁽¹¹⁾.

SGLT-2 INHIBITORS AND CHRONIC KIDNEY DISEASE

In a healthy adult without diabetes, most of glucose filtered at the glomerulus is reabsorbed in the proximal tubule up to 180mg/dL. In a patients without diabetes glucose is filtered readily in glomerulus through balancing blood pressure and plasma volume in response to tubuloglomerular feedback mechanism. Once this get disturbed due to hyperglycemia in diabetic patients by stimulating renal hypoperfusion through increased proximal glucose reabsorption and decrease salt transport to the macula densa. As a result, the TGF mechanism is stimulated, which affects afferent arteriolar dilation and efferent arteriolar constriction via different pathway. This increases intraglomerular pressure and causes hyperfiltration leading to development of chronic kidney disease in people with type 2 Diabetes. However, SGLT2 inhibitors enhances glycemic control and reduces glomerular hyperfiltration. It also induces natriuresis and osmotic effects which produces beneficial effects for

CKD patients⁽¹²⁾. In CREDENCE double blinded randomized trial reported that the patients who receives canagliflozin showed lower risk of kidney failure and cardiovascular events compared with placebo group. In the trial patients with type 2 diabetes and chronic kidney disease patients received canagliflozin 100mg daily and follow up for 2.62years. patients had an estimated GFR of 30 to <90 ml/min /1.73m² body surface area and albuminuria and who are already on ace inhibitors are included in the trial⁽¹³⁾. DAPA-CKD TRIAL conducted on 4304 participants with estimated GFR of 25 to 75 ml/min/1.73m² of body surface area and urinary albumin to creatinine ratio of 200 to 5000 received dapagliflozin 10mg/day verses placebo. the primary outcome was patient who take dapagliflozin significantly reduced the risk of a composite of end stage kidney disease, death from renal or cardiovascular causes, and a sustained decline in the estimated GFR of at least 50% in patients with chronic kidney disease, regardless of whether or not they also had diabetes.

CONCLUSION

The conclusion of the article emphasizes the significant benefits of SGLT-2 inhibitors in managing type 2 diabetes and their positive impact on cardiovascular and renal health. It highlights that these medications not only improve glycemic control but also reduce the risk of heart failure and chronic kidney disease progression. The review underscores the importance of incorporating SGLT-2 inhibitors into treatment regimens for patients with diabetes, particularly those at high risk for cardiovascular events and kidney complications. Overall, the article advocates for the continued exploration and utilization of SGLT-2 inhibitors as a vital component in the comprehensive management of diabetes and its associated co morbidities.

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CONFLICT OF INTEREST

There is no conflict of interest.

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