Available online on 15.03.2023 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Review Article

The Effectiveness of SGLT2 Inhibitors in CKD Patients

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Article Info:

Article History:

Received 08 Jan 2023
Reviewed 11 Feb 2023
Accepted 20 Feb 2023
Published 15 March 2023

Cite this article as:

Boddula H, Shivani R, Nayak SPS, Vaghasia J, Chakraborthy GS, Mandal SD, Ghatol P, The Effectiveness of SGLT2 Inhibitors in CKD Patients, Journal of Drug Delivery and Therapeutics. 2023; 13(3):141-144

DOI: http://dx.doi.org/10.22270/jddt.v13i3.5750

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Abstract

Sodium-glucose cotransporter-2 inhibitors, often known as SGLT2Is, are a class of medications used largely for anti-diabetic activity in oral dose form that lowers blood glucose levels. In recent years, numerous trials have documented the use of medications for conditions including renal and cardiovascular illness that go beyond only decreasing blood sugar. Other benefits of SGLT2Is' glucose-lowering activities include slowing or halting the progression of chronic kidney disease, lowering estimated glomerular filtration rate, lowering albuminuria, improving renal and cardiovascular health, and reducing estimated glomerular filtration rate. Published clinical trials reported all of these SGLT2I effects. The studies that we reviewed for this article are the Canagliflozin CardioVascular Assessment Study (CANVAS), Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA - CKD) trial, Effects of SGLT2I dapagliflozin on Proteinuria in Non-Diabetic Patients with The clinical studies, SGPLT2I class of medications, and their impact on cardiovascular and renal illnesses in diabetic and non-diabetic individuals are adequately covered in this review study.

Keywords: SGLT2Is, Chronic kidney disease, dapagliflozin, Canagliflozin

INTRODUCTION:

A class of FDA-approved prescription drugs known as sodium - glucose cotransporter - 2 inhibitors (SGLT2Is) is used in combination with diet and exercise to reduce blood sugar levels in type 2 diabetic patients same like Angiotensin converting enzyme inhibitors (ACEI's) used in diabetic proteinuria. [1,2]. These medications reduce blood sugar levels by limiting the reabsorption of glucose into the kidneys and by removing any extra glucose through urination[1,2]. Due to a lack of data on the safety and effectiveness of the treatments in type 1 diabetic patients, this class of medications is currently not licenced for use in these patients. Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are among the SGLT2Is [1]. Apart from the anti – diabetic action of the drugs, the SGLT2Is also have renal and cardiac functions such as slowing the progression of kidney disease, reducing heart failure, reduction in blood pressure – systolic and diastolic, reduction in atherosclerotic cardiovascular disease, heart failure, diabetic kidney disease with albuminuria, non – diabetic kidney disease with albuminuria and also lowering the estimated GFR (eGFR) [3]. The renal functions of the SGTL2Is are being evaluated through the trials for its efficacy and safety in chronic kidney disease (CKD) patients with or without diabetes. The various trials which were conducted on SGLT2Is class of drugs to estimate the indication of these drugs in cardio – renal diseases are, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA – CKD) trial, Effects of SGLT2I dapagliflozin on proteinuria in non – diabetic patients with chronic kidney disease (DIAMOND) trial, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, CANagliflozin cardioVascular Assessment Study (CANVAS), Efficacy and Safety of Empagliflozin in Patient with Type – 2 Diabetes and Renal Impairment (EMPA – REG RENAL) trial[13,16-19]. In both the presence and absence of diabetes, these research and trials have attempted to show us the data supporting the use of SGLT2Is as nephroprotective and cardioprotective medicines. However, this pharmacological class has not yet been fully understood, necessitating a great deal more study.

OBJECTIVES:

Reviewing multiple clinical studies on SGLT2Is effects in CKD patients and gathering information on all facets of SGLT2Is as a nephroprotective drug are the main goals of this study. This article will provide you all the details you need to comprehend how the major organs are affected by the SGLT2Is and how effectively they work. It is important to study the

nephroprotective effects of this class in depth in order to comprehend every potential mechanism underlying the specific action. All of the concerns stated against the usage of drugs in CKD patients will be reviewed in light of various research and trials, and conclusive arguments will be made. The effectiveness and safety of a novel approach to treating patients with severe chronic renal disease will be analysed and examined.

SGLT2Is and RENAL OUTCOMES IN CKD PATIENTS:

Due to their primary causes, such as hypertension and diabetes mellitus, kidney disorders are on the rise in all parts of the world. It has become unavoidable that primary illnesses will worsen and cause secondary renal disease. The cardiovascular system, which has a significant impact on renal health, is another source of chronic kidney disease. With diabetic kidney disease and end-stage renal disease, diabetes is seen as a global epidemic [3-4]. However, the pathophysiology of diabetic complications is estimated to include an increase in intra-glomerular pressure, an increase in single nephron glomerular filtration rate (GFR), and podocyte damage leading to renal dysfunction [4]. The hyperglycaemic condition that causes kidney disease is not fully understood. The activation of proinflammatory pathways, neurohumoral activation, and cytokine release are further complementary processes that contribute to tubulointestinal inflammation and fibrosis [4,5].

Hypertension and diabetes mellitus were found to be the major comorbidities in valvular heart disease patients in few studies[7]. Angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and renin-angiotensin-aldosterone system (RAAS) blockade have been used to treat kidney diseases by reducing intra-glomerular hypertension and neuro-humoral inactivation for the past 20 years, but they have not been successful in normalising hyperfiltration, halting the progression of disease, or preventing mortality, whereas SGLT2 are bringing a fundamental change in therapeutic efficacy of patient with CKD secondary to diabetes [4].

RENAL FINDINGS IN CLINICAL TRIALS:

According to the estimates and research from the published clinical trials, the SGLT2Is have renal functions such as an acute reduction in GFR as well as in albuminuria, reduction in intraglomerular pressure, lowering blood pressure, lowering albuminuria, and slows the progression of kidney function decline[5,6].

The SGLT2I clinical studies that were conducted using chronic kidney disease as an inclusion criterion revealed several clinical data, including renal parameters. To determine the overall clinical findings or renal findings of SGLT2Is, the trials and studies DAPA - CKD trial, DIAMOND trial, CREDENCE trial, CANVAS trial, and EMPA - REG RENAL study were all monitored and analysed.

NAME OF THE STUDY	DAPA – CKD	DIAMOND	CREDENCE	CANVAS	EMPA – REG RENAL
Clinical trial registration	NCT03036150	NCT03190694	NCT02065791	NCT01032629 and NCT01989754	NCT01164501
Intervention	Dapagliflozin versus placebo	Dapagliflozin versus placebo	Canagliflozin versus placebo	Canagliflozin versus placebo	Empagliflozin versus placebo
Inclusion criteria	Diabetic and non-diabetic patients, high CV risk	High CV risk	DM type – 2, high CV risk	DM type – 2, high CV risk	DM type – 2, renal insufficiency
Kidney function inclusion criteria	30≥ eGFR ≤ 90 ml/min/1.73m^2 (CKD 2 and 3)	Urinary protein excretion >500mg/g and≤ 3500 mg/g in a 24 - hour urine collection, eGFR ≥ 25 mL/min/1.73m^2.	30 ≥ eGFR ≤90 ml/min/1.73m^2. (CKD 2 and 3)	eGFR ≥ 30 ml/min/1.73m^2.	GFR predicted to be 90 mL/min. Male and female patients who are on a diet and exercise routine, have received any anti-diabetic medicine in the 12-week period preceding to randomization, and are taking the highest tolerable dose without changing.
Number of patients included	4000	50	4461	10142	741
Prespecified renal endpoints	≥50% sustained decline in eGFR or reaching end stage renal disease or cardiovascular or	On a stable dose of ACEI or ARB for atleast 4 weeks prior to randomization.	End stage renal disease, doubling of serum creatinine, renal or CV death.	The necessity for renal replacement treatment, the development of albuminuria, a sustained 40%	-

	renal death			decline in the eGFR, or death due to renal causes.	
Outcomes	Sustained decline in the eGFR of atleast 50%, end stage renal disease, or death from renal or cardiovascular cause was significantly lower.	Dapagliflozin medication for 6 weeks caused a 6.6 mL/min/1.73 m2 acute and reversible fall in GFR and a 1.5 kg loss in body weight, but it had no effect on proteinuria in CKD patients without diabetes.	In patients with type – 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower.	Reduction in the progression of albuminuria and 40% reduction in the eGFR, the need for renal replacement therapy or death from renal causes.	Decreased renal composite outcomes.

RENAL MECHANISMS OF SGLT2Is:

A number of potentially positive consequences can result from the selective inhibition of SGLT2 receptors in the proximal tubules, which prevents the reabsorption of glucose[6,8]. All of the SGLT2Is' beneficial or desirable effects are caused by either renal or extra-renal pathways. The renal mechanisms include, among others, glomerular hemodynamics and tubular protection, sometimes in combination with other supporting processes.

Glomerular hemodynamics:

The improvement of glomerular hypertension and hyperfiltration is brought about by the SGLT2Is' reduction of sodium absorption in the proximal convoluted tubules, which results in an increase in salt chloride distribution distally. Additionally, by raising the hydrostatic pressure in the bowman's capsule, NaCl supply to the distal nephron reduces the glomerular filtration rate[6].

Tubular protection:

Numerous studies have reported the SGLT2Is' anti-fibrotic action, which was brought about by a decrease in inflammatory markers. Additionally, by lowering the sodium and glucose tubular burden, tissue oxygenation increases, protecting the tubules. Additionally, the calories lost as a result of glucosuria may open a hunger signalling pathway, which in turn triggers gluconeogenesis, fatty acid oxidation, and ketogenesis, all of which lower cell stress and protect tubules [6].

Antioxidant activity:

Free radical production is decreased by SGLT2Is, which also demonstrates antioxidant capabilities. Additionally, SGLT2Is like dapagliflozin have reportedly slowed the development of diabetic nephropathy by lowering free radical generation or by displaying antioxidant characteristics [4].

Anti-Inflammatory activity:

SGLT2Is aid in decreasing fibrosis and inflammation by diminishing or inhibiting the release of inflammatory markers. [4].

Reduction of Cortical Hypoxia:

By controlling changes in oxygen consumption, SGLT2Is mitigate renal cortical hypoxia. Additionally, the fibroblasts may resume producing erythropoietin as cortical hypoxia recovers, which would slow the disease's course [4].

SGLT2Is IN TREATING NON-DIABETIC CKD:

The use of SGLT2Is to treat CKD or to halt the progression of the disease has greatly improved the success of the therapy, according to a number of clinical trials described in journals. Significant improvements in overall renal health or arresting the patient's deterioration in renal health have been made in relation to deaths from CKD or renal causes. Patients with CKD may be especially interested in the SGLT2Is' complementary beneficial benefits [9]. The treatment of patients with cardiovascular and renal disease, whether or not they have diabetes, can benefit from some additional favourable benefits on cardiovascular health that have also been observed [10,11]. The big trials have produced encouraging results on the benefits of SGLT2Is on delaying the progression of chronic renal disease, reducing GFR, reducing albuminuria, ensuring cardiovascular safety, and lowering blood sugar levels [12–17].

DISCUSSION:

Numerous clinical trials have investigated and clarified the non-glucose lowering effects of SGLT2Is; the ones we analysed are the DAPA-CKD trial, DIAMOND trial, CREDENCE research, CANVAS study, and EMPA-REG RENAL trial. Dapagliflozin's effects have been tested in the DAPA-CKD study and the DIAMOND trial in comparison to placebo, whilst canagliflozin's effects have been shown in the CREDENCE and CANVAS trials, and empagliflozin's effects have been demonstrated in the EMPA-REG RENAL trial. Except for the DIAMOND study, which excluded patients with diabetes, all of the trials included patients with type 2 diabetes mellitus and high cardiovascular risk. Along with hypertension and Diabetes, Autosomal dominant polycystic kidney disease (ADPKD) is another cause for CKD where SGLT2Is are to be studied [19] For all of the trials, the inclusion criterion for chronic renal disease is 30 ≥ eGFR ≤90. According to the studies' findings, eGFR decreased by at least 50% in the DAPA-CKD study and by about 40% in CANVAS, while eGFR decreased to some amount in other trials as well. Trials using diamonds have revealed weight loss of up to 1.5 kg. Elderly patients and those having chronic kidney disease with ACEIs are at greater risk of hyperkalemia. Before starting the therapy obtaining the glomerular filtration rate, baseline blood volumes of potassium, as well monitored [18]. Along with SGLT2Is more aggressive antithrombotic therapies may be necessary to prevent primary and secondary thrombotic events in diabetic patients [20,21]. In every trial, the risk of kidney failure, cardiovascular incidents, and mortality from renal or cardiovascular causes was reduced.

CONCLUSION:

In both diabetic and non-diabetic individuals, the SGLT2Is have been shown to considerably lower renal and cardiovascular events. A novel medication called SGLT2Is has been developed to either treat or reduce the progression of chronic renal disease. Despite the fact that several clinical trials have been carried out and reported, more data still needs to be assessed and examined in order to provide more precise and useful knowledge. To assess and calculate the advantages of the SGLT2Is in combination therapy with other medications to lower the renal and cardiovascular risk, more research will be needed in the future.

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