Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2023**; 28(5): 98
https://doi.org/10.31083/j.fbl2805098

Review

SGLT2i in Patients with Type 1 Diabetes: Benefits, Risks, and Preventive Strategies

Yujin Ma[1], Qian Zhao[1], Huifang Peng[1], David Lubasi Nalisa[1], Pengfei Shan[2,*], Hongwei Jiang[1,*]

[1]Endocrinology and Metabolism Center, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Henan Key Laboratory of Rare Diseases, 471003 Luoyang, Henan, China
[2]Department of Endocrinology and Metabolism, The Second Affiliated Hospital of Zhejiang University School of Medicine, 310000 Hangzhou, Zhejiang, China
*Correspondence: pengfeishan@zju.edu.cn (Pengfei Shan); jianghw@haust.edu.cn (Hongwei Jiang)
Academic Editor: Riccardo Nevola
Submitted: 12 November 2022 Revised: 5 January 2023 Accepted: 13 January 2023 Published: 22 May 2023

Abstract

Sodium-glucose cotransporter inhibitors (SGLT2i) play an increasingly important role in type 2 diabetes mellitus (T2DM) due to their significant cardiovascular benefits and renal protection in addition to their hypoglycemic effects. In recent years, the application of SGLT2i in patients with type 1 diabetes mellitus (T1DM) has attracted more and more attention. Studies have shown that SGLT2i improves glycemic control, reduces total daily insulin dose, decrease body weight in patients with T1DM, without increasing the risk of severe hypoglycemia. SGLT2i also reduces urinary protein levels, prevents atherosclerosis, and offers cardiorenal benefits in patients with T1DM. But simultaneously, they significantly increased risk of diabetic ketoacidosis (DKA), which leads to increased hospitalization and mortality. Hence SGLT2i is recommended to T1DM who are motivated, adhere to self-glucose monitoring, well-trained in identifying DKA, and closely followed to ensure the efficacy and safety.

Keywords: type 1 diabetes mellitus; SGLT2i; diabetes kidney disease; cardiovascular disease; diabetic ketoacidosis

1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease resulting in severe insulin deficiency in which patients require lifelong insulin therapy to maintain life and minimize the risk of hyperglycemic events, such as diabetic ketoacidosis. New insulin preparations, the improvement of insulin pump devices and the development of continuous glucose monitoring system have enabled T1DM patients in this era to have a longer life and better quality of life. However, they still cannot solve the defects caused by intensive insulin therapy, such as weight gain, increased hypoglycemia rate and high blood glucose volatility. Most individuals with T1DM do not achieve recommended glycaemic targets [1–3]. With the increase of new hypoglycemic drugs, studies on the combination of other hypoglycemic drugs in the treatment of T1DM are continuing, while clinical studies on the combination of metformin, dipeptidyl peptidase IV (DPP-4), glucagon-like peptide 1 receptor agonist (GLP-1RA) and other drugs in the treatment of diabetes cannot achieve effective effects. SGLT2i are usually used for patients whose blood glucose are not well-controlled with metformin or those who have high risk of heart failure or chronic kidney disease (CKD) [4,5], and given their insulin-independent mechanism of action, these agents might also be effective in patients with T1DM. Currently, a number of clinical studies have confirmed that SGLT2i can effectively reduce blood glucose in patients with T1DM, and at the same time reduce body weight without increasing the risk of hypoglycemia [6–10], dapagliflozin was authorized for the treatment of adult T1DM patients in Europe and Japan, while sotagliflozin was later approved in Europe. While SGLT2i increases the risk of ketogenesis and DKA, which deserves special attention as a serious adverse event in patients with T1DM [11–13]. What kind of patients with T1DM are suitable for SGLT2i treatment, and in addition to the hypoglycemic effect, whether the cardiac and renal benefits of SGLT2i observed in T2DM patients are also suitable for T1DM remains to be further explored. The purpose of this review is to summarize the potential benefits and risks of SGLT2i in patients with T1DM and explore strategies to reduce the risk of DKA.

2. The History of SGLT2i Application

In 1835, French scientists isolated the first natural SGLT inhibitor, phlorizin, from apple bark, and found that it can promote urine sugar excretion and lower blood sugar [14]. However, due to its non-selective inhibition of SGLT1 and SGLT2, it is easily hydrolyzed by β-glucosidase in the small intestine and has low bioavailability, As a result, it has not been used in the clinical management of diabetes. T-1095 is a derivative of phlorizin, and its inhibitory effect on SGLT2 is 4 times better that of SGLT1. It is the first orally absorbed SGLT2i, but it still does not overcome the problem of unstable pharmacokinetics of o-

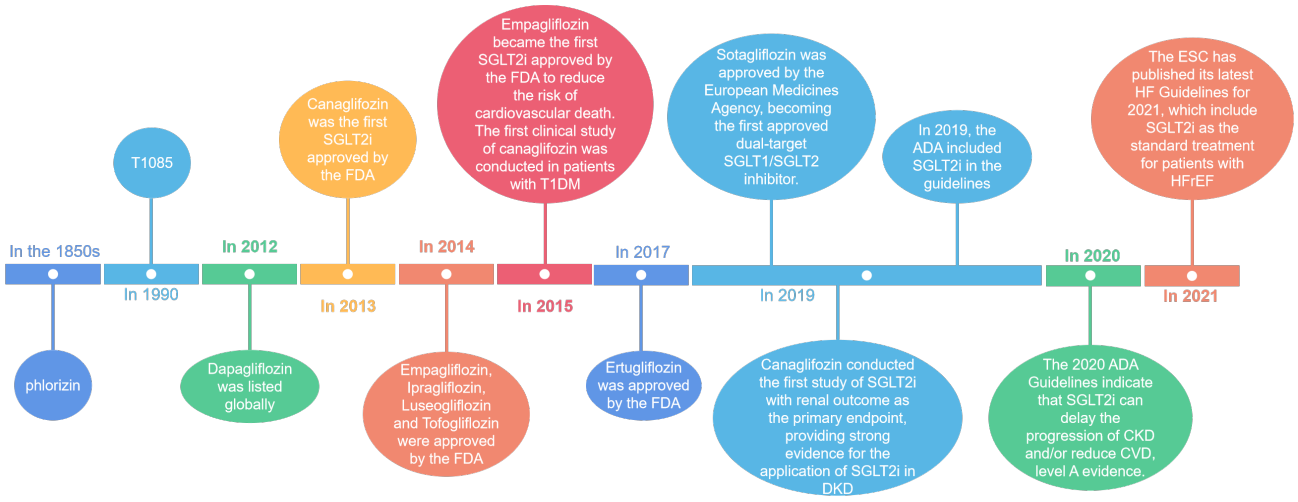

Fig. 1. The history of SGLT2i application. DKD, diabetes kidney disease; CVD, cardiovascular disease; HFrEF, heart failure with reduced ejection fraction.

glucoside analogues, so it is stopped here [15]. In order to solve the above problems and improve the bioavailability and selectivity of drugs for SGLT2, researchers developed clinically applicable SGLT2i drugs by modifying phlorizin (Fig. 1). SGLTs are found predominantly in the mucosa of the small intestine (SGLT1) and the proximal tubules of the kidney (SGLT2 and SGLT1) [16]. Experiments conducted by Yakovleva T *et al.* [17] showed that compared with healthy people, the expression of SGLT1 and SGLT2 transporters in diabetic patients and the ability of renal glucose uptake were increased. SGLT2 inhibition reduces glucose reabsorption in the renal tubule, leading to increased glucose excretion. SGLT1 inhibition reduces dietary glucose and galactose absorption in the intestine and augments the release of gastrointestinal incretins [18]. Selective SGLT2i (empagliflozin, dapagliflozin, canagliflozin) are therefore an attractive therapeutic proposition for diabetes because increased urinary glucose excretion will reduce hyperglycaemia and facilitate weight loss. As a dual SGLT1/SGLT2 inhibitors, sotagliflozin can not only reduce glucose absorption in the intestine, but can also increase urinary glucose excretion in the kidney by inhibiting SGLT1 and SGLT2 [19].

In 2015, 7020 T2DM patients with cardiovascular disease (CVD) were included in the EMPA-REG OUTCOME study. The median follow-up time was 3.1 years. Results showed that, empagliflozin was associated with a 14% reduction in the risk of major cardiovascular outcomes (including cardiac related deaths, nonfatal myocardial infarction, and nonfatal stroke events combined). Compared with secondary endpoints, it can reduce the all-cause mortality by 32%, the risk of cardiovascular death by 38%, and the risk of hospitalization for heart failure (HF) by 35% [20]. The CREDENCE study published in 2019 was the first SGLT2i study to use renal outcome as the primary endpoint, demonstrating that canagliflozin was effective in reducing the risk of renal failure and cardiovascular events in high-risk T2DM patients with renal disease. In the 2020 American Diabetes Association (ADA) guidelines, SGLT2i (evidence Level A) is recommended for T2DM patients with CKD, estimated glomerular filtration rate (eGFR) $\geq$30 mL/min/1.73 m^2 and urine albumin creatine ratio (UACR) $>$30 mg/g (especially UACR $>$300 mg/g) to reduce the risk of progression of CKD and/or cardiovascular events [21]. While there is an obvious place for such a therapy in type 2 diabetes, pre-clinical research in rodent models also suggest that these agents may be beneficial as an adjunct therapy in type 1 diabetes [22,23].

3. Benefits of SGLT2i in T1DM Patients

3.1 Efficacy of SGLT2i in T1DM

Pieber *et al.* [24] explored the potential beneficial effect of empagliflozin versus placebo as an insulin adjuvant on HbA1c in a small Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes (EASE)-1 trial of 75 T1DM patients, with a 0.49% decrease in HbA1c in the engliazine group compared to the placebo group after 28 days. Total daily insulin dose decreased by 0.09 U/kg and body weight decreased by 1.9 kg. In the EASE program, two double-blind placebo-controlled phase III trials explored the efficacy of different doses of empagliflozin and placebo as adjuvant insulin therapy, EASE-2 (comparing empagliflozin 10 mg, 25 mg, and placebo for 52 weeks) and EASE-3 (comparing empagliflozin 2.5 mg, 10 mg, 25 mg, and placebo for 26 weeks), which enrolled 1707 patients with T1DM, results showed that patients in the empagliflozin group had a significant decrease in HbA1c and an increase in time in range—TIR (TIR: the proportion of time patients had blood glucose between 3.9–10.0 mmol/L; 70–180 mg/dL). In the 5 mg and 10 mg doses, TIR increased by more than 2 hours per day, while in the

2.5 mg group, TIR increased by 1 hour per day, showing a significant dose-dependence. Moreover, the results of the study also confirmed that empagliflozin could significantly reduce systolic blood pressure by (–3.9 mmHg) and diastolic blood pressure by (–2.3 mmHg) in T1DM patients [8]. In the magic week project, two phase III placebo-controlled double-blind trials explored dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo as adjunctive insulin treatment. A total of 1591 patients with T1DM who had poor glycemic control were enrolled in this study. Patients in the dapagliflozin 5 mg and dapagliflozin 10 mg groups had significant reductions in HbA1c levels, fasting blood-glucose (FBG) and total daily insulin consumption at 52 weeks from baseline. TIR was improved (dapagliflozin 5 mg was 9.02%, dapagliflozin 10 mg was 10.70%), and 24-hour mean amplitude of glucose fluctuation (MAGE) was decreased (dapagliflozin 5 mg was –0.69 (0.08) mmol/L; –12.48 (1.37) mg/dL, dapagliflozin 10 mg was –0.72 (0.08) mmol/L; –13.06 (1.39) mg/dL) [10]. Dapagliflozin also improved treatment satisfaction [25]. Another 52-week phase III trial involving 151 patients with T1DM from Japan assessed the efficacy and safety of dapagliflozin at 5 mg and 10 mg as adjuvant therapy [26]. Patients in the 5 mg and 10 mg groups had a mean reduction in HbA1c of 0.33% and 0.36% at week 52 of the experiment. The mean daily insulin dose changes were 12.27% and 13.13%. Two clinical trials, InTandem-1 and InTandem-2 [7,8,27] evaluated the efficacy and safety of sotagliflozin in combination with insulin as compared with placebo in the treatment of T1DM and showed that sotagliflozin significantly improved HbA1c, reduced FBG and daily insulin dose in patients with T1DM compared with placebo. Moreover, patients receiving sotagliflozin were more satisfied with treatment and experienced less diabetes-related distress [7,8]. In addition, compared with baseline measurements, patients in the 400 mg sotagliflozin group had a 2.98 kg weight reduction [28]. The results of the study on the effect of sotagliflozin combined with insulin on TIR and MAGE in patients with T1DM showed that the glucose measurement within the target range of patients using sotagliflozin increased by 13.4%, and did not increase the time below 3.9 mmol/L. MAGE decreased by 0.7 $\pm$ 0.3 mmol/L; 12.7 $\pm$ 5.5 mg/dL (200 mg sotagliflozin) and 1.2 $\pm$ 0.3 mmol/L; 22.1 $\pm$ 5.4 mg/dL (400 mg sotagliflozin) [29]. Moreover, in the pooled analysis [30], compared with placebo, the net 200 and 400 mg reduction in sotagliflozin systolic blood pressure was 2.9 and 3.6 mmHg, and the diastolic blood pressure was 1.4 and 1.6 mmHg, respectively. In an 18-week, randomized, double-blind study in 351 patients with T1DM, canagliflozin 100 and 300 mg/day reduced HbA1c levels by 0.29% and 0.25% more than placebo, respectively. Canagliflozin also reduced fasting plasma glucose levels, weight and daily insulin dose [31]. Canagliflozin also improved treatment satisfaction due to reductions in glycemic variability, insulin dose and body weight [32]. In a substudy of patients undergoing continuous glucose monitoring (CGM) (n = 89), canagliflozin increased time spent within glycemic target and reduced glycemic variability [33]. In a meta-analysis of 10 randomized, placebo-controlled trials (n = 5961), SGLT2i were associated with a dosedependent reduction in HbA1c, FBG, MAGE, total daily insulin dose and in body weight (by 0.39%, 1.13 mmol/L; 20.34 mg/dL, 0.82 mmol/L; 14.81 mg/dL, 10.14% and 3.47%, respectively), subgroup analysis by dose showed a clear dose-response association of these outcomes [34]. The dual SGLT1/2 inhibitor sotagliflozin improved glycemic stability more than SGLT2 selective inhibitors (canagliflozin, dapagliflozin and empagliflozin) whereas the latter reduced total daily insulin dose more the former; other efficacy outcomes did not differ between the 2 groups [33]. In a large real-world study from Japan [35] involving T1DM patients treated with SGLT2i (combined insulin) (n = 1027) and insulin (n = 4320), systolic blood pressure (SBP) decreased and high density lipoprotein (HDL) levels increased after SGLT2i in T1DM patients. This study provides further evidence of the potential cardiovascular benefits of SGLT2i in patients with T1DM, despite taking into account differences in patient characteristics between treatment groups.

The above studies showed that different SGLT2i combined with insulin had similar effects on the reduction of HbA1c level in T1DM, and increased TIR and decreased MAGE, body weight and blood pressure. The durability of the effects was comparable even in those studies up to 52 weeks.

3.2 SGLT2i Protective Effect on Kidney

Many mechanism studies have shown that the renal protection of SGLT2i is not related to hypoglycemia [36–38] but through the reduction of glomerular pressure and urinary sodium excretion [32,39]. In high glucose conditions, SGLT2 mRNA expression increases by 36% due to excessive glucose in renal tubules, leading to increased sodium reabsorption and weakened sodium transport to dense macula [40]. This results in decreased adenosine release from macula densa cells, which causes afferent arteriole vasodilation via tubule feedback (TGF). Attenuation of TGF leads to increased glomerular perfusion, increased glomerular pressure, increased glomerular filtration rate (GFR), and ultrafiltration [41,42]. Importantly, chronic ultrafiltration is closely associated with glomerular injury and is thought to be associated with DKD progression in T1DM and T2DM [43]. Studies have shown that SGLT2i plays a role in T1DM by reducing the dilatation of the entering arteriole through tubule feedback, which has a significant impact on renal protection by attenuating the ultrafiltration process. After reducing sodium reabsorption by the proximal tubules, sodium delivery to the dense macula increases, and afferent arteriolar vasoconstriction increases, thereby restoring TGF function to normal physiological levels and causing a decrease in glomerular pressure and GFR

levels [43].

Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) was the first SGLT2i renal endpoint study in patients with CKD (participants with CKD due to T2DM and to causes other than diabetes). 4304 patients with stage 2–4 CKD were enrolled (2906 participants (68%) had a diagnosis of T2DM and of these, 396 had CKD ascribed to a cause other than diabetes), and baseline eGFR was 25–75 mL/min/1.73 m^2. UACR ranged from 200 to 5000 mg/g, and the median follow-up time was 2.4 years. The results showed that compared with the non-intervention group, the risk of reaching the primary endpoint (eGFR decline $\geq$50%, progression to end stage renal disease (ESRD), and death from renal or cardiovascular causes) and the nephro specific composite endpoint (eGFR decline $\geq$50%, progression to ESRD, and death from renal causes) were 39% and 44% lower in the dagagliflozin group, respectively. The risk of all-cause mortality was reduced by 31% [44]. The EMPEROR-Reduced trial [45] evaluated the effect of empagliflozin in a population of patients with chronic heart failure and a reduced ejection fraction (with or without diabetes), results showed that empagliflozin reduced the average slope of eGFR decline (–0.55 $\pm$ 0.23 mL/min/1.73 m^2·year vs –2.28 $\pm$ 0.23 mL/min/1.73 m^2·year, $p < 0.001$). Reduced the risk of a renal composite endpoint (dialysis, kidney transplant, or sustained eGFR decline) (HR = 0.5; 95% CI: 0.32–0.77).

In a post hoc pooled analysis of the InTandem-1 and InTandem-2 trials [30], The baseline eGFR levels of enrolled T1DM patients were 90.2 mL/min/1.73 m^2 (placebo group), 89.3 mL/min/1.73 m^2 (sotagliflozin 200 mg), and 89.1 mL/min/1.73 m^2 (sotagliflozin 400 mg). Consistent with the effect of SGLT2i in reducing glomerular pressure in T2DM patients, patients in the 200 mg and 400 mg sotagliflozin groups had lower eGFR at week 4 (2.5 mL/min/1.73 m^2 and 2.8 mL/min/1.73 m^2, respectively) compared with placebo. From week 4 to week 52, Although eGFR was lower than placebo, eGFR gradually approached baseline levels. Among participants with documented drug follow-up trials (n = 370), defined as 7 days after the last dose, eGFR increased 3.0 mL/min/1.73 m^2 in the 200 mg and 2.7 mL/min/1.73 m^2 in the 400 mg group, respectively, as compared with placebo, returning to baseline levels. Although most patients did not have proteinuria, in the subgroup with UACR $\geq$30 mg/g, proteinuria was significantly reduced in the 200 mg and 400 mg sotagliflozin groups compared with placebo at 24 weeks (16.4% and 31.4%) and 52 weeks (23.7% and 18.3%). In published SGLT2i studies, analyses showed that increased erythrocyte volume and decreased uric acid were statistically associated with improved cardiorenal outcomes [46,47], and the effects of sotagliflozin on hematocrit and uric acid were also assessed in the InTandem analysis. The extent to which sotagliflozin increased hematocrit and decreased uric acid in patients with T1DM was similar to that previously observed in T2DM patients taking SGLT2i. Data from two phase III, randomized, placebo-controlled trials in patients with T1DM, 52 weeks (EASE-2) and 26 weeks (EASE-3), reported similar observations with empagliflozin [8]: similar to the results of the InTandem trial, the UACR in the empagliflozin group was reduced in a dose-dependent manner in patients with albuminuria. Like sotagliflozin, empagliflozin also increased hematocrit and decreased uric acid levels in patients with T1DM. In a post hoc analysis of data from 251 patients with T1DM with UACR >30 mg/g in the dapagliflozin week 1 and week 2 trials [11,48], a dose-dependent reduction in UACR was observed, as in the EASE trial.

SGLT2i can significantly reduce urinary protein and delay the progression of renal dysfunction in non-diabetic CKD patients. SGLT2i can also reduce urinary protein levels in patients with T1DM, which may be favorable evidence for the selection of SGLT2i in T1DM patients. However, studies on the long-term benefits of SGLT2i in T1DM patients with DKD are still lacking. Future clinical trials need to observe the effect of SGLT2i on T1DM patients with kidney disease.

3.3 SGLT2i Protective Effect on Cardiovascular

SGLT2i can reduce cardiac preload by sodium and osmotic diuresis, and improve cardiac function by lowering blood pressure, improving arterial elasticity and vascular endothelial function by reducing cardiac afterload [49–51]. Studies have shown that SGLT2i can inhibit the sodium hydrogen exchanger 1 (NAH1) in the myocardium and reduce the levels of Na^+ and Ca^{2+} in cardiomyocytes, thereby alleviating myocardial injury and ventricular hypertrophy caused by calcium overload [52]. Kang *et al*. [53] on cardiac fibroblasts *in vitro* studies have found that empagliflozin works by inhibiting the muscle induced by transforming growth factor β-1 fibroblast activation, decreased the expression of extracellular matrix remodeling, and promote fibrosis markers, anti-fibrosis of muscle fibroblasts has direct effect, thus inhibiting ventricular remodeling and heart failure. Prior to the introduction of SGLT2i, large-scale clinical studies were conducted in patients with diabetes and CVD and in those at high risk for the disease, and these patients had significant clinical benefits for major cardiovascular events. CANVAS (Canagliflozin Cardiovascular Evaluation Study), a large randomized controlled clinical trial of 10,142 patients with CVD and T2DM, showed that compared with placebo, canagliflozin significantly improved the outcome of patients with heart failure by reducing the risk of major composite end point events by 14% and hospitalization rate by 33%, and canagliflozin also improves the quality of life [54]. In the DAPA-HF trial of 4744 patients with HF and ejection fraction $\leq$40% with or without T2DM, the dapagliflozin-treated group (10 mg, QD) had a 26% reduction in the primary end point (composite death due to cardiovascular death or exacerbation of

HF) compared with the control group after 18.2 months of follow-up. Exacerbation of HF was reduced by 30% and cardiovascular mortality by 18%. Studies have shown that patients with HF with or without diabetes had the same degree of clinical benefit (non-diabetic patients: HR = 0.73; 95% CI: 0.60–0.88 and diabetic patients: HR = 0.75; 95% CI: 0.60–0.90). Thus, dapagliflozin significantly reduced the risk of non-diabetic HFrEF patients [55].

With the increasing longevity of T1DM patients, CVD is increasingly recognized as a clinical problem in patients with T1DM, so the reversal and even prevention of CVD is an important goal for patients with T1DM. Relevant studies have provided experimental evidence [56] showing that oral administration of SGLT2i (dapagliflozin) prevents metabolic decline, cardiac hypertrophy, and myocardial injury in streptozotocin - induced T1DM within 6 weeks. The decrease in aortic intima-media thickness suggests that dapagliflozin also prevents atherosclerosis. In a small randomized study (n = 40) [57], empagliflozin - metformin significantly improved arterial stiffness compared with metformin in patients with T1DM, and endothelial function improved similarly in all treatment groups. The results from the study on the antioxidant and anti-inflammatory properties following the combination of empagliflozin - metformin in T1DM showed that, compared to a single drug or placebo, there was improved arterial function [58], empagliflozin - metformin combination increased total antioxidative status, superoxide dismutase and glutathione peroxidase level is as high as 1.1 times, Decreased pro-oxidants (advanced oxidation protein products and inopportune decreased 1.2 times, advanced glycosylation end products decreased 1.5 times), and decreased inflammatory parameters (C-reactive protein and interleukin-6 decreased 1.5 times). The antioxidant effect was related to the improvement of arterial function. Therefore, it is believed that the combination of empagliflozin and metformin has strong antioxidant and anti-inflammatory effects in T1DM, leading to the improvement in arterial function and providing strong vascular protection. A 19-week mechanistic study [59] evaluated the effect of SGLT2i (empagliflozin 25 mg QD) combined with an angiotensin-converting enzyme inhibitor (ramipril 10 mg QD) on cardiac function in T1DM patients with potential renal hyperfiltration, 30 patients were enrolled, and results showed that no significant changes in ambulatory blood pressure, arterial stiffness, heart rate variability, or cardiac output were observed with the addition of empagliflozin in patients with T1DM. This may be due to the short duration of the study and the small number of cases.

SGLT2i can not only safely reduce blood glucose in diabetic patients, but can also offer significant clinical benefits in cardiovascular endpoints, which have been observed in T2DM patients with heart failure and in non-diabetic patients with heart failure. According to these findings, SGLT2i (dapagliflozin) can prevent cardiac hypertrophy and myocardial injury, as well as atherosclerosis. However, the study period is short and the sample size is small. In addition, it is unclear whether SGLT2i is beneficial for T1DM patients with cardiovascular disease and aging. More research should be conducted to investigate the effects of SGLT2i on cardiovascular events in T1DM patients.

4. Risks of SGLT2i in T1DM Patients

4.1 Diabetic Ketoacidosis

SGLT2i stimulates glucagon secretion through the direct action of drugs on pancreatic alpha cells or indirectly by reducing insulin secretion. Glucagon inhibits acetyl-coA carboxylase and therefore increases carnitine palmitoyltransferase-I activity in the liver, resulting in increased keto production [60,61]. Adjuvant therapy with SGLT2i reduced the total daily insulin dose in patients with T1DM, and ketone bodies increase when low doses of insulin are insufficient to inhibit lipolysis in surrounding adipose tissue. Therefore, the use of SGLT2i in T1DM patients may increase the incidence of ketone-body related events.

The first trial by Henry *et al.* [31] showed that the incidence of severe DKA requiring hospitalization in T1DM patients with canagliflozin 100 mg and canagliflozin 300 mg was 4.3% and 6.0%, respectively, compared with zero events in the placebo group. Five of these patients had blood glucose levels of less than 13.9 mmol/L; 250 mg/dL, which suggests that SGLT2i may not only increase the risk of DKA but also lead to misleading clinical manifestations of DKA with normal blood glucose. In the Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT)-1 and DEPICT-2 studies, in the 24 week first published results of DEPICT - 1, no increase in DKA was observed in patients treated with dapagliflozin, while the risk of DKA at 52 weeks was 4.0%, 3.4% and 1.9% in the dapagliflozin 5 mg, 10 mg and placebo groups, respectively. Results of DEPICT-2 showed an increased risk of DKA at 24 weeks. By 52 weeks, 4.1%, 3.7%, and 0.4% of patients in the dapagliflozin 5 mg, 10 mg and placebo groups had developed DKA, respectively [12,62,63]. Another phase III study conducted in Japan with safety as the primary endpoint also showed a higher overall incidence of diabetic ketoacidosis in patients with T1DM (2.6% and 1.3% in the 5 mg and 10 mg groups, respectively), all of them were women with blood glucose levels $<$13.9 mmol/L; 250 mg/dL. There was no significant difference in DKA risk between patients with BMI $<$25 kg/m^2 and those with BMI $\geq$25 kg/m^2 in subgroup analysis [26]. In the analysis of two clinical trials on sotagliflozin, the incidence of DKA in the InTandem-2 study was 2.3%, 3.4% and 0% in the 200 mg, 400 mg and placebo groups, respectively [10]. In InTandem-1 [9], the incidence of DKA was 3.4%, 4.2% and 0.4% in the sotagliflozin 200 mg, 400 mg in placebo groups, respectively. Previous studies have shown that [64,65] compared with T1DM patients with HbA1c lower than 7.5%, patients with HbA1c 7.5%–8.9% have a 2.4-fold increased risk of DKA (OR = 2.40,

95% CI: 1.99–2.90). Patients with HbA1c above 9.0% had an 8.0-fold higher risk of DKA (OR = 8.04, 95% CI: 6.72–9.62). Meta-analysis [66] showed that a total of 85 DKA events occurred in the sotagliflozin group, of which 21 (31%) had blood glucose values ranging from 2.2–13.9 mmol/L; 40–250 mg/dL, and the occurrence of DKA was correlated with the initial HbA1c level (β = –0.331; p = 0.009) and basal insulin dose adjustment (β = –0.218; p = 0.012). By analyzing the data from EASE studies, the incidence of DKA events in T1DM patients treated with 10 mg and 25 mg of empagliflozin was 4.3% and 3.3%, while that in the placebo group was 1.2%. No significant increase in DKA was observed in the empagliflozin 2.5 mg group compared with the placebo. A total of 41 DKA events occurred, 15 of which had blood glucose levels <13.9 mmol/L; 250 mg/dL. DKA is more common in patients who use insulin pumps and often has at least one precipitant, such as concomitant disease/infection or reduced insulin intake (e.g., pump failure). In subgroup analysis, being female and using an insulin pump were identified as significant risk factors for DKA [8]. The meta-analysis showed that SGLT2i increased the risk of DKA by 3.11 times, with the total incidence of DKA in the SGLT2i and placebo groups being 2.8% and 0.9%, respectively. Notably, compared with selective SGLT2i, sotagliflozin increased the risk of DKA (5.80 times and 2.66 times, respectively) [33].

Actual data on the use of SGLT2i in patients with T1DM are still scarce, but the efficacy and safety are consistent with clinical trial data. A real-world observational study in Japan [67] also reported a higher incidence of DKA in T1DM patients who received SGLT2i than those who did not (RR = 1.66, 95% CI: 1.33–2.06, $p < 0.001$), and patients with BMI <25 kg/m^2 had a higher risk of DKA than those with BMI ≥25 kg/m^2 (RR = 1.33, 95% CI: 1.09–1.63, p = 0.005). In another large real-world study [34], it was found that T1DM patients with HbA1c ≥7.5% (58.47 mmol/mol) and BMI ≥25 kg/m^2 were more likely to have DKA than those with HbA1c <7.5% (58.47 mmol/mol) and BMI <25 kg/m^2 (26.3% vs 11.4% and 30.5% vs 15.2%, respectively). Real-world data also confirm an increased risk of DKA in T1DM patients treated with SGLT2i, which is similar to the rate reported in clinical trials. A small prospective study of 27 T1DM patients on insulin included a 43-year-old man with DKA who had received insulin pump, this patient's insulin pump malfunction and alcohol consumption have been suggested as possible triggers. Finally, patients did not have any further adverse events after the withdrawal of empagliflozin [68]. Studies have shown that DKA is more common in patients using insulin pump when SGLT2i is applied in T1DM patients (mostly due to pump failure). Therefore, for patients with insulin pumps, when pump failure occurs, insulin should not be stopped and subcutaneous insulin injection should be continued until pump failure is eliminated or solved.

Thus, all items showed an increase in DKA except for the empagliflozin 2.5 mg (EASE-3) report. The description of DKA cases in these research projects is limited, but in terms of traceability, in all cases of DKA that emerged, patients had at least one precipitant (disease, infection, lack of insulin dose, reduced carbohydrate intake, etc.). Nonetheless, more real-world research evidence is needed to guide clinicians in assessing the true DKA risk in patients with T1DM outside the strict supervision of clinical trials, with careful patient selection and intensive patient and clinical team education.

4.2 Hypoglycemia

In the trial of DEPICT, there were no significant differences in hypoglycemic events between dapagliflozin treatment and placebo in T1DM [11,12,48,62,63]. Results from the EASE test were similar to the trial of DEPICT, with no significant difference in the overall risk of hypoglycemia between the different doses of empagliflozin and placebo in T1DM [6]. Studies on canagliflozin also showed that the incidence of hypoglycemia was similar in the canagliflozin group compared with the placebo group [31]. In a study evaluating the effect of sotagliflozin on hypoglycemia in patients with T1DM, the incidence of grade 1 hypoglycemia events was 58.25%, 44.86%, and 45.68% in the placebo and sotagliflozin 200 mg and 400 mg groups. The incidence of grade 2 hypoglycemia was 15.95%, 11.51% and 11.13%, and the incidence of grade 3 hypoglycemia events was 6.3%, 2.6%, and 2.2%, respectively [69]. Grade 1 and 2 use American Diabetes Association (ADA)/European Association for the Study of Diabetes criteria: Grade 1 (<3.9 mmol/L; 70 mg/dL but >3.0 mmol/L; 54 mg/dL), grade 2 (<3.0 mmol/L; 54 mg/dL), and grade 3 hypoglycemia (with help from others or loss of consciousness or seizure). Meta-analyses [34,70] have shown no increased risk of severe hypoglycemia in patients treated with SGLT-2 inhibitors compared with placebo.

There was no significant difference in the risk of hypoglycemia in patients with T1DM treated with SGLT2i plus insulin compared with insulin alone. The different rates of hypoglycemia between drugs depended on the insulin combination regimen used in the study and were not caused by SGLT2i alone.

4.3 Urinary and Reproductive System Infections

There may be more urogenital infections with SGLT2i because urine sugar may lead to the growth of urogenital microbes. Results from all SGLT2i programs in T1DM showed a comparable occurrence of urinary tract infections with placebo, but increased genital fungal infections [6,69,70]. Results from the DEPICT studies show that the rate of urinary tract infections in the dapagliflozin treatment group and the placebo group were about the same, with depict-tract fungal infections significantly higher than those in the placebo group (14.5% vs 3.1% in DEPICT-1 and 10.7% vs 3.7% in DEPICT-2) [11,48,62,63]. In addi-

tion, sotagliflozin did not increase urinary tract infections but increased the risk of mycotic genital tract infections (RR: 3.12, 95% CI: 2.14–4.54, $p < 0.001$) [34], as in the EASE trial: Genital fungal infections occurred in 12.8% and 14.3% of patients in the 10 mg and 25 mg empagliflozin groups, respectively, compared with 4.3% of patients in the placebo group. Moreover, in the EASE trial, the risk of genital fungal infection was twice that of patients taking a placebo even in patients taking a 2.5 mg dose [8].

Although the use of SGLT2i in patients with T1DM increased the risk of genital fungal infection, no serious adverse events due to genital fungal infection were reported in the study.

4.4 Other Adverse Events

SGLT2i increased the concentration of phosphate and parathyroid hormone, but caused a small decrease in the concentration of $1,25(OH)_2$ D, which has the potential to adversely affect bone. Therefore, SGLT2i may increase fracture risk. While in the meta-analysis, no effect of SGLT2i treatment on fracture was observed (RR = 0.88; 95% CI: 0.65–1.21), in a dose-dependent subgroup analysis, compared with placebo, discontinuance (RR = 1.50; 95% CI: 1.22–1.84), diarrhea (RR = 1.54; 95% CI: 1.15–2.05) increased risk of adverse events [34].

5. Strategies to Reduce the Risk of DKA in T1DM Patients Using SGLT2i

5.1 Selection of Patients

Selecting the right patient for SGLT2i treatment is critical to reducing the risk of DKA. The most important criteria were normal blood ketone level (<0.6 mmol/L; 11 mg/dL) or negative ketones. However, the risk factors associated with each patient's lifestyle/behaviour must also be considered risk level breakdown: **Moderate/high:** (1) Reduced basal insulin by more than 10–20%; (2) Insulin pump or infusion site failure; (3) Reduced or inconsistent carbohydrate intake; (4) Excessive alcohol use; (5) Use of illicit drugs; (6) Volume depletion/dehydration; (7) Acute illness of any sort (viral or bacterial); (8) Vomiting. **Low/moderate:** (1) Vigorous or prolonged exercise; (2) Reduced prandial insulin dose by more than 10–20%; (3) Travel with disruption in usual schedule/insulin regimen; (4) Insulin pump use. **Minimal/low:** (1) Low BMI (<25 kg/m^2); (2) Inconsistent caloric intake; (3) Moderate alcohol use* (*If ketone levels increase from baseline); (4) Female sex [71].

Dapagliflozin was approved in Europe and Japan in 2019 as an oral adjuvant therapy of insulin for the treatment of adult T1DM patients with poor glycemic control with optimal insulin alone (body mass index $\geq$27 kg/m^2) [72]. Sotagliflozin was subsequently approved in Europe for the same indication [73]. Because SGLT2i has not been adequately studied in pregnant women, SGLT2i should not be used in pregnant women with T1DM.

5.2 Reduce Insulin Dose

When starting SGLT2i therapy in T1DM patients, insulin levels must be carefully reduced to prevent ketosis and DKA. In clinical trials of SGLT2i, basal insulin and meal insulin doses were reduced in similar proportions [11,48] or mainly reduced basal insulin dose [74]. However, when sotagliflozin was used, the dose reduction observed in clinical trials was mainly in mealtime insulin [28]. Therefore, clinicians need to adjust the insulin dose for each patient based primarily on the degree of hyperglycemia and the specific SGLT2i used.

In patients with close to target (HbA1c <7.5% (58.47 mmol/mol)), after starting SGLT2i, reduce basal and preprandial insulin by 10–20%, and adjust the dose of dietary and basal insulin according to frequent preprandial and postprandial blood glucose monitoring to reduce the risk of hypoglycemia [71]. In patients with less well controlled (HbA1c $\geq$7.5% (58.47 mmol/mol)), mealtime and basal insulin may require only slight or no reduction, and excessive insulin reduction may lead to DKA [71]. However, in real-world studies, insulin dose reduction in patients treated with SGLT2i has been observed to be approximately 6–10%, which is lower than in previous clinical studies [11,34]. Therefore, in addition to insulin dose reduction, there is a need for further research to arrive at an understanding of other possible causes of DKA. These results may also indicate that real-world clinicians use SGLT2i appropriately and individually, considering the risk of DKA. And an alternative reason for the lower than recommended insulin dose reduction in SGLT2i treated patients is that the clinicians may not be aware of the recommendations. DKA could lead to serious adverse consequence, including fatal event. Many SGLTi related DKA is atypical, likely to be overlooked and is prone to develop serious adverse outcome. Patients and clinicians should be advised with caution in using SGLTi + insulin and close monitoring for the potential DKA risk in real-world practice.

5.3 It is Necessary to Strengthen Patient Education, Follow the Prescribed Regimen to Monitor Blood Glucose and Ketone Bodies

In terms of diet, patients who skipped meals and/or drank alcohol heavily appeared to be at higher risk. Patients who use insulin pumps are also at higher risk due to the possibility of pump or insulin infusion failure [8]. Patients with T1DM who do not adjust their insulin dose in a timely way, have recurrent DKA or experience prolonged significant hyperglycemia (especially >19 mmol/L; 350 mg/dL) and/or show low participation in diabetes treatment regimens are at high risk for DKA when using SGLT2i. Patients should fully understand the treatment regimen, DKA risk factors, and cooperate with medical workers to adjust the insulin dose and develop a diet plan, timely monitoring of blood glucose and ketone, so as to reduce the risk of DKA.

The development of euDKA and the progression of DKA cannot be detected by glucose monitoring alone, so the detection of ketone bodies is recommended. Unlike ketone monitoring in the T1DM population without SGLT2i, ketone levels should be tested regardless of blood glucose levels if symptoms of DKA are present in the population using SGLT2i. In future clinical practice, continuous ketone monitoring will play a role in ketogenesis and DKA monitoring. Currently, there is no evidence to support specific testing protocols. However, the team agreed [71] that frequency of ketone testing needs to be individualized based on the patient's lifestyle and/or risk factors. It is recommended to measure any symptoms consistent with DKA, including discomfort, fatigue, nausea and vomiting. Ketone bodies should also be measured by changes in diet, activity, or insulin dose and accompanying events such as infection, dehydration, surgery, injury, pump blockage/dysfunction or stress. Once an elevated ketone bodies are detected, treatment must be initiated on time [71].

A meta-analysis published in 1997 [75] showed an increased risk of DKA in patients using pumps. However, recent studies have shown no increased risk of DKA in T1DM patients using pumps [65,76]. This development may have been due to developments in pump technology (such as failure alerts or higher dose accuracy), greater understanding of infusion group problems (such as tube displacement, kinks, occlusion), and subsequent intensive education and training of patients using the pump on the importance of the insulin infusion group [76]. However, studies have shown that DKA is more common in patients using insulin pump when SGLT2i is applied in T1DM patients (mostly due to pump failure) [8]. The key to treating ketosis is to get patients to inject insulin and consume carbohydrates, and to stay hydrated enough. Even if a patient is using an insulin pump, it is important to first troubleshoot the pump and administer insulin by injection until it is certain that the pump is delivering insulin and any pump or piping issues have been resolved [71].

5.4 Clinical

Before the widespread use of SGLT2i in T1DM, a survey conducted in the United Kingdom (2014–2015) showed that there were 18 cases of euDKA if the glycemic threshold of 13.9 mmol/L; 250 mg/dL was used or 29 if 16.7 mmol/L; 300 mg/dL was used. The total number of DKA cases (euDKA and non eu-DKA) was 334 [77].

Hence SGLT2i may also cause an increase in the frequency of eu-DKA with normal blood glucose. In the current medical setting, all T1DM patients taking SGLT2i should consider the possibility of DKA if they present with typical DKA symptoms, even if their blood glucose levels are normal. While patients with eu-DKA may not present with typical symptoms as they may not have significant thirst or polyuria. Symptoms may be less obvious and nonspecific, which can be challenging to diagnose if they attend the Emergency Department: e.g., they may only have nausea and vomiting. Current treatment guidelines identify DKA as a hyperglycemic emergency, it is essential to raise awareness and education of medical personnel as well as non-medical personnel about the existence of eu-DKA. Not only medical professionals, but more importantly non-professionals should be aware that DKA can occur without a significant increase in blood glucose levels in patients treated with SGLT2i.

6. Conclusions

SGLT2i as an insulin adjuvant treatment for T1DM, can improve glycemic control, reduce glycemic variability, and reduce total daily insulin dose and body weight in patients with T1DM without increasing the risk of hypoglycemic events. It is an effective option for patients with T1DM who have well above target blood glucose with insulin alone. However, it has been recognized that SGLT2i increases the risk of DKA in patients with T1DM, and multiple studies have shown that SGLT2i increases the incidence of DKA in patients with T1DM by 2- to 4-times. Therefore, clinicians should be aware of the possibility of DKA in patients with T1DM using SGLT2i, including adequate knowledge of the patient's ketone body levels and previous DKA episodes, and remind patients to regularly test ketone body levels during treatment (blood ketone testing is preferred to urine ketone testing (if available/affordable) [73]). The current use of SGLT2i in patients with BMI $\geq$27 kg/m^2, adherence to treatment, close follow-up, and education in timely DKA recognition is recommended. Studies have shown that SGLT2i improve cardiac and renal outcomes in type 2 diabetes, but not yet portrayed in type 1 diabetes (even though theoretically such benefits are likely), patients with T1DM who have developed cardiovascular or advanced kidney disease or heart failure may also be potential candidates for these agents. SGLT2i provides treatment options for patients with T1DM, but a cardiovascular-renal outcome trial demonstrating efficacy and safety in patients with T1DM who have cardiorenal complications is needed.

Abbreviations

SGLT2i, Sodium-glucose cotransporter 2 inhibitors; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; DKA, diabetic ketoacidosis; HF, heart failure; ADA, American Diabetes Association; DPP-4, dipeptidyl peptidase IV; GLP-1RA, glucagon-like peptide 1 receptor agonist; TGF, tubuloglomerular feedback; GFR, glomerular filtration rate; TIR, time in range; MAGE, mean amplitude of glucose fluctuation; CGM, continuous glucose monitoring; SBP, systolic blood pressure; HDL, high density lipoprotein; CKD, chronic kidney disease; DKD, diabetes kidney disease; CVD, Cardiovascular disease; UACR, urine albumin creatine ratio; HFrEF, heart failure with reduced ejection fraction; EASE, Empagliflozin as Adjunc-

tive to Insulin Therapy in Type 1 Diabetes; DEPICT, Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes; eu-DKA, euglycemic DKA.

Author Contributions

All authors (YM, QZ, HP, DLN, PS and HJ) have contributed to the conception and design of the manuscript. YM and QZ has been involved in drafting the manuscript. Authors have been involved in revisingit critically for important intellectual content. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreedto be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research was supported by Medical and Health Research Project in Luoyang (2001027A) and National Key R&D Program of China (2018YFC1311705).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Xu G, Liu B, Sun Y, Du Y, Snetselaar LG, Hu FB, *et al*. Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: population based study. British Medical Journal. 2018; 362: k1497.

[2] You W, Henneberg M. Type 1 diabetes prevalence increasing globally and regionally: the role of natural selection and life expectancy at birth. BMJ Open Diabetes Research & Care. 2016; 4: e000161.

[3] Pettus JH, Zhou FL, Shepherd L, Preblick R, Hunt PR, Paranjape S, *et al*. Incidences of Severe Hypoglycemia and Diabetic Ketoacidosis and Prevalence of Microvascular Complications Stratified by Age and Glycemic Control in U.S. Adult Patients with Type 1 Diabetes: A Real-World Study. Diabetes Care. 2019; 42: 2220–2227.

[4] Mirabelli M, Chiefari E, Caroleo P, Vero R, Brunetti FS, Corigliano DM, *et al*. Long-Term Effectiveness and Safety of SGLT-2 Inhibitors in an Italian Cohort of Patients with Type 2 Diabetes Mellitus. Journal of Diabetes Research. 2019; 2019: 3971060.

[5] Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, *et al*. 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. 2020; 43: 487–493.

[6] Rosenstock J, Marquard J, Laffel LM, Neubacher D, Kaspers S, Cherney DZ, *et al*. Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes: The EASE Trials. Diabetes Care. 2018; 41: 2560–2569.

[7] Buse JB, Garg SK, Rosenstock J, Bailey TS, Banks P, Bode BW, *et al*. Sotagliflozin in Combination with Optimized Insulin Therapy in Adults with Type 1 Diabetes: The North American inTandem1 Study. Diabetes Care. 2018; 41: 1970–1980.

[8] Danne T, Cariou B, Banks P, Brandle M, Brath H, Franek E, *et al*. HbA_1*c* 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. 2018; 41: 1981–1990.

[9] Mathieu C, Dandona P, Gillard P, Senior P, Hasslacher C, Araki E, *et al*. Efficacy and Safety of Dapagliflozin in Patients with Inadequately Controlled Type 1 Diabetes (the DEPICT-2 Study): 24-Week Results from a Randomized Controlled Trial. Diabetes Care. 2018; 41: 1938–1946.

[10] Mathieu C, Dandona P, Phillip M, Oron T, Lind M, Hansen L, *et al*. Glucose Variables in Type 1 Diabetes Studies with Dapagliflozin: Pooled Analysis of Continuous Glucose Monitoring Data From DEPICT-1 and -2. Diabetes Care. 2019; 42: 1081–1087.

[11] Rosenstock J, Ferrannini E. Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern with SGLT2 Inhibitors. Diabetes Care. 2015; 38: 1638–1642.

[12] Wolfsdorf JI, Ratner RE. SGLT Inhibitors for Type 1 Diabetes: Proceed with Extreme Caution. Diabetes Care. 2019; 42: 991–993.

[13] Perkins BA, Rosenstock J, Skyler JS, Laffel LM, Cherney DZ, Mathieu C, *et al*. Exploring Patient Preferences for Adjunct-to-Insulin Therapy in Type 1 Diabetes. Diabetes Care. 2019; 42: 1716–1723.

[14] Ehrenkranz JRL, Lewis NG, Kahn CR, Roth J. Phlorizin: a review. Diabetes/metabolism Research and Reviews. 2005; 21: 31–38.

[15] Oku A, Ueta K, Nawano M, Arakawa K, Kano-Ishihara T, Matsumoto M, *et al*. Antidiabetic effect of T-1095, an inhibitor of Na(+)-glucose cotransporter, in neonatally streptozotocin-treated rats. European Journal of Pharmacology. 2000; 391: 183–192.

[16] Zhao Y, Yang L, Xiang Y, Liu L, Huang G, Long Z, *et al*. Dipeptidyl peptidase 4 inhibitor sitagliptin maintains β-cell function in patients with recent-onset latent autoimmune diabetes in adults: one year prospective study. The Journal of Clinical Endocrinology and Metabolism. 2014; 99: E876–E880.

[17] Yakovleva T, Sokolov V, Chu L, Tang W, Greasley PJ, Peilot Sjögren H, *et al*. Comparison of the urinary glucose excretion contributions of SGLT2 and SGLT1: A quantitative systems pharmacology analysis in healthy individuals and patients with type 2 diabetes treated with SGLT2 inhibitors. Diabetes, Obesity & Metabolism. 2019; 21: 2684–2693.

[18] Ni L, Yuan C, Chen G, Zhang C, Wu X. SGLT2i: beyond the glucose-lowering effect. Cardiovascular Diabetology. 2020; 19: 98.

[19] Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. Nature Reviews. Endocrinology. 2012; 8: 495–502.

[20] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al*. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England Journal of Medicine. 2015; 373: 2117–2128.

[21] American Diabetes Association. 11. Microvascular Complications and Foot Care: *Standards of Medical Care in Diabetes-2020*. Diabetes Care. 2020; 43: S135–S151.

[22] Luippold G, Klein T, Mark M, Grempler R. Empagliflozin, a novel potent and selective SGLT-2 inhibitor, improves glycaemic control alone and in combination with insulin in

streptozotocin-induced diabetic rats, a model of type 1 diabetes mellitus. Diabetes, Obesity & Metabolism. 2012; 14: 601–607.
[23] Powell DR, Doree D, Jeter-Jones S, Ding Z, Zambrowicz B, Sands A. Sotagliflozin improves glycemic control in nonobese diabetes-prone mice with type 1 diabetes. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2015; 8: 121–127.
[24] Pieber TR, Famulla S, Eilbracht J, Cescutti J, Soleymanlou N, Johansen OE, *et al*. Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). Diabetes, Obesity & Metabolism. 2015; 17: 928–935.
[25] Gordon J, Beresford-Hulme L, Bennett H, Tank A, Edmonds C, McEwan P. Relationship between hypoglycaemia, body mass index and quality of life among patients with type 1 diabetes: Observations from the DEPICT clinical trial programme. Diabetes, Obesity & Metabolism. 2020; 22: 857–865.
[26] Araki E, Watada H, Uchigata Y, Tomonaga O, Fujii H, Ohashi H, *et al*. Efficacy and safety of dapagliflozin in Japanese patients with inadequately controlled type 1 diabetes (DEPICT-5): 52-week results from a randomized, open-label, phase III clinical trial. Diabetes, Obesity & Metabolism. 2020; 22: 540–548.
[27] Rodbard HW, Giaccari A, Lajara R, Stewart J, Strumph PS, Oliveira J, *et al*. Sotagliflozin added to optimized insulin therapy leads to HbA1c reduction without weight gain in adults with type 1 diabetes: A pooled analysis of inTandem1 and inTandem2. Diabetes, Obesity & Metabolism. 2020; 22: 2089–2096.
[28] Garg SK, Henry RR, Banks P, Buse JB, Davies MJ, Fulcher GR, *et al*. Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. The New England Journal of Medicine. 2017; 377: 2337–2348.
[29] Danne T, Cariou B, Buse JB, Garg SK, Rosenstock J, Banks P, *et al*. Improved Time in Range and Glycemic Variability with Sotagliflozin in Combination With Insulin in Adults With Type 1 Diabetes: A Pooled Analysis of 24-Week Continuous Glucose Monitoring Data From the inTandem Program. Diabetes Care. 2019; 42: 919–930.
[30] van Raalte DH, Bjornstad P, Persson F, Powell DR, de Cassia Castro R, Wang PS, *et al*. The Impact of Sotagliflozin on Renal Function, Albuminuria, Blood Pressure, and Hematocrit in Adults with Type 1 Diabetes. Diabetes Care. 2019; 42: 1921–1929.
[31] Henry RR, Thakkar P, Tong C, Polidori D, Alba M. Efficacy and Safety of Canagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, as Add-on to Insulin in Patients with Type 1 Diabetes. Diabetes Care. 2015; 38: 2258–2265.
[32] Kidokoro K, Cherney DZI, Bozovic A, Nagasu H, Satoh M, Kanda E, *et al*. Evaluation of Glomerular Hemodynamic Function by Empagliflozin in Diabetic Mice Using *In Vivo* Imaging. Circulation. 2019; 140: 303–315.
[33] Rodbard HW, Peters AL, Slee A, Cao A, Traina SB, Alba M. The Effect of Canagliflozin, a Sodium Glucose Cotransporter 2 Inhibitor, on Glycemic End Points Assessed by Continuous Glucose Monitoring and Patient-Reported Outcomes Among People with Type 1 Diabetes. Diabetes Care. 2017; 40: 171–180.
[34] Lu J, Tang L, Meng H, Zhao J, Liang Y. Effects of sodium-glucose cotransporter (SGLT) inhibitors in addition to insulin therapy on glucose control and safety outcomes in adults with type 1 diabetes: A meta-analysis of randomized controlled trials. Diabetes/metabolism Research and Reviews. 2019; 35: e3169.
[35] Abiru N, Shoji S, Kosakai Y, Snijder R, Asakawa K, Rokuda M. Demographic and clinical characteristics of patients with type 1 diabetes mellitus initiating sodium-glucose cotransporter 2 inhibitors in Japan: A real-world administrative database analysis. Diabetes Research and Clinical Practice. 2022; 190: 109973.
[36] Lawler PR, Liu H, Frankfurter C, Lovblom LE, Lytvyn Y, Burger D, *et al*. Changes in Cardiovascular Biomarkers Associated with the Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor Ertugliflozin in Patients with Chronic Kidney Disease and Type 2 Diabetes. Diabetes Care. 2021; 44: e45–e47.
[37] Škrtić M, Cherney DZI. Sodium-glucose cotransporter-2 inhibition and the potential for renal protection in diabetic nephropathy. Current Opinion in Nephrology and Hypertension. 2015; 24: 96–103.
[38] Lytvyn Y, Bjornstad P, Katz A, Singh SK, Godoy LC, Chung LT, *et al*. SGLT2 inhibition increases serum copeptin in young adults with type 1 diabetes. Diabetes & Metabolism. 2020; 46: 203–209.
[39] Bjornstad P, Laffel L, Tamborlane WV, Simons G, Hantel S, von Eynatten M, *et al*. Acute Effect of Empagliflozin on Fractional Excretion of Sodium and eGFR in Youth with Type 2 Diabetes. Diabetes Care. 2018; 41: e129–e130.
[40] Vestri S, Okamoto MM, de Freitas HS, Aparecida Dos Santos R, Nunes MT, Morimatsu M, *et al*. Changes in sodium or glucose filtration rate modulate expression of glucose transporters in renal proximal tubular cells of rat. The Journal of Membrane Biology. 2001; 182: 105–112.
[41] Heerspink HJL, Perkins BA, Fitchett DH, Husain M, Cherney DZI. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. Circulation. 2016; 134: 752–772.
[42] Vallon V, Richter K, Blantz RC, Thomson S, Osswald H. Glomerular hyperfiltration in experimental diabetes mellitus: potential role of tubular reabsorption. Journal of the American Society of Nephrology: JASN. 1999; 10: 2569–2576.
[43] Cherney DZI, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, *et al*. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation. 2014; 129: 587–597.
[44] Wheeler DC, Stefansson BV, Batiushin M, Bilchenko O, Cherney DZI, Chertow GM, *et al*. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics. Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association. 2020; 35: 1700–1711.
[45] Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, *et al*. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. The New England Journal of Medicine. 2020; 383: 1413–1424.
[46] Li J, Neal B, Perkovic V, de Zeeuw D, Neuen BL, Arnott C, *et al*. Mediators of the effects of canagliflozin on kidney protection in patients with type 2 diabetes. Kidney International. 2020; 98: 769–777.
[47] Li J, Woodward M, Perkovic V, Figtree GA, Heerspink HJL, Mahaffey KW, *et al*. Mediators of the Effects of Canagliflozin on Heart Failure in Patients With Type 2 Diabetes. JACC. Heart Failure. 2020; 8: 57–66.
[48] Dandona P, Mathieu C, Phillip M, Hansen L, Griffen SC, Tschöpe D, *et al*. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. The Lancet. Diabetes & Endocrinology. 2017; 5: 864–876.
[49] Verma S, McMurray JJV, Cherney DZI. The Metabolodiuretic Promise of Sodium-Dependent Glucose Cotransporter 2 Inhibition: The Search for the Sweet Spot in Heart Failure. JAMA Cardiology. 2017; 2: 939–940.
[50] Sternlicht H, Bakris GL. Blood Pressure Lowering and Sodium-Glucose Co-transporter 2 Inhibitors (SGLT2is): More Than Osmotic Diuresis. Current Hypertension Reports. 2019; 21: 12.
[51] Uthman L, Homayr A, Juni RP, Spin EL, Kerindongo R,

Boomsma M, *et al*. Empagliflozin and Dapagliflozin Reduce ROS Generation and Restore NO Bioavailability in Tumor Necrosis Factor α-Stimulated Human Coronary Arterial Endothelial Cells. Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology. 2019; 53: 865–886.

[52] Packer M. Response by Packer to Letter Regarding Article, "Activation and Inhibition of Sodium-Hydrogen Exchange Is a Mechanism That Links the Pathophysiology and Treatment of Diabetes Mellitus with That of Heart Failure". Circulation. 2018; 137: 1981–1982.

[53] Kang S, Verma S, Hassanabad AF, Teng G, Belke DD, Dundas JA, *et al*. Direct Effects of Empagliflozin on Extracellular Matrix Remodelling in Human Cardiac Myofibroblasts: Novel Translational Clues to Explain EMPA-REG OUTCOME Results. The Canadian Journal of Cardiology. 2020; 36: 543–553.

[54] Rådholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, *et al*. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program. Circulation. 2018; 138: 458–468.

[55] Bhatt DL, Verma S, Braunwald E. The DAPA-HF Trial: A Momentous Victory in the War against Heart Failure. Cell Metabolism. 2019; 30: 847–849.

[56] Hodrea J, Saeed A, Molnar A, Fintha A, Barczi A, Wagner LJ, *et al*. SGLT2 inhibitor dapagliflozin prevents atherosclerotic and cardiac complications in experimental type 1 diabetes. PLoS ONE. 2022; 17: e0263285.

[57] Lunder M, Janić M, Japelj M, Juretič A, Janež A, Šabovič M. Empagliflozin on top of metformin treatment improves arterial function in patients with type 1 diabetes mellitus. Cardiovascular Diabetology. 2018; 17: 153.

[58] Janić M, Cankar M, Šmid J, France Štiglic A, Jerin A, Šabovič M, *et al*. Empagliflozin-Metformin Combination Has Antioxidative and Anti-Inflammatory Properties that Correlate with Vascular Protection in Adults with Type 1 Diabetes. Journal of Diabetes Research. 2022; 2022: 6796470.

[59] Lytvyn Y, Kimura K, Peter N, Lai V, Tse J, Cham L, *et al*. Renal and Vascular Effects of Combined SGLT2 and Angiotensin-Converting Enzyme Inhibition. Circulation. 2022; 146: 450–462.

[60] Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. Journal of Diabetes Investigation. 2016; 7: 135–138.

[61] Kibbey RG. SGLT-2 inhibition and glucagon: Cause for alarm? Trends in Endocrinology and Metabolism: TEM. 2015; 26: 337–338.

[62] Dandona P, Mathieu C, Phillip M, Hansen L, Tschöpe D, Thorén F, *et al*. Efficacy and Safety of Dapagliflozin in Patients with Inadequately Controlled Type 1 Diabetes: The DEPICT-1 52-Week Study. Diabetes Care. 2018; 41: 2552–2559.

[63] Mathieu C, Rudofsky G, Phillip M, Araki E, Lind M, Arya N, *et al*. Long-term efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 study): 52-week results from a randomized controlled trial. Diabetes, Obesity & Metabolism. 2020; 22: 1516–1526.

[64] Karges B, Rosenbauer J, Holterhus P, Beyer P, Seithe H, Vogel C, *et al*. Hospital admission for diabetic ketoacidosis or severe hypoglycemia in 31,330 young patients with type 1 diabetes. European Journal of Endocrinology. 2015; 173: 341–350.

[65] Kalscheuer H, Seufert J, Lanzinger S, Rosenbauer J, Karges W, Bergis D, *et al*. Event Rates and Risk Factors for the Development of Diabetic Ketoacidosis in Adult Patients with Type 1 Diabetes: Analysis from the DPV Registry Based on 46,966 Patients. Diabetes Care. 2019; 42: e34–e36.

[66] Musso G, Gambino R, Cassader M, Paschetta E. Efficacy and safety of dual SGLT 1/2 inhibitor sotagliflozin in type 1 diabetes: meta-analysis of randomised controlled trials. BMJ (Clinical Research Ed.). 2019; 365: l1328.

[67] Horii T, Oikawa Y, Atsuda K, Shimada A. On-label use of sodium-glucose cotransporter 2 inhibitors might increase the risk of diabetic ketoacidosis in patients with type 1 diabetes. Journal of Diabetes Investigation. 2021; 12: 1586–1593.

[68] Bayona Cebada A, Nattero-Chávez L, Alonso Díaz S, Escobar-Morreale HF, Luque-Ramírez M. Efficacy and Safety of SGLT2 Inhibitors in Type 1 Diabetes After the Introduction of an Off-Label Use Protocol for Clinical Practice. Diabetes Technology & Therapeutics. 2020; 22: 208–215.

[69] Danne T, Pettus J, Giaccari A, Cariou B, Rodbard H, Weinzimer SA, *et al*. Sotagliflozin Added to Optimized Insulin Therapy Leads to Lower Rates of Clinically Relevant Hypoglycemic Events at Any HbA1c at 52 Weeks in Adults with Type 1 Diabetes. Diabetes Technology & Therapeutics. 2019; 21: 471–477.

[70] Yamada T, Shojima N, Noma H, Yamauchi T, Kadowaki T. Sodium-glucose co-transporter-2 inhibitors as add-on therapy to insulin for type 1 diabetes mellitus: Systematic review and meta-analysis of randomized controlled trials. Diabetes, Obesity & Metabolism. 2018; 20: 1755–1761.

[71] Danne T, Garg S, Peters AL, Buse JB, Mathieu C, Pettus JH, *et al*. International Consensus on Risk Management of Diabetic Ketoacidosis in Patients with Type 1 Diabetes Treated with Sodium-Glucose Cotransporter (SGLT) Inhibitors. Diabetes Care. 2019; 42: 1147–1154.

[72] European Commission. Forxiga approved in Europe for type-1 diabetes. 2019. Available at: https://www.astrazeneca.com/media-centre/press-releases/2019/forxiga-approved-in-europe-for-type-1-diabetes22032019.html/ (Accessed: 25 March 2019).

[73] European Commission. ZYNQUISTA™ Now Approved In The European Union for Treatment of Adults with Type 1 Diabetes. 2019. Available at: https://www.lexpharma.com/media-center/news/709-zynquista-now-approved-in-the-european-union-for-treatment-of-adults-with-type-1-diabetes/ (Accessed: 26 April 2019).

[74] Perkins BA, Cherney DZI, Partridge H, Soleymanlou N, Tschirhart H, Zinman B, *et al*. Sodium-glucose cotransporter 2 inhibition and glycemic control in type 1 diabetes: results of an 8-week open-label proof-of-concept trial. Diabetes Care. 2014; 37: 1480–1483.

[75] Egger M, Davey Smith G, Stettler C, Diem P. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. Diabetic Medicine: a Journal of the British Diabetic Association. 1997; 14: 919–928.

[76] Ehrmann D, Kulzer B, Schipfer M, Lippmann-Grob B, Haak T, Hermanns N. Efficacy of an Education Program for People with Diabetes and Insulin Pump Treatment (INPUT): Results from a Randomized Controlled Trial. Diabetes Care. 2018; 41: 2453–2462.

[77] Macfarlane J, Dhatariya K. Incidence of Euglycemic Diabetic Ketoacidosis in Adults with Type 1 Diabetes in the United Kingdom Before the Widespread Use of Sodium Glucose Cotransporter 2 Inhibitors. Mayo Clinic Proceedings. 2019; 94: 1909–1910.