SGLT2 role in diabetes management and cardiorenal protection

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic and intricate metabolic condition. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are the recent category of oral medicines that are FDA-approved for treating T2DM. Significant advancements have been made in this class of drugs' safety and effectiveness over the previous years. By decreasing renal tubular glucose uptake, SGLT2 inhibitors lower blood sugar levels without triggering the release of insulin. The beneficial impacts of SGLT2 in T2DM have been confirmed in preliminary clinical studies with satisfactory safety and high tolerability. SGLT2 inhibitors have recently received FDA approval for a variety of uses, including heart failure (HF) treatment for reduced and preserved ejection fraction, diabetic kidney disease (DKD) treatment, and reduction of hospitalizations for HF in patients with T2DM and DKD. In T2DM persons with cardiovascular disease (CVD), these advantages include lowering cardiovascular mortality as well as the risk of cardiac arrest and stroke. The present article summarizes the SGLT2 inhibitors and their clinical benefits in diabetes management and cardiorenal protection.

Keywords: Diabetes mellitus; Sodium-glucose cotransporter-2 (SGLT2) inhibitors; cardiac protection, renal protection; Insulin

Introduction

Chronic hyperglycemia is a feature of T2DM, which is marked by inadequate insulin signaling brought on by impaired insulin secretion and insulin resistance. Endogenous glucose production (EGP) or glucagon production is also associated with T2DM (1). When chronic renal impairment is present, the likelihood of cardiovascular disease (CVD) rises by two to three times in T2DM patients. Patients with T2DM are more likely to experience heart failure (HF) and diabetic kidney disease (DKD) along with atherosclerosis (2).

Major diabetes consequences including myocardial infarction and stroke are becoming more common, leading to hospitalizations (3). Drug therapy aims to stop microvascular consequences, such as blindness and end-stage kidney disease (ESKD) (4). The treatment options for T2DM have proliferated as our understanding of the underpinning pathophysiological deficiencies continues to advance (5). It has been advocated that lifestyle modifications and monotherapy, particularly metformin, be the initial course of action for the treatment of T2DM. Drugs like insulin, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP1) receptor agonists, sulfonylureas, thiazolidinediones, and sodium-glucose cotransporter 2 (SGLT2) inhibitors are being used often to manage blood sugar. These medications have had an incredible degree of clinical success (5).

Inhibitors of SGLT2 promote glucose excretion in urine by preventing the reabsorption of glucose in the renal proximal tubules (6). Exercise and diet can be paired with SGLT2 inhibitors. They can be used alone or in conjunction with some antidiabetic medications, including metformin (7). In comparison to placebo, SGLT-2 inhibitors caused higher adverse events in research studies including T2DM patients, particularly vaginal infections, amputations and fractures (8). SGLT-2 inhibitors were associated with a decreased probability of adverse events leading to patient withdrawal when compared to GLP-1 agonists (9).

In addition, the major risk factor for cardiovascular (CV) and chronic kidney disease (CKD) is believed to be diabetes mellitus (DM). (10). Up until a few years ago, managing blood pressure, regulating glucose levels, and preventing renal hyperfiltration injury were the three main strategies for preventing the onset of CVD and DKD with class of drugs such as angiotensin-receptor-blockers (ARBs) or ACE inhibitors (11). Regardless of receiving the best possible medical care, a substantial number of patient population still experience progression of the said disease. Over the past few years, individuals with T2D have received both direct and indirect proof of considerable CV and renal protective effects from clinical trials with SGLT2 inhibitors. (12,13). Despite the apparent clinical advantages, the underlying mechanisms are not well understood. Heart failure (HF) and DKD progress due to fibrosis, oxidative stress, inflammation, and hemodynamic dysfunction. These channels' attenuations caused by SGLT2 inhibitors probably help to protect the kidneys and cardiovascular system.

The current review compiles the literature based on the approved class of SGLT2 inhibitors for managing diabetes. It also overviews a list of clinical studies implying the cardiorenal protection offered by the said class of drugs.

Role of SGLT2 inhibitors for managing diabetes

a. Mode of action of SGLT2 inhibitors

A vital biological function of the SGLT-2 proteins found in proximal convoluted tubules (PCTs) of the kidneys is to reabsorb glucose from the lumen of the tubules. Reports suggest the fact that inhibitors of SGLT2 reduce HbA1c level by 0.7% (14).

Since they are accountable for about 90% of the filtered glucose reabsorption, these transporters are excellent targets for the therapy of diabetes (15). The standard renal threshold for the action of glucose reabsorption is similar to a blood glucose level of about 180 mg/dL. This threshold may rise in T2DM patients, and the expression of the SGLT2 may be elevated, leading to an unfavorable reaction that exacerbates hyperglycemia (16). The use of SGLT2 inhibitors allows for the selective suppression of the said threshold (17). In contrast, people with familial renal glucosuria (FRG), do not have active SGLT2 proteins. In an episode of normoglycemia, they exhibit glycosuria. Hypotension and hypoglycemia are uncommon in FRG patients, indicating the safety of both their short and long term usage (18).

The renin-angiotensin-aldosterone pathway is known to be inhibited, afterload and preload are decreased, and cardioprotection is achieved by blocking the SGLT-2-dependent glucose and sodium reabsorption. In a research, empagliflozin lowered ambulatory arterial stiffness index and mean arterial pressure (19). In preclinical trials, vasodilation caused by dapagliflozin is observed. Additionally, dapagliflozin therapy lowered oxidative stress, increased endothelial function, decreased arterial stiffness, and generally had a positive impact on the vasculature (20).

Inhibitors of SGLT2 may perform their nephroprotection by increasing distal sodium supply and preventing tubuloglomerular feedback, which results in afferent vasoconstriction and decreased intraglomerular pressure. Albuminuria decreases as intraglomerular pressure is reduced. Natriuresis is caused by interference with proximal sodium and glucose reabsorption. Considerable weight loss, lowered blood pressure, and a decrease in effective circulatory volume are side effects of SGLT2 inhibitors. Furthermore, SGLT2 inhibitors reduce renal hypoxia, affect mitochondrial metabolism in kidney tissue, and change variables that cause inflammation and fibrosis (21,22).

b. List of FDA approved SGLT2 inhibitors in management of diabetes

Several SGLT2 inhibitors are presently undergoing clinical studies or have received approval for the treatment of T2DM. Four SGLT2 selective inhibitors namely canagliflozin, dapagliflozin, ertugliflozin and empagliflozin

have been authorized for mono, dual, and triple therapy (23). In addition, a number of other comparable compounds are in development and could receive approval soon (24). Canagliflozin/metformin, dapagliflozin/metformin, empagliflozin/metformin, and empagliflozin/linagliptin are four other combination drugs that have received FDA approval.

On March 29, 2013, the first SGLT-2 inhibitor, canagliflozin, was approved by the FDA. Used in combination with diet and exercise, it is suggested for adult patients with T2DM. In addition, it has been demonstrated to lessen the risk of unfavorable CV events in T2DM individuals with preexisting CVD as well as the dangers of end-stage renal disease (ESRD), CV mortality and albuminuria in diabetic nephropathy patients (25).

In January 2014, the FDA approved dapagliflozin. Along with diet and exercise, the medication is intended for type 2 DM adult patients to help regulate blood glucose levels. Other indications include lowering the risk of CV mortality and hospitalization rates in older individuals with underlying HF, as well as lowering EF (26). Dapagliflozin is also recommended for CKD patients at risk of progressive kidney disease to reduce the risk of ongoing deterioration in ESRD, estimated glomerular filtration rate (eGFR), CV mortality, and hospitalization for HF. The FDA broadened the indication for dapagliflozin in May 2023 to cover heart failure over the full range of left ventricular ejection fraction (LVEF). Both HF with intact ejection fraction (HFpEF) and HF with modestly reduced ejection fraction (HFmrEF) fall under this category (27).

The FDA approved empagliflozin following the approval of dapagliflozin in the year 2014 (28). In combination with diet and exercise, empagliflozin is recommended for adult patients with T2DM to help improve blood glucose control. It is also recommended for patients with ASCVD, T2DM, and adult patients with underlying HF and reduced EF to reduce the risk of CV mortality and heart failure related hospitalization (29).

c. List of studies implying the application of SGLT2 inhibitors for managing diabetes

According to Chen et al. (2013), SGLT2 is mostly expressed in the PCT and is known for its low affinity, high volume, and role in glucose reabsorption from the glomerular filtrate back into the systemic circulation (30). SGLT2 inhibitors increase urine glucose excretion by decreasing renal reabsorption and lowering renal glucose threshold (31,32). This lowers HbA1c by about 0.6 to 1.0%. A summary of clinical studies demonstrating the utility of several SGLT2 inhibitors for treating T2DM is provided in Table 1.

Table 1: Use of SGLT2 inhibitors for managing diabetes

SGLT2 inhibitor	Objective	Study result	Reference
Empagliflozin	Evaluation of safety and long-term effectiveness of metformin, sitagliptin, and the sodium glucose cotransporter 2 inhibitor, empagliflozin in T2DM patients	T2DM patients who received long-term empagliflozin medication reported good tolerance, maintained glycemic and weight management, and a minimal risk of hypoglycemia was noted.	Ferrannini et al., 2013 (33)
canagliflozin	To investigate the effects of canagliflozin on HbA1c levels	When compared to a placebo at week 26, canagliflozin treatments of 100 and 300 mg significantly lowered HbA1c levels.	Bode et al., 2015 (34)
ertugliflozin	To assess ertugliflozin's effectiveness and safety in Asian patients with T2DM that is not properly managed by metformin, including a subgroup from China.	In Asian T2DM patients, ertugliflozin dramatically lowered systolic blood pressure, body weight, and provided adequate glycaemic control. Overall, ertugliflozin was well tolerated by the treated group of patients. The outcomes in the China subpopulation were in agreement with the population as a whole.	Ji et al., 2019 (35)
canagliflozin	To evaluate the effectiveness and safety of glimepiride against canagliflozin, an SGLT2 inhibitor, in individuals with T2DM that is not effectively managed by metformin.	Greater HbA1c lowering was achieved with canagliflozin than with glimepiride, and it was well tolerated in type 2 diabetics using metformin.	Cefalu et al., 2013 (36)
dapagliflozin	To assess the effectiveness and safety of combining the SGLT2 inhibitor, dapagliflozin with the GLP-1 receptor agonist, exenatide in individuals with T2DM where metformin management has not been effective.	Exenatide and dapagliflozin were introduced together to enhance a number of glycemic measurements and CV risk factors of T2DM patients that metformin alone was unable to adequately treat. The two-treatment plan was well tolerated and had the anticipated safety profile.	Frias et al., 2016 (37)

Table 1: Use of SGLT2 inhibitors for managing diabetes (continued)

ertugliflozin	To assess ertugliflozin's safety and long-term effectiveness in T2DM patients that is not effectively managed by metformin.	Through week 104, ertugliflozin continued to show gains over baseline in body weight, HbA1c, fasting blood glucose, and systolic blood pressure. With slight modifications in bone mineral density that were not clinically significant, ertugliflozin was well tolerated in the treated group of patients.	Gallo et al., 2019 (38)
canagliflozin	To compare the efficiency and safety of canagliflozin, a medication for T2DM, with placebo and sitagliptin in patients receiving background metformin therapy.	T2DM patients taking metformin, canagliflozin lowered body weight and improved glycemia compared to placebo (week 26) and sitagliptin (week 52), and it was well-tolerated in general.	Lavalle-González et al., 2013 (39)
ertugliflozin	To compare the safety and effectiveness of co-administration of ertugliflozin and sitagliptin in T2DM patients whose condition is not sufficiently controlled by metformin to those of the individual drugs.	Co-administration of ertugliflozin and sitagliptin, compared to the use of the two medications separately, significantly improved glycemic control over the course of 52 weeks in patients with uncontrolled T2DM who were also taking metformin.	Pratley et al., 2018 (40)

List of studies implying the role of SGLT2 in cardiorenal protection

a. Clinical studies about the role of SGLT2 in cardiovascular protection

Despite the fact that diabetes affects a wide range of target organs, cardio-renal consequences impose the greatest burden on the National Health System in terms of morbidity and mortality (41,42). Table 2 entails a list of clinical studies employing the effects of SGLT2 inhibitors such as Canagliflozin, dapagliflozin, and empagliflozin in cardiovascular protection.

Table 2: List of clinical studies employing the effects of SGLT2 inhibitors in cardiovascular protection.

Identifier	Title	Objective	Intervention	Study phase	Result	Reference
NCT04252287	Canagliflozin: Impact on Health Status, Quality of Life, and Functional Status in Heart Failure (CHIEF-HF)	Comparison of the efficiency of canagliflozin 100 mg dosed daily with placebo for enhancing the overall Total Symptom Score (TSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ) in people with symptomatic heart failure (HF).	Drug: Canagliflozin 100 mg Drug: Placebo	III	KCCQ TSS for 12 weeks was 4.3 points (P = 0.016) greater with canagliflozin than with placebo. Canagliflozin effectively reduced HF's symptom burden, irrespective of EF or diabetes status, as evidenced by the similar results seen in individuals with HFpEF, HFrEF, and participants with and without diabetes.	Spertus et al., 2022 (43)
NCT01131676	A Phase III, Multicentre, International, Randomised, Parallel Group, Double Blind Cardiovascular Safety Study of BI 10773 (10 mg and 25 mg Administered Orally Once Daily) Compared to Usual Care in T2DM Patients With Increased CV Risk	To examine the safety of using BI 10773 in those who have T2DM and are at high CV risk.	Drug: BI 10773 low dose Drug: Placebo BI 10773 high dose Drug: BI 10773 high dose	III	When empagliflozin was included in addition to standard therapy, patients with T2DM with high risk for cardiovascular events experienced a decreased rate of the primary composite cardiovascular outcome and mortality from any cause when compared with those who received a placebo.	Zinman et al., 2015 (44)
NCT03057951	A Phase III Randomised, Double-blind Trial to Evaluate Efficacy and Safety of Once Daily Empagliflozin 10 mg Compared to Placebo, in Patients With Chronic Heart Failure With Preserved Ejection Fraction (HFpEF)	To determine whether empagliflozin increases patient survival and reduces the likelihood that patients with heart failure will need to be admitted to the hospital.	Drug: Empagliflozin Drug: Placebo	III	Irrespective of the presence or absence of diabetes, empagliflozin decreased the combined risk of CV death or hospitalization for HF in individuals with HF and a preserved EF.	Anker et al., 2021(45)

Table 2: List of clinical studies employing the effects of SGLT2 inhibitors in cardiovascular protection (continued)

NCT01730534	Dapagliflozin Effect on Cardiovascular Events. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients With Type 2 Diabetes	To ascertain the impact of dapagliflozin on outcomes for individuals with T2DM who have either developed CVD or have CV risk factors when incorporated into background treatment.	Drug: Dapagliflozin 10 mg Drug: Placebo tablet	III	Treatment with dapagliflozin did not end up resulting in a higher or lower rate of MACE compared to placebo inT2DM patients who had or were at risk for atherosclerotic cardiovascular disease, but it ultimately resulted in a reduced likelihood of cardiovascular death or hospitalization for heart failure, an outcome which indicates a lower rate of hospitalization for patients with heart failure.	Wiviott et al., 2019 (46)
NCT03036124	To investigate Dapagliflozin's effect on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure With Reduced Ejection Fraction	To assess dapagliflozin's impact on the CVD occurrence or worsening HF in people with chronic HF and a low EF.	Drug: Dapagliflozin Drug: Placebo	III	Regardless of a history of diabetes, dapagliflozin treatment was associated with a lower risk of progressive heart failure or death from cardiovascular disease among patients with HF and a reduced EF.	McMurray et al., 2019 (47)

b. Clinical studies about the role of SGLT2 in renal protection

The major PCT hyper-reabsorption characteristic of diabetic illness is mitigated by SGLT2 inhibitors. By enhancing salt transport to the macula densa, SGLT2 inhibitors improve glycosuria and natriuresis, restore tubuloglomerular feedback (TGF), and encourage the constriction of afferent and the dilatation of efferent arterioles (48). SGLT2 inhibitors can lessen glomerular hypertension, hyperfiltration, barotrauma, and albuminuria by modifying renal hemodynamics. These are all essential early indicators for preventing diabetic kidney disease (DKD), because SGLT2 inhibitors slow down the disease's progression over time. The following section (Table 3) entails a list of clinical studies employing the effects of SGLT2 inhibitors such as Canagliflozin, dapagliflozin, empagliflozin in renal protection.

Table 3: List of clinical studies employing the effects of SGLT2 inhibitors in renal protection

Identifier	Title	Objective	Intervention	Study phase	Result	Reference
NCT01032629.	A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With T2DM	The study aimed to evaluate the cardiovascular (CV) risk for major adverse cardiac events (MACE) associated with using canagliflozin (JNJ-28431754) in the treatment of patients with type 2 diabetes mellitus (T2DM). A further goal was to assess canagliflozin's general safety, tolerability, and efficacy.	Drug: Placebo Drug: Canagliflozin (JNJ-28431754) 100 mg Drug: Canagliflozin (JNJ-28431754) 300 mg	III	Patients using canagliflozin had a lower likelihood of cardiovascular complications than those taking a placebo, but they also had a higher chance of amputation, mostly at the toe or metatarsal level.	Neal et al., 2017 (49)
NCT03036150	A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and CV Mortality in Patients With CKD	This study aimed to assess dapagliflozin's impact on CV mortality and renal endpoints in patients with chronic kidney disease.	Drug: Dapagliflozin Drug: Placebo	III	Dapagliflozin substantially decreased the risk of a composite of ESKD, death from renal or CV-related causes, or an ongoing decrease in estimated GFR of at least 50% among patients with CKD, irrespective of the presence or absence of diabetes.	Heerspink et al., 2019 (50)
NCT02065791	A Randomized, Double-blind, Event-driven, Placebo-controlled, Multicenter Study of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Subjects With Type 2 Diabetes Mellitus and Diabetic Nephropathy	To determine whether canagliflozin, when given to participants with T2DM, Stage 2 or 3 CKD, and macroalbuminuria who were obtaining standard of care, which involves a maximum tolerated labeled daily dose of an ACEi or ARB, has a renal and vascular protective impact that minimizes the development of renal impairment compared with placebo.	Drug: Canagliflozin Drug: Placebo	III	At a median follow-up of around 2.62 years, the likelihood of kidney failure and cardiovascular incidents was lower in the canagliflozin group than in the placebo group among individuals with T2DM and renal disease.	Perkovic et al., 2019 (51)

Table 3: List of clinical studies employing the effects of SGLT2 inhibitors in renal protection (continued)

NCT03190694	A Study to Assess the Renoprotective Effects of the SGLT2 Inhibitor Dapagliflozin in Non-Diabetic Patients With Proteinuria: a Randomized Double Blind 6-Weeks Cross-Over Trial	The hypothesis being tested in this trial is that dapagliflozin decreases proteinuria in those with non-diabetic chronic kidney disease.	Drug: Dapagliflozin 10mg	II	In patients with chronic renal disease but without diabetes, dapagliflozin medication for a time period of 6 weeks caused an immediate and temporary fall in mGFR as well as a decrease in bodyweight.	Cherney et al., 2020 (52)
NCT02413398	A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group, Randomized, Phase III Study to Evaluate the Glycemic Efficacy and Renal Safety of Dapagliflozin in Patients With T2DM and Moderate Renal Impairment (CKD 3A) Who Have Inadequate Glycemic Control.	To determine if dapagliflozin can lower blood sugar levels in those with Type 2 diabetes and significant renal impairment	Drug: Dapaglifloz in 10 mg Drug: Matching Placebo for Dapagliflozin	III	At Week 24, dapagliflozin caused higher reductions in eGFR from baseline than the placebo. However, eGFR returned to baseline levels at week 27.	Fioretto et al., 2018 (53)

Conclusion

The evidence from large RCTs has recently shown that SGLT2 inhibitors have unforeseen but effective and undeniable cardiorenal protective effects that develop soon after the beginning of treatment and are therefore effective even in people without diabetes. These characteristics go far beyond their initial therapeutic target of minimizing glucose. SGLT2 inhibitors require to be specifically investigated as prospective treatment options against the so-called “cardiorenal syndrome,” an acronym established about two decades ago to explain the significant connection between HF and renal disorders. This is predicated on the significant advantages of cardiorenal protection that showed up from a handful of clinical trials. In order to increase the number of individuals who can utilize these medications, the clinical data that has been collected will assist to identify the patients who will benefit from them the most. Clinicians should be aware that SGLT2 inhibitors may be administered in this situation, devoting close attention to patients with moderate CKD, and that elderly patients are more likely to experience side effects. Additionally, it is essential that gliflozins are delivered under strict control and following earlier patient training in ketosis-prone situations, such as alcoholism, the ketogenic diet, and prolonged fasting states for whatever cause.

References

1. Khoo CM, Deerochanawong C, Chan SP, Matawaran B, Sheu WH, Chan J, et al. Use of sodium-glucose co-transporter-2 inhibitors in Asian patients with type 2 diabetes and kidney disease: An Asian perspective and expert recommendations. Diabetes Obes Metab 2021; 23(2): 299-17. doi: 10.1111/dom.14251.
2. Bonner C, Kerr-Conte J, Gmyr V, Queniat G, Moerman E, Thévenet J, et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med 2015; 21(5): 512-7. doi: 10.1038/nm.3828.
3. Giugliano D, Longo M, Scappaticcio L, Caruso P, Esposito K. Sodium-glucose transporter-2 inhibitors for prevention and treatment of cardiorenal complications of type 2 diabetes. Cardiovasc Diabetol 2021; 20(1): 17. doi: 10.1186/s12933-021-01213-w.
4. Xu B, Li S, Kang B, Zhou J. The current role of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes mellitus management. Cardiovasc Diabetol 2022; 21(1): 83. doi: 10.1186/s12933-022-01512-w.
5. Thrasher J. Pharmacologic Management of Type 2 Diabetes Mellitus: Available Therapies. Am J Cardiol 2017; 120(1S): S4-S16. doi: 10.1016/j.amjcard.2017.05.009.
6. Saisho Y. SGLT2 Inhibitors: the Star in the Treatment of Type 2 Diabetes? Diseases. 2020; 8(2): 14. doi: 10.3390/diseases8020014.
7. Food US and Drug Administration. Sodium-glucose cotransporter-2 (SGLT2) inhibitors. Silver Spring: U.S. Food and Drug Administration. 2016.
8. Palmer SC, Tendal B, Mustafa RA, Vandvik PO, Li S, Hao Q, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. BMJ 2021; 372: m4573. doi: 10.1136/bmj.m4573.
9. Zheng SL, Roddick AJ, Aghar-Jaffar R, Shun-Shin MJ, Francis D, Oliver N, et al. Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis. JAMA 2018; 319(15): 1580-91. doi: 10.1001/jama.2018.3024.
10. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019; 157: 107843. doi: 10.1016/j.diabres.2019.107843.
11. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019; 393(10166): 31-9. doi: 10.1016/S0140-6736(18)32590-X.
12. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020; 383(15): 1436-46. doi: 10.1056/NEJMoa2024816.
13. McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz JA, Giannetti N, et al. CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction. Can J Cardiol 2021; 37(4): 531-46. doi: 10.1016/j.cjca.2021.01.017.
14. Plosker GL. Canagliflozin: a review of its use in patients with type 2 diabetes mellitus. Drugs 2014; 74(7): 807-24. doi: 10.1007/s40265-014-0225-5.
15. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. Drugs 2015; 75(1): 33-59. doi: 10.1007/s40265-014-0337-y. PMID: 25488697.
16. Moses RG, Colagiuri S, Pollock C. SGLT2 inhibitors: New medicines for addressing unmet needs in type 2 diabetes. Australas Med J 2014; 7(10): 405-15. doi: 10.4066/AMJ.2014.2181.
17. Desouza CV, Gupta N, Patel A. Cardiometabolic Effects of a New Class of Antidiabetic Agents. Clin Ther 2015; 37(6): 1178-94. doi: 10.1016/j.clinthera.2015.02.016.
18. Santer R, Kinner M, Lassen CL, Schneppenheim R, Eggert P, Bald M, et al. Molecular analysis of the SGLT2 gene in patients with renal glucosuria. J Am Soc Nephrol 2003; 14(11): 2873-82. doi: 10.1097/01.asn.0000092790.89332.d2.
19. Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC, et al. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. Diabetes Obes Metab 2015; 17(12): 1180-93. doi: 10.1111/dom.12572.
20. Solini A, Giannini L, Seghieri M, Vitolo E, Taddei S, Ghiadoni L, et al. Dapagliflozin acutely improves endothelial dysfunction, reduces aortic stiffness and renal resistive index in type 2 diabetic patients: a pilot study. Cardiovasc Diabetol 2017; 16(1): 138. doi: 10.1186/s12933-017-0621-8.
21. Yau K, Dharia A, Alrowiyti I, Cherney DZI. Prescribing SGLT2 Inhibitors in Patients With CKD: Expanding Indications and Practical Considerations. Kidney Int Rep 2022; 7(7): 1463-76. doi: 10.1016/j.ekir.2022.04.094.
22. Larmour K, Levin A. Slowing Progression in CKD: DAPA CKD and Beyond. Clin J Am Soc Nephrol 2021; 16(7): 1117-19. doi: 10.2215/CJN.20211220.
23. Watts NB, Bilezikian JP, Usiskin K, Edwards R, Desai M, Law G, et al. Effects of Canagliflozin on Fracture Risk in Patients With Type 2 Diabetes Mellitus. J Clin Endocrinol Metab 2016; 101(1): 157-66. doi: 10.1210/jc.2015-3167.
24. Shubrook JH, Bokaie BB, Adkins SE. Empagliflozin in the treatment of type 2 diabetes: evidence to date. Drug Des Devel Ther 2015; 9: 5793-803. doi: 10.2147/DDDT.S69926.
25. Nespoux J, Vallon V. Renal effects of SGLT2 inhibitors: an update. Curr Opin Nephrol Hypertens 2020; 29(2): 190-98. doi: 10.1097/MNH.0000000000000584.
26. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia 2018; 61(10): 2108-17. doi: 10.1007/s00125-018-4670-7.
27. Nassif ME, Windsor SL, Gosch K, Borlaug BA, Husain M, Inzucchi SE, et al. Dapagliflozin Improves Heart Failure Symptoms and Physical Limitations Across the Full Range of Ejection Fraction: Pooled Patient-Level Analysis From DEFINE-HF and PRESERVED-HF Trials. Circ Heart Fail 2023; 16(7): e009837. doi: 10.1161/CIRCHEARTFAILURE.122.009837.

28. Sizar O, Podder V, Talati R. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Empagliflozin. 2023.
29. Hu J, Deng A, Zhao Y. Ertugliflozin as a monotherapy for the treatment of type 2 diabetes. Expert Opin Pharmacother 2018; 19(16): 1841-47. doi: 10.1080/14656566.2018.
30. Chen LH, Leung PS. Inhibition of the sodium glucose co-transporter-2: its beneficial action and potential combination therapy for type 2 diabetes mellitus. Diabetes Obes Metab 2013; 15(5): 392-02. doi: 10.1111/dom.12064.
31. Scott LJ. Empagliflozin: a review of its use in patients with type 2 diabetes mellitus. Drugs 2014; 74(15): 1769-84.
32. Markham A. Ertugliflozin: first global approval. Drugs 2018; 78(4): 513-19. doi: 10.1007/s40265-018-0878-6.
33. Ferrannini E, Berk A, Hantel S, Pinnetti S, Hach T, Woerle HJ, et al. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care 2013;36(12): 4015-21. doi: 10.2337/dc13-0663.
34. Bode B, Stenlöf K, Sullivan D, Fung A, Usiskin K. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hosp Pract (1995) 2013; 41(2): 72-84. doi: 10.3810/hp.2013.04.1020.
35. Ji L, Liu Y, Miao H, Xie Y, Yang M, Wang W, et al. Safety and efficacy of ertugliflozin in Asian patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: VERTIS Asia. Diabetes Obes Metab 2019; 21(6): 1474-82. doi: 10.1111/dom.13681.
36. Cefalu WT, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet 2013; 382(9896): 941-50. doi: 10.1016/S0140-6736(13)60683-2.
37. Frías JP, Guja C, Hardy E, Ahmed A, Dong F, Öhman P, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol 2016; 4(12): 1004-16. doi: 10.1016/S2213-8587(16)30267-4.
38. Gallo S, Charbonnel B, Goldman A, Shi H, Huyck S, Darekar A, Lauring B, Terra SG. Long-term efficacy and safety of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: 104-week VERTIS MET trial. Diabetes Obes Metab 2019; 21(4): 1027-36. doi: 10.1111/dom.13631.
39. Lavalle-González FJ, Januszewicz A, Davidson J, Tong C, Qiu R, Canovatchel W, et al. Meininger G. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia 2013; 56(12): 2582-92. doi: 10.1007/s00125-013-3039-1.
40. Pratley RE, Eldor R, Raji A, Golm G, Huyck SB, Qiu Y, et al. Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: The VERTIS FACTORIAL randomized trial. Diabetes Obes Metab 2018; 20(5): 1111-20. doi: 10.1111/dom.13194.
41. Galiero R, Ricciardi D, Pafundi PC, Todisco V, Tedeschi G, Cirillo G, et al. Whole plantar nerve conduction study: A new tool for early diagnosis of peripheral diabetic neuropathy. Diabetes Res Clin Pract 2021; 176: 108856. doi: 10.1016/j.diabres.2021.
42. Masarone M, Rosato V, Aglitti A, Bucci T, Caruso R, Salvatore T, et al. Liver biopsy in type 2 diabetes mellitus: Steatohepatitis represents the sole feature of liver damage. PLoS One 2017; 12(6): e0178473. doi: 10.1371/journal.pone.0178473.
43. Spertus JA, Birmingham MC, Nassif M, Damaraju CV, Abbate A, Butler J, et al. The SGLT2 inhibitor canagliflozin in heart failure: the CHIEF-HF remote, patient-centered randomized trial. Nat Med 2022; 28(4): 809-13. doi: 10.1038/s41591-022-01703-8.
44. inman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373(22): 2117-28. doi: 10.1056/NEJMoa1504720.
45. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med 2021; 385(16): 1451-61. doi: 10.1056/NEJMoa2107038.
46. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019; 380(4): 347-57. doi: 10.1056/NEJMoa1812389.
47. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019; 381(21): 1995-08. doi: 10.1056/NEJMoa1911303.
48. DeFronzo RA, Reeves WB, Awad AS. Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors. Nat Rev Nephrol 2021; 17(5): 319-34. doi: 10.1038/s41581-021-00393-8.
49. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017; 377(7): 644-57. doi: 10.1056/NEJMoa1611925.
50. Heerspink HJL, Karasik A, Thuresson M, Melzer-Cohen C, Chodick G, Khunti K, et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. Lancet Diabetes Endocrinol 2020; 8(1): 27-5. doi: 10.1016/S2213-8587(19)30384-5.
51. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 2019; 380(24): 2295-06. doi: 10.1056/NEJMoa1811744.
52. Cherney DZI, Dekkers CCJ, Barbour SJ, Cattran D, Abdul Gafor AH, Greasley PJ, et al. Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial. Lancet Diabetes Endocrinol 2020; 8(7): 582-93. doi: 10.1016/S2213-8587(20)30162-5.
53. Fioretto P, Del Prato S, Buse JB, Goldenberg R, Giorgino F, Reyner D, et al. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): The DERIVE Study. Diabetes Obes Metab 2018; 20(11): 2532-40. doi: 10.1111/dom.13413.