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SGLT2 Inhibitors: Dapagliflozin or Canagliflozin for Chronic Kidney Disease – A Review of the Evolving Treatments

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ABSTRACT: There is currently an unmet need for effective treatment of chronic kidney disease (CKD) that slows disease progression, prevents development of end-stage kidney disease and cardiovascular disease, and prolongs survival of patients with CKD. In the last 20 years, the only agents to show a reduction in the risk of CKD progression in patients with and without type 2 diabetes (T2D) were angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, but neither drug class has provided a decreased risk of all-cause mortality in patients with CKD and evidence for their use in patients with CKD without T2D is relatively limited. This review discusses the mechanisms underlying the progression of CKD, its associated risk factors, and summarizes the potential therapeutic approaches for managing CKD. There is increasing evidence to support the role of sodium–glucose cotransporter 2 (SGLT2) inhibitor therapy in patients with CKD, including data from the designated kidney outcome trials in patients with T2D (CRENDENCE) and in patients with or without T2D (DAPA-CKD). These studies showed a significant reduction in the risk of CKD progression with canagliflozin (in patients with T2D) or dapagliflozin (in patients with or without T2D), respectively, with DAPA-CKD being the first trial to show a reduced risk of all-cause mortality. On the basis of these data, individualized treatment with SGLT2 inhibitors represents a promising therapeutic option for patients with diabetic and nondiabetic CKD to slow disease progression.

KEYWORDS: SGLT2 Inhibitor, Chronic Kidney Disease, DAPA-CKD, Dapagliflozin, Canagliflozin.

I. INTRODUCTION

DAPAGLIFLOZIN:

Dapagliflozin, sold under the brand names **Farxiga** (US) and **Forxiga** (EU) among others, is a medication used to treat Type 2 Diabetes [1]. It is also used to treat adults with heart failure and chronic kidney disease. It works by removing sugar from the body with the urine [2]. Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT-2) inhibitor. By inhibiting SGLT2, dapagliflozin blocks reabsorption of filtered glucose in the kidney, increasing urinary glucose excretion and reducing blood glucose levels. Its mechanism of action is independent of pancreatic β cell function and modulation of insulin sensitivity [3]. Common side effects include hypoglycemia (low blood sugar), urinary tract infections, genital infections, and volume depletion (reduced amount of water in the body). Diabetic ketoacidosis is a common side effect in type 1 diabetic patients [4].

CANAGLIFLOZIN:

Canagliflozin, sold under the brand name **Invokana** among others, is a medication used to treat Type 2 diabetes. It is used together with exercise and diet. It is not recommended in Type 1 diabetes. It is taken by mouth [5]. It works by increasing the amount of glucose lost in the urine [6]. Canagliflozin is a Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitor [7]. Canagliflozin is an SGLT-2 inhibitor that increases glucose excretion in the urine by reducing re-absorption of filtered glucose and lowering the renal glucose threshold. It is also used to lower the risk of heart attack, stroke, or death in patients with type 2 diabetes and heart or blood vessel disease. This medicine works in the kidneys to prevent absorption of glucose (blood sugar) [8]. Common side effects include vaginal yeast infections, nausea, constipation, and urinary tract infections. Serious side effects may include low blood sugar, Fourier's gangrene, leg amputation, kidney problems, high blood potassium and low blood pressure. Diabetic ketoacidosis may occur despite nearly normal blood sugar levels. Use in pregnant and breastfeeding is not recommended [9].

SGLT-2 INHIBITOR: SGLT2 inhibitors are a class of prescription medicines that are FDA-approved for use with diet

and exercise to lower blood sugar in adults with type 2 diabetes [10]. Medicines in the SGLT2 inhibitor class include canagliflozin, dapagliflozin, and empagliflozin. They are available as single-ingredient products and also in combination with other diabetes medicines such as metformin [11]. SGLT2 inhibitors lower blood sugar by causing the kidneys to remove sugar from the body through the urine. The safety and efficacy of SGLT2 inhibitors have not been established in patients with type 1 diabetes, and FDA has not approved them for use in these patients [12].

CHRONIC KIDNEY DISEASE

Chronic kidney disease, also called chronic kidney failure, involves a gradual loss of kidney function. Your kidneys filter wastes and excess fluids from your blood, which are then removed in your urine [13]. Advanced chronic kidney disease can cause dangerous levels of fluid, electrolytes and wastes to build up in your body [14]. In the early stages of chronic kidney disease, you might have few signs or symptoms. You might not realize that you have kidney disease until the condition is advanced. Treatment for chronic kidney disease focuses on slowing the progression of kidney damage, usually by controlling the cause. But, even controlling the cause might not keep kidney damage from progressing [15]. Chronic kidney disease can progress to end-stage kidney failure, which is fatal without artificial filtering (dialysis) or a kidney transplant [16].

Dapagliflozin and Canagliflozin are the first two Sodium Glucose Co-Transporter 2 (SGLT2) inhibitors used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) [17]. CKD is a condition in which the kidneys are damaged and cannot filter blood as well as they should because of this, excess fluid and waste from blood remain in the body and may cause other health problems such as heart disease and stroke [18]. SGLT2 inhibitors, which are also called gliflozins, are a class of drugs that lower your blood sugar levels by preventing your kidneys from reabsorbing sugar that is created by your body and the extra sugar leaves through in your urine. In patients with severe CKD, the use of SGLT2 inhibitors is contraindicated [19].

TREATMENT

SGLT2 inhibitors have been studied as monotherapy or in combination with other oral agents or insulin for the management of hyperglycemia in type 2 diabetes. SGLT2 inhibitors achieved reduction in HbA_{1c} of 4.4–12.1 mmol/mol (0.4–1.1%), depending on the baseline HbA_{1c} and the specific drug and dose used. In the last 20 years, the only agents to show a reduction in the risk of CKD progression in patients with and without type 2 diabetes (T2D) were angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, but neither drug class has provided a decreased risk of all-cause mortality in patients with CKD and evidence for their use in patients with CKD without T2D is relatively limited. There is increasing evidence to support the role of sodium–glucose cotransporter 2 (SGLT2) inhibitor therapy in patients with CKD, including data from the designated kidney outcome trials in patients. These studies showed a significant reduction in the risk of CKD progression with Dapagliflozin (in patients with or without T2D) or canagliflozin (in patients with T2D), respectively, with DAPA-CKD being the first trial to show a reduced risk of all-cause mortality [20].

PREVALANCE

Communities who consume water from natural springs showed a low prevalence of this disease. GPS mapping showed that most of the affected villages were located below the reservoirs and canals with stagnant water is developed with CKD [21]. The prevalence of CKD in Asia was estimated to be 434.3 million (95% confidence interval (CI) 350.2 to 519.7) in a recent systematic review and meta-analysis. The average prevalence of CKD stages 3–5 in Asia was 11.2%; the prevalence of CKD stages 3–5 varied among subregions (East Asia: 8.6%, South-East Asia: 12.0%, Western Asia: 13.1%, South Asia: 13.5%).¹⁷ In 2017, the prevalence of CKD in Southeast Asia was almost 70 million people. Asian patients with T2D have high rates of kidney disease with 58.6% having microalbuminuria or macroalbuminuria. Furthermore, a higher proportion of Southeast Asian patients with T2D develop nephropathy and progressive kidney failure at a much younger age than their European counterparts. There is an unmet need for additional effective treatments for CKD that slow disease progression, prevent development prolong survival of patients with CKD [22].

SIGNIFICANCE

In the last 20 years, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been the only classes of agents recommended for patients with CKD and hypertension, with or without T2D. More recently, large, randomized placebo-controlled studies of sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with T2D investigated the cardiovascular safety of this class of glucose-lowering therapies [23]. In addition to significantly reducing the risk of cardiovascular events, SGLT2 inhibitors reduced the risk of clinically relevant renal

outcomes compared with placebo, indicating that SGLT2 inhibitors are associated with significantly lower risk of worsening of kidney function. However, these studies were not designed to evaluate treatment benefits in patients with CKD, with only 7–26% of participants having an eGFR of less than 60 mL/min/1.73 m². Subsequently, designated kidney outcome trials showed a marked reduction in the risk of CKD progression with SGLT2 inhibitors in patients with diabetic kidney disease (DKD) with canagliflozin in CREDENCE and DKD as well as nondiabetic CKD with dapagliflozin in DAPA-CKD. Additionally, the FIDELIO-DKD trial evaluating the long-term effects of the mineralocorticoid antagonist (MRA) finerenone on kidney and cardiovascular outcomes reported a reduced risk of CKD progression in patients with DKD [24].

Canagliflozin 300 mg and Dapagliflozin 10 mg had similar effects on UGE and RTG for 4 h after dosing, but Canagliflozin was associated with higher UGE and greater RTG reductions for the remainder of the day. Mean 24-h UGE was ~25% higher with Canagliflozin than with Dapagliflozin, and 24-h mean RTG was ~0.4 mmol/l lower with Canagliflozin than with Dapagliflozin. Dapagliflozin had no effect on PPG excursion. Canagliflozin delayed and reduced PPG excursion (between-treatment difference in PPG Δ AUC 0–2 h from baseline expressed as a percentage of baseline mean, -10.2%; p=0.0122). Canagliflozin and Dapagliflozin were generally well tolerated. In healthy participants, Canagliflozin 300 mg provided greater 24-h UGE, a lower RTG and smaller PPG excursions than Dapagliflozin 10 mg [25].

(UGE – URINARY GLUCOSE EXCRETION

RTG – RENAL THRESHOLD FOR GLUCOSE

PPG- POSTPRANDIAL GLUCOSE)

II. MATERIALS & METHOD

The Review study aims to assess the SGLT2 Inhibitors. A literature was conducted between [2014 and 2023]. The literature search was limited to SGLT2 uses in chronic kidney disease with or without diabetes. The study conducted to identify the wise choice of drug selection between SGLT2 inhibitors, Dapagliflozin, Canagliflozin for treating the chronic kidney disease.

III. DISCUSSION

MARY C. BIRMINGHAM (2022) [26] she concludes that the benefits of Canagliflozin is significantly improving patient's symptom burden, regardless of CKD, further underscoring the benefits of SGLT2. This study is similar to the study conducted by KENNETH W. MAHAFFEY (2019) [27], ANDREAS HEINZEL (2019) [28], RAJIV AGARWAL (2019) [29] and CLARE ARNOTT (2021) [30] whereas, MICHAL NOWICKI (2022) [31] he concludes that the Dapagliflozin has become the first SGLT2 inhibitor which are more often recommended in patients with kidney disease regardless of the concomitance of diabetes which is similar to the study conducted by S.SHA (2014) [32], HIDEO J L HEERSPINK (2021) [33], DAVID C WHEELER (2021) [34] and JIAOJIAO LIU (2021) [35]. This study results are controversial to the above studies result. Thus, it concludes like CHRISTIAN W. MENDE (2021) [36] he concludes that his study shows the risk of CKD progression with SGLT2 inhibitors canagliflozin and dapagliflozin in patient reduces and are effective with and without T2D which is similar to the study conducted by KATHERINE R. TUTTLE (2021) [37] and REY ISIDTO (2023) [38]

IV. CONCLUSION

In Conclusion, SGLT2 Inhibitors have an important role in the management of T2DM. SGLT2 Inhibitors could manage uncontrolled glycemic in patients with T2DM. Adding to the currently available treatment options that can assist with individualization of therapy. The pleiotropic effects of SGLT2 Inhibitors have the potential to produce benefits beyond blood glucose control, and there is increasing evidence to indicate that these agents may reduce the risk of progression of renal impairment in patients with T2D. The findings of ongoing and future clinical trials will help shed further light on the role of SGLT2 Inhibitors in the long-term protection of renal and CV function in patients with T2DM. The CREDENCE and DAPA-CKD studies showed a significant reduction in the risk of CKD progression with the SGLT2 Inhibitors Canagliflozin and Dapagliflozin in patients with CKD. With DAPA-CKD being the first trial to report that SGLT2 Inhibitors are effective in patients with or without T2D for slowing CKD progression and reducing the risk of all-cause mortality. On the basis of these data, individualized treatment with SGLT2 Inhibitors represents an unprecedented therapeutic option and an opportunity to slow the progression of CKD and the development of associated cardiovascular complications in patients with CKD, whether



or not they also have T2D.

TABLE

DRUGNAME	PRIMARY USES	SECONDARY USES	SIDE EFFECTS
Canagliflozin ^[39]	<p>1. Canagliflozin is used with a proper diet and exercise program to control high blood sugar in people with type 2 diabetes.</p> <p>2. Canagliflozin works by increasing the removal of sugar by your kidneys.</p>	<p>1. Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual problems.</p> <p>2. Canagliflozin is also used by people with type 2 diabetes and heart disease to lower the risk of death from heart attack or stroke.</p>	<p>More common</p> <ul style="list-style-type: none"> • Bladder pain • Bloating • Bloody or Cloudy Urine • Decreased frequency or amount of urine. • Difficult burning or painful urination.
Dapagliflozin ^[40]	<p>1. Dapagliflozin is a highly selective SGLT2 inhibitor that controls blood glucose levels by blocking the SGLT2 receptors expressed in the S1 segment of the proximal kidney tubules leading to reduced renal glucose absorption.</p> <p>2. Dapagliflozin has been shown to lower HbA1c, body weight, BP, and serum uric acid in clinical trials.</p>	<p>1. Dapagliflozin reduces HbA1c similar to other OAMs, but it also has the beneficial effects on T2DM comorbidities. CVDs are the most serious complication of T2DM. Hyperglycemia damages vessel endothelium which can lead to atherosclerosis. The resultant CVD is also the leading cause of morbidity and mortality in patients with T2DM.</p> <p>2. Dapagliflozin is not associated with increased CV risk It is important to have additional evidence on effective therapies for high risk-patients and design therapies that provide not only good glycemic control but other clinical benefits.</p>	<ul style="list-style-type: none"> • Nausea • Vomiting • Stomach (abdominal) pain • Tiredness • Trouble breathing • Frequent, urgent, burning or painful Urination • Urine that is cloudy, red, pink or brown.
SGLT2 Inhibitors ^[41]	<p>SGLT2 inhibitors were developed as oral antidiabetic (blood sugar lowering) drugs.</p>	<p>SGLT2 inhibitors, are a class of drugs that lower your bloodsugar levels by preventing your kidneys from reabsorbing sugar that is created by your body and the extra sugar leaves through inyour urine.</p>	<ul style="list-style-type: none"> • Urinating a lot, including at night • Increased thirst

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