Scientific Research Publishing

Pharmacology & Pharmacy, 2024, 15, 490-507
https://www.scirp.org/journal/pp
ISSN Online: 2157-9431
ISSN Print: 2157-9423

SGLT-2 Inhibitors: The Magic Bullet for Cardio-Renal Protection in Type 2 DM

Rushi Patel, Terry Oroszi

Department of Pharmacology and Toxicology, Boonshoft School of Medicine, Wright State University, Fairborn, OH, USA
Email: terry.oroszi@wright.edu

How to cite this paper: Patel, R. and Oroszi, T. (2024) SGLT-2 Inhibitors: The Magic Bullet for Cardio-Renal Protection in Type 2 DM. *Pharmacology & Pharmacy*, **15**, 490-507.
https://doi.org/10.4236/pp.2024.1512027

Received: March 20, 2024
Accepted: December 27, 2024
Published: December 30, 2024

Abstract

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are a promising class of medications for type 2 diabetes mellitus (DM2) treatment. This study aims to evaluate the clinical efficacy, safety, and potential benefits of SGLT-2 inhibitors in improving cardiovascular and renal outcomes in DM2 patients. A comprehensive review of clinical trials and studies on SGLT-2 inhibitors was conducted. SGLT-2 inhibitors significantly improve glycemic control, reduce cardiovascular mortality, and lower the risk of renal events in DM2 patients. SGLT-2 inhibitors offer substantial cardio-renal protection in DM2 management, though further research is needed to optimize their use.

Keywords

SGLT-2 Inhibitors, Type 2 Diabetes Mellitus, Cardiovascular Outcomes, Renal Protection, Glycemic Control

1. Introduction

The US Food and Drug Administration (FDA) has recently approved a group of medications known as sodium-glucose cotransporter 2 (SGLT-2) inhibitors. These drugs are intended for the treatment of adult patients who have been diagnosed with type 2 diabetes mellitus (DM2) [1]. SGLT-2 inhibitors act on SGLT-2 proteins found in the convoluted tubules of the renal proximal to reduce the amount of glucose being reabsorbed and increase the amount of glucose excreted in the urine, lowering blood glucose levels [2]. Although the precise processes by which SGLT-2 inhibitors improve these outcomes are still unclear, it is assumed that they do so by reducing glucose reabsorption, which lowers intrarenal glucose levels and oxidative stress [3]. The adverse effects of SGLT-2 inhibitors can include increased urination, increased risk of female yeast infections and urinary tract infections, and low blood pressure (FDA, 2021). Therefore, careful monitoring of kidney function

is required before and during treatment with SGLT-2 inhibitors [4].

The use of SGLT-2 inhibitors in patients with heart failure, whether they have type 2 diabetes or not, has shown good results in recent studies, lowering the risk of cardiovascular death and hospitalization for heart failure [5]. Furthermore, SGLT-2 inhibitors have shown the potential to lower the risk of progression of kidney disease in people with chronic kidney disease. More research is needed to fully understand how these medications improve these outcomes and assess their overall benefits and risks in patients with type 2 diabetes [6] [7].

Additional investigations are required to understand the complete scope of the possible uses of SGLT-2 inhibitors in various populations and disease conditions. The use of SGLT-2 inhibitors is restricted by the FDA to adult patients with type 2 diabetes and is contraindicated in those with type 1 diabetes or severe renal impairment.

2. What Are SGLT-2 and SGLT-2 Inhibitors?

Sodium-glucose cotransporters (SGLTs) are responsible for glucose transport in various tissues. SGLT-1 functions primarily in glucose uptake from the diet in the small intestine while SGLT-2 is responsible for glucose reabsorption in the kidney [8] [9]. SGLT-4 and SGLT-5 have unknown physiological functions related to glucose transport [9]. Although SGLT-3 has been observed to transport several substrates, such as glucose, fructose, and galactose, its physiological function remains unclear.

The SLC5A2 gene, located on chromosome 16q23.3, encodes the sodium-glucose cotransporter-2 (SGLT-2) protein. The primary physiological function of SGLT-2 is to facilitate glucose reabsorption from the renal tubules into the bloodstream, thus regulating the levels of glucose in the blood [9]. SGLT-2 is found predominantly in the renal proximal tubules, where it facilitates the reabsorption of glucose from urine into the bloodstream. In people without diabetes, SGLT-2 reabsorbs almost all the filtered glucose in the kidney; but in people with diabetes, glucose is affected, causing elevated glucose excretion in urine. SGLT-2 inhibitors inhibit SGLT-2 function, leading to the prevention of glucose reabsorption in the kidney, thus reducing blood glucose levels and improving glycemic control in individuals with diabetes [10].

Sodium-glucose cotransporter-2 inhibitors (SGLT-2) are a novel group of drugs that can ameliorate symptoms of type 2 diabetes mellitus (DM2). Their mechanism of action involves inhibiting the reabsorption of glucose in the kidneys, resulting in elevated excretion of glucose in the urine and a subsequent decrease in blood glucose levels. The discovery and development of SGLT-2 inhibitors is a relatively recent event in the history of diabetes treatment. In 1835, German chemist Friedrich Wöhler discovered the first sugar transporter, which he named "Glukosurie" (glucose carrier).

More than a century later, in the 1960s, researchers discovered the existence of SGLT-2 in the kidney tubules of animals. However, it was not until the late 1990s and early 2000s that SGLT-2 inhibitors began to be developed as a treatment for

diabetes [11]. The first SGLT-2 inhibitor to be developed was phlorizin, a natural compound found in the bark of apple trees. It was discovered in the early 1800s, but its use as a diabetes treatment was limited due to its poor pharmacokinetics and side effects, such as gastrointestinal upset and hypotension [2]. In the early 2000s, researchers began to develop synthetic SGLT-2 inhibitors that were more effective and better tolerated than phlorizin. Canagliflozin was the first SGLT-2 inhibitor approved by the FDA in 2013, followed by dapagliflozin and empagliflozin. After the initial approval of canagliflozin, other SGLT-2 inhibitors such as ertugliflozin, ipragliflozin, and tofogliflozin have been developed and approved for the treatment of DM2 [12].

SGLT-2 inhibitors can be classified according to their chemical structure, mechanism of action, and pharmacokinetics. Chemically, they are all derivatives of phlorizin, with modifications to improve pharmacokinetic properties and reduce side effects. Mechanically, they all work by inhibiting the reabsorption of glucose in the kidneys, but may have different affinities for SGLT-2 versus SGLT-1, which is another glucose transporter found in the small intestine [13]. Pharmacokinetically, SGLT-2 inhibitors differ in their half-lives, renal clearance, and potential for drug-drug interactions. Some SGLT-2 inhibitors are metabolized by cytochrome P450 enzymes, which can be inhibited or induced by other drugs. For example, canagliflozin is metabolized by CYP3A4 and is contraindicated with strong inhibitors of CYP3A4, while dapagliflozin and empagliflozin are not metabolized by CYP enzymes and have a lower potential for drug interactions [14].

Phlorizin First-generation SGLT-2 inhibitors:

(a natural compound found in apple tree bark)

Dapagliflozin (FDA approval in 2014)

Canagliflozin (FDA approval in 2013)

Second-generation SGLT-2 inhibitors:

Empagliflozin (FDA approval in 2014)

Ertugliflozin (approved by the FDA in 2017)

Ipragliflozin (approved in Japan in 2014)

Tofogliflozin (approved in Japan in 2014)

Each SGLT-2 inhibitor has unique pharmacokinetic and pharmacodynamic properties, which may affect its clinical efficacy and safety. See **Table 1** for more details on SGLT-2.

3. Importance of Studying the Effects on Cardio and Renal Health

Recent studies have shown that sodium-glucose cotransporter 2 (SGLT-2) inhibitors significantly improve cardiovascular and renal outcomes in patients with type 2 diabetes (T2D) as well as in patients without diabetes and acute or chronic heart failure [5]-[7] [20]-[22]. These inhibitors have been associated with a reduction in the risk of hospitalization for heart failure, major adverse cardiovascular events, and all-cause mortality [5]-[7] [20]-[22].

Table 1. SGLT-2 Inhibitors.

SGLT-2 Inhibitors	Half-Life	Affinity	Effects	Adverse Effects
Dapagliflozin [15]	~12 hours	High for SGLT-2, lower for SGLT-1	Reduces HbA1c levels, body weight, and blood pressure	Low risk of hypoglycemia, but may increase risk of genital and urinary tract infections
Canagliflozin [7] [16]	~13 hours	Higher for SGLT-2 than for SGLT-1, may inhibit other transporters	Reduces HbA1c levels, body weight, and blood pressure	May increase the risk of genital and urinary tract infections, and lower limb amputations
Empagliflozin [12]	~12 hours	High for SGLT-2, lower for SGLT-1	Reduces HbA1c levels, body weight, and cardiovascular events	Low risk of hypoglycemia, might reduce risk of heart failure, but could increase risk of genital and urinary tract infections
Ertugliflozin [17]	~15 hours	High for SGLT-2, lower for SGLT-1	Reduces HbA1c levels and body weight	Low risk of hypoglycemia, but can increase risk of genital and urinary tract infections
Ipragliflozin [18]	~8 hours	High for SGLT-2, lower for SGLT-1	Reduces HbA1c levels, body weight, and blood pressure	May increase the risk of genital and urinary tract infections, and may be associated with an increased risk of diabetic ketoacidosis
Tofogliflozin [19]	~60 hours	High for SGLT-2, lower for SGLT-1	Reduces HbA1c levels and body weight	May increase the risk of genital and urinary tract infections, and may be associated with an increased risk of bone fractures

SGLT-2 inhibitors have also shown improvements in hypertriglyceridemia, obesity, and blood pressure, and have shown promising outcomes in cardiovascular diseases such as arrhythmias, ischemic heart disease, and heart failure [5]-[7] [20]-[22]. However, it is important to note that SGLT-2 inhibitors may cause potential side effects, including acute kidney injuries, vulvovaginal candidiasis, and frequent urinary tract infections, so counseling patients about these potential side effects is crucial [5] [6] [20].

The magnitude of the observed cardiovascular benefits of SGLT-2 inhibitors suggests that these benefits may extend beyond glucose-lowering effects [6] [7] [20]-[22]. However, the potential mechanisms behind these cardiovascular benefits are still being studied. Monitoring potential side effects is crucial, and further research is needed to determine the potential mechanisms behind the cardiovascular benefits of SGLT-2 inhibitors.

SGLT-2 inhibitors are a group of medications that have been shown to improve endothelial function and reduce arterial stiffness in patients with type 2 diabetes (DM2) through a combination of glucose-independent and glucose-dependent

mechanisms. A study by Wei *et al.* [23] reported that SGLT-2 inhibitors significantly reduced arterial stiffness, measured by pulse wave velocity, and that this effect was associated with a reduction in oxidative stress. This reduction in oxidative stress and inflammation is a possible glucose-independent mechanism by which SGLT-2 inhibitors improve endothelial function and reduce arterial stiffness. SGLT-2 inhibitors have been shown to decrease reactive oxygen species (ROS) and pro-inflammatory cytokine levels, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are involved in the development of endothelial dysfunction and arterial stiffness. Modulation of the renin-angiotensin-aldosterone system (RAAS) is another potential glucose-independent mechanism by which SGLT-2 inhibitors improve endothelial function and reduce arterial stiffness. SGLT-2 inhibitors have been shown to decrease angiotensin II levels and increase angiotensin (1 - 7) levels, which leads to vasodilation and improved endothelial function. Dysregulation of RAAS has been implicated in the development of cardiovascular disease [24].

SGLT-2 inhibitors also have glucose-dependent mechanisms that can improve endothelial function and reduce arterial stiffness. By reducing hyperglycemia, SGLT-2 inhibitors decrease the formation of advanced glycation end products (AGEs), which can impair endothelial function and increase arterial stiffness. AGEs are formed when glucose reacts with proteins in the body, leading to the formation of cross-linked molecules that can cause damage to tissues and organs. AGEs have been implicated in the development of various complications of diabetes, including cardiovascular disease [24].

Furthermore, SGLT-2 inhibitors can increase nitric oxide (NO) bioavailability, which promotes vasodilation and improves endothelial function. Nitric oxide is a signaling compound that plays an important role in the regulation of vascular tone and endothelial function [24]. It has been proposed that the improved availability of NO could be attributed to a decrease in oxidative stress and inflammation, along with an improvement in mitochondrial function [25]. Overall, SGLT-2 inhibitors improve endothelial function and reduce arterial stiffness in patients with DM2 through various mechanisms. These mechanisms include the reduction of oxidative stress and inflammation, modulation of the RAAS system, reduction of AGE formation, and increased NO bioavailability. These effects of SGLT-2 inhibitors suggest that they may have significant long-term cardiovascular benefits beyond glucose-lowering effects in patients with DM2 [23] [24].

4. Background

SGLT-2 inhibitors have been found to improve both renal and cardiovascular outcomes in patients with type 2 diabetes. These drugs work by inhibiting sodium-glucose cotransporter 2, which is responsible for glucose reabsorption in the kidneys. By blocking this transporter, SGLT-2 inhibitors increase glucose excretion in urine, leading to a reduction in blood glucose levels [26]. The beneficial effects of SGLT-2 inhibitors on cardiovascular outcomes have been demonstrated in

multiple clinical trials. One of the largest and most well-known trials is the EMPA-REG OUTCOME trial, which investigated the cardiovascular effects of empagliflozin in high-risk patients with type 2 diabetes [12]. This trial found that empagliflozin significantly reduced the risk of cardiovascular mortality and hospitalization for heart failure compared to a placebo.

Other trials have investigated the effects of SGLT-2 inhibitors on specific subgroups of patients with cardiovascular disease. For example, the DAPA-HF trial found that dapagliflozin reduced the risk of hospitalization for heart failure and cardiovascular death in patients with heart failure and reduced ejection fraction [21]. The EMPEROR-Reduced trial investigated the effects of empagliflozin in patients with heart failure and a reduced ejection fraction and found that empagliflozin significantly reduced the risk of cardiovascular death and hospitalization for heart failure [5].

SGLT-2 inhibitors have also been found to improve kidney outcomes in patients with type 2 diabetes. The CREDENCE trial investigated the effects of canagliflozin on renal outcomes in patients with type 2 diabetes and chronic kidney disease and found that canagliflozin significantly reduced the risk of kidney failure and cardiovascular events [22]. In addition to their effects on cardiovascular and renal outcomes, SGLT-2 inhibitors have also been found to lead to weight loss and a reduction in body mass index (BMI). This is likely due to the reduction in blood glucose levels and the increased glucose excretion in urine [27]. In addition, SGLT-2 inhibitors have been shown to improve renal outcomes. In the Canagliflozin Cardiovascular Assessment Study (CANVAS), canagliflozin was found to reduce the risk of renal outcomes, including renal failure and albuminuria, in patients with type 2 diabetes [7]. Another trial, the study Empagliflozin, Cardiovascular outcomes and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME), demonstrated that empagliflozin reduced the risk of incident or worsening nephropathy [12].

The mechanisms of action underlying the beneficial effects of SGLT-2 inhibitors are still being investigated. A proposed mechanism involves the improvement in skeletal muscle bioenergetics [28]. SGLT-2 inhibitors have also been suggested to reduce inflammation and oxidative stress, leading to a reduction in cardiovascular risk [29]. Despite promising results, there are some potential adverse effects associated with SGLT-2 inhibitors. These include an increased risk of urinary tract infections and genital mycotic infections. However, these adverse effects are generally mild and can be managed with proper monitoring and treatment [7].

Type 2 diabetes is a chronic disease that affects millions of people worldwide. The disease is characterized by high blood glucose levels resulting from the body's inability to use insulin effectively. Although lifestyle modifications such as diet and exercise may be effective, they may be insufficient to reduce the risk of complications in many patients with DM2, hence requiring medications. A class of medications used to treat type 2 diabetes is sodium-glucose cotransporter 2 (SGLT-2) inhibitors [30]. This helps to lower blood glucose levels and reduce the risk of cardiovascular events [31]. Other medications used to treat type 2 diabetes

include metformin, sulfonylureas, meglitinides, thiazolidinediones, and dipeptidyl peptidase-4 (DPP-4) inhibitors. These medications work in different ways to help the body use insulin more effectively or reduce the amount of glucose produced by the liver. It is important to note that medications are not a cure for type 2 diabetes and should be used in conjunction with lifestyle changes such as healthy eating and regular physical activity. Complications of type 2 diabetes include cardiovascular disease, kidney disease, nerve damage, and blindness, among others. Therefore, it is important to work with a healthcare professional to manage type 2 diabetes and reduce the risk of complications.

5. Cardiovascular Effects of SGLT-2 Inhibitors

In recent years, several clinical trials have demonstrated the beneficial effects of SGLT-2 inhibitors on cardiovascular outcomes. The EMPA-REG OUTCOME trial was one of the first clinical trials to demonstrate the cardiovascular benefits of SGLT-2 inhibitors. In this trial, empagliflozin was found to significantly reduce the risk of major adverse cardiovascular events (MACE), cardiovascular death, and hospitalization for heart failure compared to a placebo [12]. The CANVAS program also found that canagliflozin significantly reduced the risk of MACE, cardiovascular death, and hospitalization for heart failure compared to a placebo [7]. The DAPA-HF trial found that dapagliflozin effectively decreased the probability of cardiovascular death or deterioration of heart failure in patients with a reduced ejection fraction compared to the placebo [21]. The EMPEROR-Reduced trial demonstrated that empagliflozin could significantly reduce the risk of cardiovascular death or hospitalization for heart failure [5]. See **Table 2** for a summary of Clinical Trial Outcomes.

Table 2. Clinical trial outcomes.

Trial	Drug	Population	Key Outcomes
EMPA-REG OUTCOME	Empagliflozin	High-risk DM2	Reduced cardiovascular mortality, hospitalization for heart failure
CANVAS	Canagliflozin	High-risk DM2	Reduced MACE, cardiovascular death, hospitalization for heart failure
DAPA-HF	Dapagliflozin	Heart failure	Reduced cardiovascular death, deterioration of heart failure
EMPEROR-Reduced	Empagliflozin	Heart failure	Reduced cardiovascular death, hospitalization for heart failure
CREDENCE	Canagliflozin	Chronic kidney disease	Reduced kidney failure, cardiovascular events

The mechanisms underlying the cardiovascular benefits of SGLT-2 inhibitors are not yet fully understood but are thought to involve both hemodynamic and

metabolic effects. SGLT-2 inhibitors have been shown to reduce blood pressure, improve arterial stiffness, and decrease myocardial fibrosis. They also improve glycemic control, reduce body weight, and lower serum uric acid levels, which may also contribute to their cardiovascular benefits [32]. Therefore, the clinical trials discussed above demonstrate that SGLT-2 inhibitors significantly benefit cardiovascular outcomes and could be a treatment option for patients with type 2 diabetes and/or heart failure.

6. Potential Mechanisms of the Effects of SGLT-2 Inhibitors on Cardiovascular Outcomes

One of the mechanisms behind these effects is the improvement in endothelial function. Endothelial dysfunction is a key feature of cardiovascular disease and is characterized by a reduction in the bioavailability of nitric oxide (NO), which plays an essential role in the regulation of vascular tone and the prevention of the development of atherosclerosis [33]. Several studies have demonstrated that SGLT-2 inhibitors can improve endothelial function by increasing NO production and reducing oxidative stress. Empagliflozin was found to increase the levels of circulating endothelial progenitor cells, which are involved in the repair of damaged endothelium [34]. The activation of the AMP-activated protein kinase (AMPK) pathway, responsible for controlling energy metabolism and cell stress responses, mediates this effect [35].

Another mechanism underlying the cardiovascular benefits of SGLT-2 inhibitors is the reduction in arterial stiffness. Arterial stiffness, which is characterized by reduced elasticity in the arterial walls, is a crucial determinant of cardiovascular risk, as it contributes to the pathogenesis of hypertension, myocardial infarction, and stroke [36]. SGLT-2 inhibitors can reduce arterial stiffness by reducing the accumulation of advanced glycation end products (AGEs). AGEs are known to crosslink collagen fibers and alter the mechanical properties of arterial walls. SGLT-2 inhibitors have been shown to reduce AGE levels by reducing hyperglycemia and ROS production [37].

In addition to improvements in endothelial function and arterial stiffness, SGLT-2 inhibitors have been found to reduce blood pressure, improve lipid profiles, and reduce inflammation, all of which are important contributors to cardiovascular disease [32]. These effects are likely mediated by a combination of direct and indirect mechanisms, including reductions in insulin resistance, reductions in sympathetic nervous system activity, and improvements in adipose tissue function. Furthermore, SGLT-2 inhibitors have been shown to reduce the occurrence of heart failure in patients with type 2 diabetes, likely due to a combination of their effects on cardiovascular risk factors and their direct effects on cardiac function [38].

SGLT-2 inhibitors have also been found to have anti-inflammatory effects, which may contribute to their cardioprotective effects. Chronic low-grade inflammation is known to contribute to the development and progression of cardiovascular disease, and SGLT-2 inhibitors have been shown to reduce inflammation

biomarkers such as C-reactive protein (CRP) and interleukin-6 (IL-6) [39]. SGLT-2 inhibitors have been shown to improve cardiac contractility and reduce cardiac fibrosis in animal models of heart failure [40]. The exact mechanisms underlying the cardiovascular benefits of SGLT-2 inhibitors are not yet fully understood and require further investigation. However, the available evidence suggests that these drugs have a multifactorial effect on the cardiovascular system, with improvements seen in endothelial function, arterial stiffness, and other cardiovascular risk factors. These findings have important implications for the prevention and treatment of cardiovascular disease in patients with type 2 diabetes.

7. Renal Effects of SGLT-2 Inhibitors

SGLT-2 inhibitors have been shown to have significant renal benefits in patients with type 2 diabetes. These drugs act by inhibiting sodium-glucose cotransporter 2 (SGLT-2) in the proximal tubules of the kidneys, leading to increased glucose excretion and improved glycemic control. One of the vital renal benefits of SGLT-2 inhibitors is their ability to reduce albuminuria, which is a marker of kidney damage and a predictor of renal and cardiovascular outcomes in patients with diabetes. Several large randomized controlled trials have shown the effectiveness of SGLT-2 inhibitors in reducing albuminuria [32]. The EMPA-REG OUTCOME trial, which investigated empagliflozin, showed a 38% reduction in the risk of progression of albuminuria compared to a placebo [26]. The CANVAS trial, which investigated canagliflozin, showed a 27% reduction in albuminuria progression [22]. Similarly, the DECLARE-TIMI 58 trial, which investigated dapagliflozin, demonstrated a 24% reduction in albuminuria progression [6].

In addition to reducing albuminuria, SGLT-2 inhibitors have been shown to reduce the risk of renal events, such as the onset of end-stage renal disease or the need for renal replacement therapy, in patients with type 2 diabetes. In the EMPA-REG OUTCOME trial, empagliflozin was found to lead to a 39% decrease in the risk of developing or deteriorating nephropathy compared to the placebo [26]. The CANVAS trial demonstrated a 40% reduction in the risk of renal replacement therapy [7], and the CREDENCE trial, which investigated canagliflozin, showed a 34% reduction in the risk of end-stage renal disease or renal death [22].

8. Potential Mechanisms of SGLT-2 Inhibitors' Reno-Protective Effects

The mechanisms underlying these effects are not fully understood, but recent research has shed light on several potential mechanisms. One of the proposed mechanisms is the reduction of glomerular hyperfiltration. A study demonstrated that SGLT-2 inhibitors could reduce glomerular hyperfiltration in patients with type 2 diabetes, which is commonly associated with the disease [24]. The study found that dapagliflozin treatment reduced the glomerular filtration rate (GFR) in patients with type 2 diabetes, suggesting a reduction in glomerular hyperfiltration. The authors suggested that this reduction could be due to increased tubuloglomerular feedback (TGF) and reduced intraglomerular pressure [41].

Another potential mechanism underlying the renal benefits of SGLT-2 inhibitors is the improvement of tubulointerstitial fibrosis. It showed that treatment with an SGLT-2 inhibitor reduced tubulointerstitial fibrosis in a mouse model of diabetic nephropathy. The authors suggested that this effect could be related to the reduction of oxidative stress and inflammation in renal tubular cells [6] [42]. In addition to these mechanisms, SGLT-2 inhibitors can also have direct effects on endothelial function of the renal vasculature. A study by Kong *et al.* [43] demonstrated that treatment with an SGLT-2 inhibitor improved endothelial function in patients with type 2 diabetes and renal impairment. The authors suggested that this effect may be related to the reduction of oxidative stress and inflammation in the renal vasculature [6].

In addition, SGLT-2 inhibitors can have a reno-protective effect by reducing the risk of acute kidney injury (AKI) in patients with type 2 diabetes. A study evaluated the effects of dapagliflozin on AKI in patients with chronic heart failure and reduced ejection fraction, and the results showed that dapagliflozin reduced the incidence of AKI. The authors suggested that this renoprotective effect might be related to the reduction of volume overload and hemodynamic instability [44].

Furthermore, SGLT-2 inhibitors may have an impact on albuminuria, which is a marker of early kidney damage. A study by Heerspink *et al.* [45] evaluated the effects of canagliflozin on albuminuria in patients with type 2 diabetes and chronic kidney disease. The study found that canagliflozin reduced albuminuria and the risk of end-stage renal disease. The authors suggested that this effect might be due to reduction of intraglomerular pressure and improvement of tubular function. In general, the mechanisms underlying the renal benefits of SGLT-2 inhibitors are multifactorial and involve several processes, including the reduction of glomerular hyperfiltration, improvements in tubulointerstitial fibrosis, and improvements in endothelial function. These drugs also have renoprotective effects, such as reducing the risk of AKI and improving albuminuria. SGLT-2 inhibitors may improve glomerular hemodynamics by reducing intraglomerular pressure and hyperfiltration [46]. They may also reduce oxidative stress and inflammation, which are known to contribute to renal damage. Furthermore, SGLT-2 inhibitors may reduce intrarenal fat accumulation, which has been implicated in the development of renal dysfunction [10]. In general, the renal benefits of SGLT-2 inhibitors represent a significant advance in the management of type 2 diabetes and its associated complications. These findings suggest that SGLT-2 inhibitors could be considered first-line therapy for patients with type 2 diabetes at risk of renal disease.

9. Liver Disease and SGLT-2 Inhibitors

Nonalcoholic fatty liver disease (NAFLD) is a common comorbidity in patients with type 2 diabetes, and it is estimated that up to 70% of patients with type 2 diabetes have NAFLD. NAFLD is characterized by the accumulation of fat in the liver, which can lead to inflammation and liver damage. It is a significant risk factor for the development of liver fibrosis, cirrhosis, and hepatocellular carcinoma.

SGLT-2 inhibitors have been shown to improve liver function and reduce liver fat content in patients with NAFLD. A study investigated the effect of dapagliflozin on liver fat content and liver enzymes in patients with type 2 diabetes and NAFLD. The study included 50 patients who were randomized to receive dapagliflozin 10 mg/day or a placebo for 24 weeks. The primary endpoint was the change in liver fat content, as assessed by magnetic resonance imaging. Secondary endpoints included changes in liver enzymes, insulin sensitivity, and body weight. The study found that dapagliflozin treatment resulted in a significant reduction in liver fat content compared to placebo, with a mean decrease of 20% - 30%. Dapagliflozin also led to significant improvements in liver enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The reduction in liver fat content was associated with improvements in insulin sensitivity and body weight [47].

Other studies have also shown the beneficial effects of SGLT-2 inhibitors on liver function. A study investigated the effect of canagliflozin on liver fat content and liver enzymes in patients with type 2 diabetes and NAFLD. The study included 32 patients who were randomized to receive canagliflozin 100 mg/day or placebo for 12 weeks. The study found that treatment with canagliflozin led to a significant reduction in liver fat content and liver enzymes compared to a placebo [48]. The exact mechanism by which SGLT-2 inhibitors improve liver function in patients with NAFLD is not fully understood. It is believed that increased urinary glucose excretion leads to a reduction in hepatic glucose production, which may reduce fat accumulation in the liver. SGLT-2 inhibitors may also have anti-inflammatory effects, which could contribute to improvements in liver function [49]. SGLT-2 inhibitors have been shown to improve liver function and reduce liver fat content in patients with type 2 diabetes and NAFLD. These effects make SGLT-2 inhibitors a promising option for the management of NAFLD and its associated complications.

10. Liver Disease and SGLT-2 Inhibitors

Nonalcoholic fatty liver disease (NAFLD) is a common comorbidity in patients with type 2 diabetes, and it is estimated that up to 70% of patients with type 2 diabetes have NAFLD. NAFLD is characterized by the accumulation of fat in the liver, which can lead to inflammation and liver damage. It is a significant risk factor for the development of liver fibrosis, cirrhosis, and hepatocellular carcinoma.

SGLT-2 inhibitors have been shown to improve liver function and reduce liver fat content in patients with NAFLD. A study investigated the effect of dapagliflozin on liver fat content and liver enzymes in patients with type 2 diabetes and NAFLD. The study included 50 patients who were randomized to receive dapagliflozin 10 mg/day or a placebo for 24 weeks. The primary endpoint was the change in liver fat content, as assessed by magnetic resonance imaging. Secondary endpoints included changes in liver enzymes, insulin sensitivity, and body weight. The study found that dapagliflozin treatment resulted in a significant reduction

in liver fat content compared to placebo, with a mean decrease of 20% - 30%. Dapagliflozin also led to significant improvements in liver enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The reduction in liver fat content was associated with improvements in insulin sensitivity and body weight (Fioretto *et al.*, 2018). Other studies have also shown the beneficial effects of SGLT-2 inhibitors on liver function. A study investigated the effect of canagliflozin on liver fat content and liver enzymes in patients with type 2 diabetes and NAFLD. The study included 32 patients who were randomized to receive canagliflozin 100 mg/day or placebo for 12 weeks. The study found that treatment with canagliflozin led to a significant reduction in liver fat content and liver enzymes compared to a placebo [48]. The exact mechanism by which SGLT-2 inhibitors improve liver function in patients with NAFLD is not fully understood. It is believed that increased urinary glucose excretion leads to a reduction in hepatic glucose production, which may reduce fat accumulation in the liver. SGLT-2 inhibitors may also have anti-inflammatory effects, which could contribute to improvements in liver function [49].

SGLT-2 inhibitors have been shown to improve liver function and reduce liver fat content in patients with type 2 diabetes and NAFLD. These effects make SGLT-2 inhibitors a promising option for the management of NAFLD and its associated complications.

11. Future Applications

SGLT-2 inhibitors are effective in the treatment of type 2 diabetes by improving glucose control and reducing the risk of cardiovascular and renal events. However, ongoing research suggests that these drugs may have potential applications beyond diabetes treatment. One area of research is the possible use of SGLT-2 inhibitors in the treatment of heart failure. Heart failure is a medical condition in which the heart is unable to effectively pump enough blood to meet the demands of the body. SGLT-2 inhibitors have been shown to improve heart failure outcomes in patients with and without diabetes in clinical trials. These benefits may be due to the diuretic effect of SGLT-2 inhibitors, which reduces fluid build-up in the body, improves glucose control, and reduces inflammation [5] [21].

Sotagliflozin is a type of drug known as a dual inhibitor of SGLT-1 and SGLT-2. It works by blocking the function of two proteins, SGLT-1 and SGLT-2, which are involved in glucose absorption in the intestines and kidneys, respectively. Inhibition of these proteins by sotagliflozin results in a decrease in glucose absorption into the bloodstream, ultimately leading to reduced blood glucose levels. An advantage of sotagliflozin over SGLT-2 inhibitors is that it also blocks SGLT-1, which is responsible for glucose absorption in the intestines. By blocking this protein, sotagliflozin reduces glucose absorbed from food, leading to additional glucose-lowering effects. In clinical trials, sotagliflozin is more effective than SGLT-2 inhibitors alone in improving blood glucose control in patients with type 1 diabetes. Although SGLT-2 inhibitors are primarily used in the treatment of type 2

diabetes, sotagliflozin is also effective in improving glucose control in patients with type 1 diabetes [50].

12. Conclusions

Sodium-glucose cotransporter 2 inhibitors (SGLT-2) are a relatively new class of medication used to treat type 2 diabetes mellitus (T2DM). These drugs block glucose reabsorption in the kidneys, thus increasing glucose excretion and lowering blood glucose levels. Over the past few years, evidence has indicated that SGLT-2 inhibitors could potentially benefit cardiovascular and renal outcomes among people with type 2 diabetes mellitus.

Several clinical trials have studied how SGLT-2 inhibitors impact cardiovascular outcomes in people with type 2 diabetes mellitus. For example, the EMPA-REG OUTCOME trial found that empagliflozin (an SGLT-2 inhibitor) reduced the risk of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke by 14% compared to placebo in patients with DM2 and established cardiovascular disease [12]. Similarly, the CANVAS program found that canagliflozin (another SGLT-2 inhibitor) reduced the risk of major adverse cardiovascular events (MACE) by 14% compared to placebo in patients with DM2 and high cardiovascular risk [7].

In addition to these cardiovascular benefits, SGLT-2 inhibitors have also been shown to have renal protective effects in patients with DM2. For example, the CREDENCE trial found that canagliflozin reduced the risk of end-stage kidney disease, doubled serum creatinine, and renal or cardiovascular death by 30% compared to placebo in patients with DM2 and chronic kidney disease [22]. Similarly, the EMPA-REG OUTCOME trial found that empagliflozin reduced the risk of incident or worsening nephropathy by 39% compared to placebo in patients with DM2 and established cardiovascular disease [26].

A potential mechanism by which SGLT-2 inhibitors exert their cardiovascular and renal protective effects is through their ability to lower blood pressure. Studies have shown that SGLT-2 inhibitors can reduce systolic and diastolic blood pressure by 3 - 5 mmHg, and this effect is seen even in patients with normal blood pressure at baseline [51]. In addition to their blood pressure-lowering effects, SGLT-2 inhibitors can also have direct cardioprotective and renoprotective effects through a variety of mechanisms, including reduction of oxidative stress, inflammation, and fibrosis, and improvement of endothelial function [10] [32] [51] [52].

Another potential mechanism by which SGLT-2 inhibitors may exert their beneficial effects is through their ability to promote weight loss. Studies have shown that SGLT-2 inhibitors can significantly reduce body weight, with empagliflozin and canagliflozin leading to mean weight losses of 2.5 - 3.5 kg and 2.5 - 4.5 kg, respectively, over 26 - 104 weeks. This weight loss may have additional cardiovascular and metabolic benefits, including improved insulin sensitivity, reduced visceral adiposity, and improved lipid profiles [12] [53] [54].

In conclusion, SGLT-2 inhibitors have emerged as a promising class of drugs

for the treatment of T2DM, with growing evidence suggesting that they may have beneficial effects on cardiovascular and renal outcomes. These effects may be mediated through a variety of mechanisms, including reduction in blood pressure, weight loss, and direct cardioprotective and renoprotective effects. Ongoing research is needed to elucidate further the mechanisms underlying these effects and to identify which patients may benefit the most from SGLT-2 inhibitor therapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Barnett, A.H., Mithal, A., Manassie, J., Jones, R., Rattunde, H., Woerle, H.J., *et al.* (2014) Efficacy and Safety of Empagliflozin Added to Existing Antidiabetes Treatment in Patients with Type 2 Diabetes and Chronic Kidney Disease: A Randomized, Double-Blind, Placebo-Controlled Trial. *The Lancet Diabetes & Endocrinology*, **2**, 369-384. https://doi.org/10.1016/s2213-8587(13)70208-0

[2] DeFronzo, R.A., Davidson, J.A. and Del Prato, S. (2011) The Role of the Kidneys in Glucose Homeostasis: A New Path Towards Normalizing Glycaemia. *Diabetes, Obesity and Metabolism*, **14**, 5-14. https://doi.org/10.1111/j.1463-1326.2011.01511.x

[3] Vallon, V. and Thomson, S.C. (2016) Targeting Renal Glucose Reabsorption to Treat Hyperglycaemia: The Pleiotropic Effects of SGLT2 Inhibition. *Diabetologia*, **60**, 215-225. https://doi.org/10.1007/s00125-016-4157-3

[4] Buse, J.B., Wexler, D.J., Tsapas, A., Rossing, P., Mingrone, G., Mathieu, C., *et al.* (2019) 2019 Update To: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*, **43**, 487-493. https://doi.org/10.2337/dci19-0066

[5] Packer, M., Anker, S.D., Butler, J., Filippatos, G., Pocock, S.J., Carson, P., *et al.* (2020) Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *New England Journal of Medicine*, **383**, 1413-1424. https://doi.org/10.1056/nejmoa2022190

[6] Heerspink, H.J.L., Stefánsson, B.V., Correa-Rotter, R., Chertow, G.M., Greene, T., Hou, F., *et al.* (2020) Dapagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine*, **383**, 1436-1446. https://doi.org/10.1056/nejmoa2024816

[7] Neal, B., Perkovic, V., Mahaffey, K.W., de Zeeuw, D., Fulcher, G., Erondu, N., *et al.* (2017) Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *New England Journal of Medicine*, **377**, 644-657. https://doi.org/10.1056/nejmoa1611925

[8] Gorboulev, V., Schürmann, A., Vallon, V., Kipp, H., Jaschke, A., Klessen, D., *et al.* (2011) Na^+-D-Glucose Cotransporter SGLT1 Is Pivotal for Intestinal Glucose Absorption and Glucose-Dependent Incretin Secretion. *Diabetes*, **61**, 187-196. https://doi.org/10.2337/db11-1029

[9] Wright, E.M., Loo, D.D.F. and Hirayama, B.A. (2011) Biology of Human Sodium Glucose Transporters. *Physiological Reviews*, **91**, 733-794. https://doi.org/10.1152/physrev.00055.2009

[10] Heerspink, H.J.L., Perkins, B.A., Fitchett, D.H., Husain, M. and Cherney, D.Z.I. (2016) Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus. *Circulation*, **134**, 752-772.

https://doi.org/10.1161/circulationaha.116.021887

[11] Turk, E. and Wright, E.M. (2004) The Sodium/glucose Cotransport Family SLC5. *European Journal of Physiology*, **447**, 510-518. https://doi.org/10.1007/s00424-003-1063-6

[12] Zinman, B., Wanner, C., Lachin, J.M., Fitchett, D., Bluhmki, E., Hantel, S., *et al.* (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine*, **373**, 2117-2128. https://doi.org/10.1056/nejmoa1504720

[13] Simes, B.C. and MacGregor, G.G. (2019) Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors: A Clinician's Guide. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, **12**, 2125-2136. https://doi.org/10.2147/dmso.s212003

[14] Scheen, A.J. (2015) Pharmacokinetics, Pharmacodynamics and Clinical Use of SGLT2 Inhibitors in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease. *Clinical Pharmacokinetics*, **54**, 691-708. https://doi.org/10.1007/s40262-015-0264-4

[15] Bailey, C.J., Gross, J.L., Hennicken, D., Iqbal, N., Mansfield, T.A. and List, J.F. (2013) Dapagliflozin Add-On to Metformin in Type 2 Diabetes Inadequately Controlled with Metformin: A Randomized, Double-Blind, Placebo-Controlled 102-Week Trial. *BMC Medicine*, **11**, Article No. 43. https://doi.org/10.1186/1741-7015-11-43

[16] Rosenstock, J., Aggarwal, N., Polidori, D., Zhao, Y., Arbit, D., Usiskin, K., *et al.* (2012) Dose-Ranging Effects of Canagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, as Add-On to Metformin in Subjects with Type 2 Diabetes. *Diabetes Care*, **35**, 1232-1238. https://doi.org/10.2337/dc11-1926

[17] Budoff, M.J., Davis, T.M.E., Palmer, A.G., Frederich, R., Lawrence, D.E., Liu, J., *et al.* (2021) Efficacy and Safety of Ertugliflozin in Patients with Type 2 Diabetes Inadequately Controlled by Metformin and Sulfonylurea: A Sub-Study of VERTIS CV. *Diabetes Therapy*, **12**, 1279-1297. https://doi.org/10.1007/s13300-021-01033-x

[18] Kashiwagi, A., Kazuta, K., Goto, K., Yoshida, S., Ueyama, E. and Utsuno, A. (2014) Ipragliflozin in Combination with Metformin for the Treatment of Japanese Patients with Type 2 Diabetes: illuminate, a Randomized, Double-Blind, Placebo-Controlled Study. *Diabetes, Obesity and Metabolism*, **17**, 304-308. https://doi.org/10.1111/dom.12331

[19] Terauchi, Y., Tamura, M., Senda, M., Gunji, R. and Kaku, K. (2017) Efficacy and Safety of Tofogliflozin in Japanese Patients with Type 2 Diabetes Mellitus with Inadequate Glycaemic Control on Insulin Therapy (J-Step/Ins): Results of a 16-Week Randomized, Double-Blind, Placebo-Controlled Multicentre Trial. *Diabetes, Obesity and Metabolism*, **19**, 1397-1407. https://doi.org/10.1111/dom.12957

[20] Bhatt, D.L., Szarek, M., Pitt, B., Cannon, C.P., Leiter, L.A., McGuire, D.K., *et al.* (2021) Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *New England Journal of Medicine*, **384**, 129-139. https://doi.org/10.1056/nejmoa2030186

[21] McMurray, J.J.V., Solomon, S.D., Inzucchi, S.E., Køber, L., Kosiborod, M.N., Martinez, F.A., *et al.* (2019) Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *New England Journal of Medicine*, **381**, 1995-2008. https://doi.org/10.1056/nejmoa1911303

[22] Perkovic, V., Jardine, M.J., Neal, B., Bompoint, S., Heerspink, H.J.L., Charytan, D.M., *et al.* (2019) Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *New England Journal of Medicine*, **380**, 2295-2306. https://doi.org/10.1056/nejmoa1811744

[23] Wei, R., Wang, W., Pan, Q. and Guo, L. (2022) Effects of SGLT-2 Inhibitors on

Vascular Endothelial Function and Arterial Stiffness in Subjects with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Frontiers in Endocrinology*, **13**, Article 826604. https://doi.org/10.3389/fendo.2022.826604

[24] Fioretto, P., Zambon, A., Rossato, M., Busetto, L. and Vettor, R. (2016) SGLT2 Inhibitors and the Diabetic Kidney. *Diabetes Care*, **39**, S165-S171. https://doi.org/10.2337/dcs15-3006

[25] Shiva, S. (2010) Mitochondria as Metabolizers and Targets of Nitrite. *Nitric Oxide*, **22**, 64-74. https://doi.org/10.1016/j.niox.2009.09.002

[26] Wanner, C., Inzucchi, S.E., Lachin, J.M., Fitchett, D., von Eynatten, M., Mattheus, M., *et al.* (2016) Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *New England Journal of Medicine*, **375**, 323-334. https://doi.org/10.1056/nejmoa1515920

[27] Bolinder, J., Ljunggren, Ö., Johansson, L., Wilding, J., Langkilde, A.M., Sjöström, C.D., *et al.* (2013) Dapagliflozin Maintains Glycaemic Control While Reducing Weight and Body Fat Mass over 2 Years in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin. *Diabetes, Obesity and Metabolism*, **16**, 159-169. https://doi.org/10.1111/dom.12189

[28] Ferrannini, E., Muscelli, E., Frascerra, S., Baldi, S., Mari, A., Heise, T., *et al.* (2014) Metabolic Response to Sodium-Glucose Cotransporter 2 Inhibition in Type 2 Diabetic Patients. *Journal of Clinical Investigation*, **124**, 499-508. https://doi.org/10.1172/jci72227

[29] Winiarska, A., Knysak, M., Nabrdalik, K., Gumprecht, J. and Stompór, T. (2021) Inflammation and Oxidative Stress in Diabetic Kidney Disease: The Targets for SGLT2 Inhibitors and GLP-1 Receptor Agonists. *International Journal of Molecular Sciences*, **22**, Article 10822. https://doi.org/10.3390/ijms221910822

[30] Ferrannini, E. and Solini, A. (2012) SGLT2 Inhibition in Diabetes Mellitus: Rationale and Clinical Prospects. *Nature Reviews Endocrinology*, **8**, 495-502. https://doi.org/10.1038/nrendo.2011.243

[31] Ferrannini, G., Hach, T., Crowe, S., Sanghvi, A., Hall, K.D. and Ferrannini, E. (2015) Energy Balance after Sodium–Glucose Cotransporter 2 Inhibition. *Diabetes Care*, **38**, 1730-1735. https://doi.org/10.2337/dc15-0355

[32] Zelniker, T.A., Wiviott, S.D., Raz, I., Im, K., Goodrich, E.L., Bonaca, M.P., *et al.* (2019) 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. *The Lancet*, **393**, 31-39. https://doi.org/10.1016/s0140-6736(18)32590-x

[33] Giacco, F. and Brownlee, M. (2010) Oxidative Stress and Diabetic Complications. *Circulation Research*, **107**, 1058-1070. https://doi.org/10.1161/circresaha.110.223545

[34] Hess, D.A., Terenzi, D.C., Trac, J.Z., Quan, A., Mason, T., Al-Omran, M., *et al.* (2019) SGLT2 Inhibition with Empagliflozin Increases Circulating Provascular Progenitor Cells in People with Type 2 Diabetes Mellitus. *Cell Metabolism*, **30**, 609-613. https://doi.org/10.1016/j.cmet.2019.08.015

[35] Sun, X., Han, F., Lu, Q., Li, X., Ren, D., Zhang, J., *et al.* (2020) Empagliflozin Ameliorates Obesity-Related Cardiac Dysfunction by Regulating Sestrin2-Mediated AMPK-mTOR Signaling and Redox Homeostasis in High-Fat Diet-Induced Obese Mice. *Diabetes*, **69**, 1292-1305. https://doi.org/10.2337/db19-0991

[36] Laurent, S., Boutouyrie, P., Asmar, R., Gautier, I., Laloux, B., Guize, L., *et al.* (2001) Aortic Stiffness Is an Independent Predictor of All-Cause and Cardiovascular

Mortality in Hypertensive Patients. *Hypertension*, **37**, 1236-1241. https://doi.org/10.1161/01.hyp.37.5.1236

[37] Joubert, M., Jagu, B., Montaigne, D., Marechal, X., Tesse, A., Ayer, A., *et al.* (2017) The Sodium–Glucose Cotransporter 2 Inhibitor Dapagliflozin Prevents Cardiomyopathy in a Diabetic Lipodystrophic Mouse Model. *Diabetes*, **66**, 1030-1040. https://doi.org/10.2337/db16-0733

[38] Mudaliar, S., Alloju, S. and Henry, R.R. (2016) Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis. *Diabetes Care*, **39**, 1115-1122. https://doi.org/10.2337/dc16-0542

[39] Inzucchi, S.E., Zinman, B., Fitchett, D., Wanner, C., Ferrannini, E., Schumacher, M., *et al.* (2017) How Does Empagliflozin Reduce Cardiovascular Mortality? Insights from a Mediation Analysis of the EMPA-REG OUTCOME Trial. *Diabetes Care*, **41**, 356-363. https://doi.org/10.2337/dc17-1096

[40] Liang, B., Zhao, Y. and Gu, N. (2020) Empagliflozin Improves Cardiac Function in Heart Failure with Reduced Ejection Fraction Independent of Loading Conditions. *Cardiovascular Diabetology*, **19**, Article No. 29. https://doi.org/10.1186/s12933-020-01004-9

[41] Dekkers, C.C.J., Petrykiv, S., Laverman, G.D., Cherney, D.Z., Gansevoort, R.T. and Heerspink, H.J.L. (2018) Effects of the SGLT-2 Inhibitor Dapagliflozin on Glomerular and Tubular Injury Markers. *Diabetes, Obesity and Metabolism*, **20**, 1988-1993. https://doi.org/10.1111/dom.13301

[42] Hatanaka, T., Ogawa, D., Tachibana, H., Eguchi, J., Inoue, T., Yamada, H., *et al.* (2016) Inhibition of SGLT2 Alleviates Diabetic Nephropathy by Suppressing High Glucose-Induced Oxidative Stress in Type 1 Diabetic Mice. *Pharmacology Research & Perspectives*, **4**, e00239. https://doi.org/10.1002/prp2.239

[43] Kong, S.H., Koo, B.K. and Moon, M.K. (2019) Effects of Dapagliflozin on Endothelial Function, Renal Injury Markers, and Glycemic Control in Drug-Naïve Patients with Type 2 Diabetes Mellitus. *Diabetes & Metabolism Journal*, **43**, 711-717. https://doi.org/10.4093/dmj.2018.0208

[44] Iskander, C., Cherney, D.Z., Clemens, K.K., Dixon, S.N., Harel, Z., Jeyakumar, N., *et al.* (2020) Use of Sodium–Glucose Cotransporter-2 Inhibitors and Risk of Acute Kidney Injury in Older Adults with Diabetes: A Population-Based Cohort Study. *Canadian Medical Association Journal*, **192**, E351-E360. https://doi.org/10.1503/cmaj.191283

[45] Heerspink, H.J.L., Kosiborod, M., Inzucchi, S.E. and Cherney, D.Z.I. (2018) Renoprotective Effects of Sodium-Glucose Cotransporter-2 Inhibitors. *Kidney International*, **94**, 26-39. https://doi.org/10.1016/j.kint.2017.12.027

[46] Abdul-Ghani, M.A., Norton, L. and DeFronzo, R.A. (2015) Renal Sodium-Glucose Cotransporter Inhibition in the Management of Type 2 Diabetes Mellitus. *American Journal of Physiology-Renal Physiology*, **309**, F889-F900. https://doi.org/10.1152/ajprenal.00267.2015

[47] Fioretto, P., Del Prato, S., Buse, J.B., Goldenberg, R., Giorgino, F., Reyner, D., *et al.* (2018) Efficacy and Safety of Dapagliflozin in Patients with Type 2 Diabetes and Moderate Renal Impairment (Chronic Kidney Disease Stage 3A): The DERIVE Study. *Diabetes, Obesity and Metabolism*, **20**, 2532-2540. https://doi.org/10.1111/dom.13413

[48] Itani, T. and Ishihara, T. (2018) Efficacy of Canagliflozin against Nonalcoholic Fatty Liver Disease: A Prospective Cohort Study. *Obesity Science & Practice*, **4**, 477-482.

https://doi.org/10.1002/osp4.294

[49] Xing, B., Zhao, Y., Dong, B., Zhou, Y., Lv, W. and Zhao, W. (2020) Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Non-Alcoholic Fatty Liver Disease in Patients with Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials. *Journal of Diabetes Investigation*, **11**, 1238-1247. https://doi.org/10.1111/jdi.13237

[50] Danne, T., Cariou, B., Banks, P., Brandle, M., Brath, H., Franek, E., *et al.* (2018) HbA_{1c} and Hypoglycemia Reductions at 24 and 52 Weeks with Sotagliflozin in Combination with Insulin in Adults with Type 1 Diabetes: The European Intandem2 Study. *Diabetes Care*, **41**, 1981-1990. https://doi.org/10.2337/dc18-0342

[51] Furtado, R.H.M., Bonaca, M.P., Raz, I., Zelniker, T.A., Mosenzon, O., Cahn, A., *et al.* (2019) Dapagliflozin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus and Previous Myocardial Infarction. *Circulation*, **139**, 2516-2527. https://doi.org/10.1161/circulationaha.119.039996

[52] Mancia, G., Cannon, C.P., Tikkanen, I., Zeller, C., Ley, L., Woerle, H.J., *et al.* (2016) Impact of Empagliflozin on Blood Pressure in Patients with Type 2 Diabetes Mellitus and Hypertension by Background Antihypertensive Medication. *Hypertension*, **68**, 1355-1364. https://doi.org/10.1161/hypertensionaha.116.07703

[53] Cherney, D.Z.I., Zinman, B., Inzucchi, S.E., Koitka-Weber, A., Mattheus, M., von Eynatten, M., *et al.* (2017) Effects of Empagliflozin on the Urinary Albumin-to-Creatinine Ratio in Patients with Type 2 Diabetes and Established Cardiovascular Disease: An Exploratory Analysis from the Empa-Reg Outcome Randomized, Placebo-Controlled Trial. *The Lancet Diabetes & Endocrinology*, **5**, 610-621. https://doi.org/10.1016/s2213-8587(17)30182-1

[54] Wilding, J.P.H., Woo, V., Rohwedder, K., Sugg, J. and Parikh, S. (2013) Dapagliflozin in Patients with Type 2 Diabetes Receiving High Doses of Insulin: Efficacy and Safety over 2 Years. *Diabetes, Obesity and Metabolism*, **16**, 124-136. https://doi.org/10.1111/dom.12187

[55] Leiter, L.A., Cefalu, W.T., de Bruin, T.W.A., Gause-Nilsson, I., Sugg, J. and Parikh, S.J. (2014) Dapagliflozin Added to Usual Care in Individuals with Type 2 Diabetes Mellitus with Preexisting Cardiovascular Disease: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with a 28-Week Extension. *Journal of the American Geriatrics Society*, **62**, 1252-1262. https://doi.org/10.1111/jgs.12881