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SGLT inhibitors in type 1 diabetes: weighing efficacy and side effects

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***Abstract*:** Even before sodium-glucose cotransporter inhibitors (SGLTi) became popular agents for the treatment of people with type 2 diabetes (T2DM), clinicians had explored their potential as adjunct therapies in type 1 diabetes (T1DM). Several trials have demonstrated improved glycemic control (compared with placebo) and a decrease in glucose variability with a clinically relevant increase of time in range. In addition, weight loss and decreased systolic blood pressure are observed. The magnitude of the effects observed depends on the type of SGLTi, the dose administrated, and the duration of observation in the studies. As seen in T2DM, there was an increase in the risk of urogenital mycotic infections, but no increase in the risk of severe hypoglycemia. However, concerns arose regarding an increase in incidence of diabetic ketoacidosis. Mitigation strategies, including careful patient selection, extensive education of patients and (para)medical personnel, adequate insulin dose titration, and the adoption of a ketone-centered approach, are suggested.

In different areas of the world, SGLTi are approved for use in T1DM with restrictions concerning patient selection and SGLTi dose. Real-world data on the effect of introduction of SGLTi in people with T1DM will yield insight on the robustness of glycemic effects over time, and allow us to determine whether the positive risk–benefit profile observed in clinical trials can be translated to the real world.

Keywords: diabetic ketoacidosis, SGLT inhibition, time in range, type 1 diabetes, unmet medical need

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Introduction

Despite improvements in insulin formulations, delivery systems, and glucose monitoring, only a third of people with type 1 diabetes (T1DM) patients achieve a target glycated hemoglobin (HbA1c) level of <7.0%/53 mmol/mol.[1] Tight glycemic control is most important because it prevents and slows down the progression of long-term complications.[2] It is estimated that approximately 1.6 million United States (US) citizens of all ages are affected with T1DM as of 2018, with an estimated 1.5 million new cases of diabetes among US adults aged ⩾18 years in 2018. Of those, approximately 210,000 are new cases of T1DM in patients <20 years of age.[3] Although the quality of life of people with T1DM has improved, problems such as hypoglycemia, weight gain, and variability in glucose profiles remain.[4] This defines a clear unmet medical need for an insulin-independent adjuvant therapy.

SGLTi are already a mainstay in the treatment of people with type 2 diabetes (T2DM), as several publications[5–8] were able to demonstrate beneficial effects not only on glucose control but also on cardiovasculair and renal outcomes.[9] Their place in guidelines and consensus reports of international learned societies is prominent.[10–12] Ever since their presentation to the scientific and clinical community, their potential for use as adjunct therapies in people with T1DM has been proposed, and several trials have studied their potential, providing insight into benefit–risk. However, the interpretation of this ratio has been different

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in different areas of the world, with different penetration in the real world. In Europe and Japan, SGLTi are approved for use as adjunct therapies; in the US, the Food and Drug Administration (FDA) has not allowed their use in T1DM.

This review article targets clinicians treating people with T1DM. The aim is to summarize the status of the efficacy of SGLT inhibitors in the treatment of T1DM, and to reflect on its safety and tolerability aspects, focusing on risk and management for diabetic ketoacidosis (DKA). We will discuss clinical trials using the SGLT2 inhibitors canagliflozin, empagliflozin, and dapagliflozin, as well as the SGLT1/2i sotagliflozin,[13–24] and introduce real-world observations.[4,25]

Efficacy

One of the first major trials was carried out by Henry *et al.* in 2015 with canagliflozin in a double-blind phase II study in 351 T1DM patients. The primary end point (HbA1c reduction of more than 0.4% and no increase in body weight) at 18 weeks was reached in 36.9% patients with insulin and canagliflozin 100 mg, 41.4% with insulin and canagliflozin 300 mg, and 14.5% with insulin and placebo ($p < 0.001$).[23]

Pieber *et al.* explored the potential beneficial effect of empagliflozin and insulin *versus* placebo and insulin on HbA1c in the small EASE-1 trial in 75 patients. A statistically significant ($p < 0.05$) decrease in HbA1c of 0.49% was noted for the empagliflozin group after 28 days in comparison with the placebo group.[24] Two double-blind placebo-controlled phase III trials, called EASE-2 (comparison of empagliflozin 10 mg, empagliflozin 25 mg, and placebo for 52 weeks) and EASE-3 (comparison of empagliflozin 2.5 mg, empagliflozin 10 mg, empagliflozin 25 mg, and placebo for 26 weeks), studied empagliflozin addition in 1707 people with T1DM on intensive insulin therapy. These showed a significant decrease in HbA1c, reduction in mean body weight, and increase in glucose time-in-range (TIR; proportion of time that a patient's glucose is between 70–180 mg/dl/3.9–10.0 mmol/l per day) for every dose (Table 1). Interestingly, there was a clear dose-dependency, with even the very low dose of 2.5 mg (not used routinely in T2DM) showing a small, but significant effect: HbA1c decreased by 0.28% ($p < 0.0001$) and body weight reduced by 1.8 kg ($p < 0.0001$). Whereas the glucose TIR increased for more than 2 h per day in the 5 and 10 mg doses, this TIR increased for an extra 1 h per day in the 2.5 mg arm ($p = 0.1063$).[22]

In the DEPICT-program, the efficacy of dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo as add-on therapy to insulin was explored in two phase III placebo-controlled double-blind clinical trials. Combined, 813 patients with inadequately controlled T1DM were studied.[17–21] HbA1c decreased significantly with both doses of dapagliflozin up to 52 weeks (Table 1). There was an improvement in TIR of approximately 10% (9.02% for dapaglilozin 5 mg and 10.70% for dapagliflozin 10 mg), which meant that patient's glucose levels were within the target zone for an extra 2 h a day ($p < 0.0001$) (Table 1).[20]

The InTandem trials with sotagliflozin found similar results on Hba1c, weight loss, and blood pressure control. InTandem3 ($n = 1402$), a multicenter phase III placebo-controlled double-blind clinical trial, found that significantly more patients in the group with sotagliflozin (28.6%) than in the placebo group (15.2%) reached the primary outcome: HbA1c below 7%/53 mmol/mol, without DKA or episodes of severe hypoglycemia ($p < 0.001$). Also, compared with baseline measurements, patients in the sotagliflozin group had a reduction in systolic blood pressure of 3.5 mmHg ($p = 0.002$) and in body weight of 2.98 kg ($p < 0.001$).[15] In the sotagliflozin group, 13.4% more glycemic measures were within the desired range. This translates to approximately 3 h extra time per day within target without increasing the time spent below <54 mg/dl ($p < 0.001$) (Table 1).[13–16]

Taking together all these programs, it is interesting to see how consistently this class of medications can affect glucose control, with similar levels of HbA1c reduction and in particular increases in TIR. Even the time course of onset of effect and durability of effect in those studies reporting up to 52 weeks are comparable. Effects are strongest when doses above the maximal glucosuria-inducing dose (those used in T2DM) are used. Then no further gain of increasing dose seems to be present, whereas the EASE program shows that when agents are used at doses with less induction of glucosuria, efficacy is less.

Table 1. Selected efficacy and safety data in seven clinical trials of SGLTi inhibitors as adjunctive therapy in combination with insulin in patients with T1DM.

	HbA1c% change *versus* placebo	Increase in time in range *versus* placebo h/day (⩾70–⩽180 mg/dl)¥	Severe hypoglycemia	Genital mycotic infections	Adjudicated DKA	Relative risk for DKA (95% CI)
6-month endpoint			–	–	–	–
InTandem1[13]			–	–	–	–
Sotagliflozin 200 mg	−0.36†	Not significant	–	–	–	–
Sotafgliflozin 400 mg	−0.41†	+2.50†	–	–	–	–
Placebo			–	–	–	–
InTandem2[14]			–	–		–
Sotagliflozin 200 mg	−0.37†	+2.0 ($p < 0.044$)	–	–	–	–
Sotafgliflozin 400 mg	−0.35†	+3.2†	–	–		–
InTandem1 & 2[16]			–	–	–	–
Sotagliflozin 200 mg	–	+1.3£ ($p = 0.03$)	–	–	–	–
Sotagliflozin 400 mg	–	+2.8£†	–	–	–	–
Placebo			–	–	–	–
inTandem3[15]						
Sotagliflozin 400 mg	−0.46†	–	3.0 (21/699)	6.4 (45/699)	3.0 (21/699)	5.28 (1.82–15.30)
Placebo		–	2.4 (17/703)	2.1 (15/703)	0.6 (4/703)	
DEPICT-1[17]						
Dapagliflozin 5 mg	−0.42*	+2.2*	7.6 (21/277)	12.3 (34/277)	1.4 (4/277)	1.25 (0.28–5.54)
Dapagliflozin 10 mg	−0.45*	+2.6*	6.4 (19/296)	11.2 (33/296)	1.7 (5/296)	1.46 (0.35–6.07)
Placebo			7.3 (19/260)	2.7 (7/260)	1.2 (3/260)	
DEPICT-2[19,20]						
Dapagliflozin 5 mg	−0.37*	–	1.8 (5/271)	10.0 (27/271)	2.6 (7/271)	15.06 (0.86–262.31)
Dapagliflozin 10 mg	−0.42*	–	0.0 (0/270)	7.8 (21/270)	2.2 (6/270)	13.10 (0.74–231.34)
Placebo			0.4 (1/272)	1.8 (5/272)	0.0 (0/272)	
EASE-3[22]						
Empagliflozin 2.5 mg	−0.28*	–	1.2 (3/241)	5.4 (13/241)	0.8 (2/241)	0.18 (0.04–0.81)
Empagliflozin 10 mg	−0.45*	+2.6*	–	–	–	–
Empagliflozin 25 mg	−0.52*	+1.8 ($p < 0.01$)	–	–	–	–
Placebo			2.5 (6/241)	2.5 (6/241)	4.6 (11/241)	

(Continued)

Table 1. (Continued)

	HbA1c% change *versus* placebo	Increase in time in range *versus* placebo h/day (⩾70–⩽180 mg/dl)¥	Severe hypoglycemia	Genital mycotic infections	Adjudicated DKA	Relative risk for DKA (95% CI)
1 Year endpoint						
DEPICT-1[18,20]						
Dapagliflozin 5 mg	−0.33*	–	10.5 (29/277)	15.5 (43/277)	4.0 (11/277)	2.07 (0.72–5.86)
Dapagliflozin 10 mg	−0.36*	–	8.4 (25/296)	13.5 (40/296)	3.4 (10/296)	1.76 (0.61–5.07)
Placebo			11.5 (30/260)	3.1 (8/260)	1.9 (5/260)	
DEPICT-2[21]						
Dapagliflozin 5 mg	−0.20*	–	8.9 (24/271)	11.1 (30/271)	4.1 (11/271)	11.04 (1.44–84.93)
Dapagliflozin 10 mg	−0.25*	–	9.6 (26/270)	10.4 (28/270)	3.7 (10/270)	10.07 (1.30–78.16)
Placebo			8.5 (23/272)	3.7 (10/272)	0.4 (1/272)	
EASE-2[22]						
Empagliflozin 10 mg	−0.39*	+2.9*	4.1 (20/491)ϕ	12.8 (62/491)ϕ	4.3 (21/491)ϕ	3.45 (1.40–8.47)
Empagliflozin 25 mg	−0.45*	+3.1*	2.7 (13/489)ϕ	14.3 (70/489)ϕ	3.3 (16/489)ϕ	2.64 (1.04–6.69)
Placebo			3.1 (15/484)ϕ	4.3 (21/484)ϕ	1.2 (6/484)ϕ	
inTandem1[13]						
Sotagliflozin 200 mg	−0.25	–	6.5 (17/263)	9.1 (24/263)	3.4 (9/263)	9.17 (1.17–71.88)
Sotafgliflozin 400 mg	−0.31	–	6.5 (17/262)	13 (24/262)	4.2 (11/262)	11.25 (1.46–86.54)
Placebo			9.7 (26/268)	3.4 (9/268)	0.4 (1/268)	
inTandem2[14]						
Sotagliflozin 200 mg	−0.21†	–	5.0 (13/261)	9.2 (24/261)	2.3 (6/261)	12.85 (0.73–226.96)
Sotagliflozin 400 mg	−0.32†	–	2.3 (6/263)	11 (29/263)	3.4 (9/263)	18.64 (1.09–318.62)
Placebo			5.0 (13/258)	2.3 (6/258)	0.0 (0/258)	

Data are % (n/N), unless specified otherwise.
*$p < 0.0001$.
†$p < 0.001$.
¥⩾3.9–⩽10 mmol/l.
ϕParticipants taking 10 and 25 mg of empagliflozin in the two components of the EASE program were pooled for this analysis.
£Pooled CGM data from inTandem1 and inTandem2.
CGM, continuous *glucose monitoring*; DKA, diabetic ketoacidosis; HbA1c, glycated hemoglobin; T1DM, type 1 diabetes mellitus.

Safety and tolerability

Hypoglycemia

SGLTi do not cause hypoglycemia by themselves, but they do raise the risk of hypoglycemia when added to insulin therapy in people with T1DM. In the DEPICT-trials, there was no significant difference in hypoglycemic events between the treated groups and the placebo groups (Table 1).[17–21] The use of sotagliflozin was associated with a reduced incidence of hypoglycemia and severe hypoglycemia. Sotagliflozin 200 mg and

400 mg (in comparison with placebo) reduced level 1 hypoglycemia by 22%. Level 2 hypoglycemia evens were reduced by 28% and 30%, respectively, for 200 mg and 400 mg. Level 1 and 2 were defined using American Diabetes Association (ADA)/European Association for the Study of Diabetes criteria [level 1 (<70 mg/dl/3.9 mmol/l but ⩾54 mg/dl) and level 2 (<54 mg/dl/3.0 mmol/l)]. Level 3 hypoglycemia (assistance from another person or loss of consciousness or a seizure) occurred, respectively, in 2.6%, 2.2%, and 6.3% of patients receiving sotagliflozin 200 mg, 400 mg, and placebo. Effects persisted after correction for HbA1c.[26] Meta-analysis showed a weighted mean difference of −9.09 evens per patient year of hypoglycemic events with sotagliflozin in comparison with placebo.[27] The EASE-group showed a similar overall risk of symptomatic hypoglycemia for empagliflozin 2.5 mg, 10 mg, and 25 mg *versus* placebo. Severe hypoglycemic events respectively occurred in 1.2%, 4.1%, 2.7%, and 3.1% of patients (Table 1).[22] For canagliflozin, the incidence of severe hypoglycemic episodes was 2.6%, 6.8%, and 1.7% with canagliflozin 100 mg, 300 mg, and placebo, respectively (Table 1).[23] Meta-analysis showed no increased risk of severe hypoglycemia in SGLTi treated patients compared with placebo.[28,29]

Overall, it can be concluded that different hypoglycemia rates depend on the underlying insulin-adaptation scheme used in the studies, rather than the individual SGLTi.

Urogenital infections

One could expect more urogenital infections when using SGLT inhibitors, as urinary glucose may cause additional growth of commensal urogenital microorganisms.

All SGLTi programs in T1DM showed equipoise in urinary tract infections, but an increase in mycotic genital infections, exceeding the rates seen in people with T2DM.[27–29]

In DEPICT-1 and DEPICT-2, the rate of urinary tract infections was comparable between treatment arms and placebo arms (respectively 8.4% *versus* 8.1%; 4.4% *versus* 5.5%). Genital mycotic tract infections were, however, clearly more common in the dapagliflozin groups then in the placebo groups at 52 weeks, with a similar frequency in both dapagliflozin groups (14.5% *versus* 3.1% in DEPICT-1 and 10.7% *versus* 3.7% in DEPICT-2). Like in type 2 diabetes, genital mycotic infections occurred more commonly in females than in males.[17–19,21] Also, sotagliflozin did not increase urinary tract infections (relative risk 0.97, 95% confidence interval 0.71–1.33, $p = 0.84$), but increased mycotic genital tract infections (3.12, 95% confidence interval 2.14–4.54, $p < 0.001$),[27] as was the case for empagliflozin in the EASE-trials: 12.8% and 14.3% of the patients for empagliflozin 10 mg and 25 mg, respectively, had a genital mycotic infection, *versus* only 4.3% of the patients on placebo (Table 1). Of interest, in EASE-3, even patients on empagliflozin 2.5 mg faced double the risk of getting a genital mycotic infection than patients on placebo (Table 1).[22]

Diabetic ketoacidosis

SGLTi lowers blood glucose levels in a non-insulin-dependent manner. As a consequence, the insulin dose often needs to be reduced to avoid hypoglycemia. However, when the insulin dose is decreased, a critical level can be reached, leading to increased lipolysis, gluconeogenesis, ketone body formation, and, eventually, DKA.

The first trial by Henry *et al.* shocked the clinical community by showing a DKA risk of 4.3% in the canagliflozin 100 mg group and 6.0% in the canagliflozin 300 mg group, *versus* 0 events in the placebo arm.[23] Of interest, five of these patients had a blood glucose level of less than 250 mg/dl/13.9 mmol/l, introducing the disturbing observation that SGLTi have the potential not only to increase the risk of DKA, but also lead to the misleading clinical presentation of euglycemic DKA. The program with canagliflozin was stopped at this stage.

In subsequent programs, mitigation strategies were introduced, with patient selection (excluding those with recent history of DKA) and stringent educational and follow-up measures, implementing ketone measurements at prespecified timepoints and when DKA evolution was suspected. In all programs, external adjudication committees were installed.

Caution needs to be taken, however, when comparing reported risk of DKA as different definitions were used from program to program. All

programs dropped 'hyperglycemia' (>250 mg/dl/13.9 mmol/l) as a criterion in the ADA definition of DKA, to allow assessment of the full blown picture of DKA risk, including the euglycemic presentations.

In the first publication of the DEPICT-1 results at 24 weeks, no increase in DKA was observed in dapagliflozin-treated patients. An imbalance in DKA did, however, appear at 52 weeks, and was already present at 24 weeks in DEPICT-2. By 52 weeks, DKA occurred in the DEPICT program in 4.1%, 3.7%, and 0.4% of patients in the 5 mg, 10 mg, and placebo groups, respectively (Table 1).[17–19,21] In InTandem2, DKA respectively occurred in 2.3%, 3.4%, and 0% in sotagliflozin 200 mg, 400 mg, and placebo (Table 1).[14] In the North American version (InTandem1), DKA occurred in 3.4%, 4.2%, and 0.4% in sotagliflozin 200 mg, 400 mg, and placebo, respectively (Table 1).[13] A total of 85 events occurred, of which 21 (31%) had blood glucose values between 150–250 mg/dl/2.2–13.9 mmol/l.[27] In the EASE program, the rate for confirmed adjudicated DKA for the 10 mg and 25 mg empagliflozin dose was higher than for placebo, at 4.3%, 3.3%, and 1.2%, respectively (Table 1). A total of 41 events of DKA occurred, of which 15 had a blood glucose level <250 mg/dl/13.9 mmol/l. Interestingly, no increase of DKA was observed by 26 weeks in the group on empagliflozin 2.5 mg compared with placebo (0.8% *versus* 1.2%) (Table 1). As in the other trials, DKA was more frequent in patients on insulin pumps, and an additional provocative factor was needed to cross the DKA threshold.[22]

Of interest is the relationship between dose and DKA risk. A meta analysis by Lu *et al.* showed a similar dose effect where high dose (sotagliflozin 400 mg, dapagliflozin 10 mg, canagliflozin 300 mg, and empagliflozin 25 mg) SGLTi had an odds ratio of 3.11 (95% confidence interval 2.11–4.58) *versus* low dose (sotagliflozin 75 mg, sotagliflozin 200 mg, dapagliflozin 5 mg, canagliflozin 100 mg, empagliflozin 2.5 mg, and 10 mg) SGLTi of 2.90 (95% confidence interval 1.64–5.12).[29] Fitting with this concept are the results of EASE-3, where the very low dose of empagliflozin (2.5 mg) did not show an imbalance in DKA *versus* placebo.[22,29]

Thus, all programs show an increase in DKA, with the exception of the 24-week report on empagliflozin 2.5 mg (EASE-3). Description of DKA cases in publications of these trials is limited, but as far as is traceable, in all cases of DKA, patients had at least one provocative factor (illness, infection, material failure, omitted insulin doses, decrease in carbohydrate intake, etc.). Still, real-world evidence is needed to guide clinicians in their evaluation of the real DKA risk in people living with T1DM outside the strict regulation of clinical trials, with careful patient selection and intensive education of patients and clinical teams.

DKA prevention and pre-emptive measures

Patients

Patient selection. Careful selection of patients with T1DM eligible for SGLTi is critical in minimizing DKA risk. Patients with a HbA1c >10%/86 mmol/mol or basal ketone blood measurement >0.6 mmol/l (or positive for ketones on urine stick) should not be considered for SGLTi.[19,20,30–33] In addition, risk factors associated with each patient's lifestyle/behavior should also be taken into consideration. It is a prerequisite that patients show willingness/ability to follow prescribed regimens for measuring ketones, and to respond appropriately to elevated levels. SGLTi should not be prescribed to patients on a ketogenic or low-carbohydrate diet as they tend to have a higher basal ketogenesis, increasing the risk of adverse ketosis effects. Patients using insulin pumps are at a higher risk for DKA compared with patients on injectable insulin, due to the possibility of pump or infusion set malfunction.[15–32,34] Patients who skip meals, miss insulin doses, and/or consume large amounts of alcohol also seem to be at increased risk.[30–32] SGLTi should also not be used in pregnant women with T1DM because no adequate studies are available and pregnancy inherently decreases the DKA threshold.

Patient education. Patients should be instructed to stop SGLTi in all circumstances predisposing them to ketosis. As such, stopping SGLTi should be advocated before surgery, when prolonged fasting is envisaged or in circumstances of infection and fever (like during COVID-19 infection).

Patients should be familiarized with terms such as DKA, DKA risk factors, ketone measuring, and treatment protocols. They should be equipped with a blood ketone meter (or urine test strips) for self-testing. Ketone (β-hydroxybutyrate) measuring should be performed when any symptoms of DKA (nausea, fatigue, and vomiting) is present, when

changes in diet occur, insulin dose is adjusted, physical activity is increased, or with occurrence of DKA-related events such as infection, surgery, injury, dehydration, pump malfunction, etc.

Ketones should be measured repetitively for as long as symptoms persist or stressors remain. Patients should be instructed which events lead to increased DKA risk and how they should react regarding SGLTi. They should also be taught to anticipate situations in which they may wish to temporarily withhold SGLTi. Patients should be given access to educational materials (STICH protocol/STOP DKA protocol/. . .) which include DKA risk factors, ketone levels interpretation, and early treatment paradigms.[31,32] Of importance, patients should be instructed not to limit ketone measurements to moment of hyperglycemia, but to dissociate the concept of ketonemia from glucose control.

Clinicians

Insulin dosage. When starting SGLTi therapy, insulin dose should be reduced carefully to prevent hypoglycemia, but not to a level where ketosis sets in and DKA risk increases. The degree of insulin reduction, and whether to reduce basal or bolus insulin, is product- and patient-specific. In DEPICT-1 and DEPICT-2, insulin dose reductions were proportional for basal and bolus.[17–19,21] By contrast, with sotagliflozin, a mixed SGLT1/2i, the insulin dose reductions were mainly prandial.[13–15] Therefore, it is left to the physician's discretion to decide to which degree insulin doses should be reduced, and how to implement the reduction for each individual patient. In patients who are relatively well-controlled (HbA1c 7.5%/58 mmol/mol), no more than 20% reduction in insulin dose is recommended, as this increases the risk of DKA. For less well-controlled patients (HbA1c $\geq$ 7.5%/58 mmol/mol), only slight or no reductions in prandial and basal insulin could be considered. Whatever course is pursued, frequent blood glucose monitoring (preferably by continuous *glucose monitoring*) and ketone monitoring is recommended when adjustments to insulin doses are made, or SGLTi is initiated.

DKA prevention and treatment. Diabetes teams should incorporate intensive education on ketones, ketone measurements, and prevention of ketosis in their patient education, and provide educational materials as well as emergency contact points to people with T1DM on SGLTi.

When patients with type 1 diabetes mellitus on SGLTi present with symptoms compatible with DKA, diagnosis and initiation of treatment should be ketone-centered and no longer glycemic-based. This is because glycemic levels are not as high as clinicians and patients are used to when not taking SGLT inhibitors, because of glucosuria. Glycemic levels in DKA cases in SGLT inhibitor-treated individuals are often below the 250 mg/dl/13.9 mmol/l threshold used by the American Diabetes Association in its definition of DKA, thus called euglycemic DKA (eu-DKA). The cornerstone of ketosis treatment is to inject insulin, consume carbohydrates, and maintain adequate hydration. Insulin should never be stopped. Insulin is best provided by injection even for patients who have an insulin pump. For patients on pump insulin, injections should be continued until pump/infusion set malfunction has been ruled out or has been resolved. SGLTi should be discontinued until clinical reevaluation by the patient his or her diabetic team/prescriber. If, despite these measures, symptoms and/or ketone measurements worsen/persist, the patient should seek immediate medical assistance. If patients present themselves to the emergency department or an urgent care center, an evaluation is necessary that includes measurements of capillary/venous pH, blood bicarbonate, anion gap, and blood ketones (β-hydroxybutyrate). It is important that emergency departments are made aware that DKA can, and will, present without overtly elevated glucose levels in patients treated with SGLT inhibitors.[30–32]

Real-world evidence

A major worry about the use of SGLTi is that the observed increased risk in DKA would be multiplied when these agents would be used in the real world. Indeed, in all trials after the canagliflozin program, very intensive educational tools were used, with education on ketone measurements and mitigation strategies in case of ketone level elevations. In addition, medical teams who took care of these patients were alerted to the risk of DKA.

To date, no information on worrying increases in DKA rates in those regions of the world where SGLTi are used in people with T1DM have been reported.

Overall, real-world data on use of SGLT2i in people with T1DM are still scarce, but are in line with clinical trial data on efficacy and safety. A small

prospective cohort of 27 patients on empagliflozin 10 mg showed a significant improvement in glycemic control, TIR, insulin dose reduction, and metabolic parameters during 52 weeks of follow up. HbA1c decreased by 0.8% ($p < 0.001$), which is more than seen in the clinical trials; TIR increased by 12% ($p < 0.008$). On average, systolic blood pressure decreased by 7 mmHg and weight by 8 kg. No increases in hypoglycemia rates were noted. One event of DKA was described in a 43-year old man on continuous subcutaneous insulin infusion. Insulin pump failure and alcohol consumption were identified as probable triggers.[4] However, a recent real-world evaluation for off-label use of sotagliflozin, by using the US Sentinel program, revealed a standardized incidence rate of 1.8 (95% CI 1.45–2.28) for DKA events, which is higher than would be expected based on the clinical trials. The data were consistent with the fact that women of younger age (25–44 years) are at greatest risk for DKA.[25]

One of the troubling phenomena to arise since the introduction of SGLTi is the increased frequency of eu-DKA, whereas, in the past, eu-DKA was a rarity seen in pregnancy, decreased caloric intake, heavy alcohol consumption, chronic liver disease, post-bariatric surgery, or glycogen storage disorders. A survey conducted in the United Kingdom (UK) (2014–2015), before widespread use of SGLTi, showed a background risk of 18 eu-DKA events per 334 DKA for when the glycaemia threshold was set on <250 mg/dl/13.9 mmol/l and 29/334 events for glycaemia <300 mg/dl/16.7 mmol/l.[33] However, raising awareness and educating emergency department (para)medic staff on the existence of eu-DKA should result in similar morbidity and mortality as for hyperglycemic DKA.

Conclusion

It is clear that SGLTi improves glycemic control compared with placebo, lowering HbA1c between 0.28% and 0.46% and improving TIR with more than 2 h, without weight gain, without increased risk of (severe) hypoglycemia, and with a reduction in insulin dose, as demonstrated in randomized clinical trials lasting up to 52 weeks.

However, some concerns have arisen regarding an imbalance of DKA-events in SGLTi-treated patients. After the initial large imbalance in DKA in the canagliflozin trial by Henry *et al.*,[23] implementation of careful patient selection, intensive ketone monitoring, and installation of intensive education programs for clinical teams and patients has reduced the DKA risk in later trials. However, an imbalance still exists, increasing the risk of DKA to 2–4 fold with SGLTi.

So, is the juice worth the squeeze or are we heading for a pyrrhic victory? Based on the data of the eight major trials, the use of SGLTi would result in 1 extra case of DKA for every 26 patient-years of adjunctive therapy or 4000 extra cases of DKA for every 100,000 T1DM patients treated with SGLTi, resulting in 16 extra DKA deaths per year per 100,000 adjunctive-treated patients.[35] Are we willing to take those risks when we have no studies about long-term feasibility, sustainability, and a lot of unanswered questions? Will the glycemic effect be robust over time? How long do we need to treat to provide clinically significant protection against chronic complications? What is the optimal dose to minimize DKA-risk and maximize efficacy? How will SGLTi act in the real world? Will it provide a benefit-to-risk profile similar to that seen in clinical trials or not?[36]

At the moment, several regulatory agencies, e.g., the European Medicines Agency, have approved the use of SGLTi in people with T1DM with careful patient selection (BMI > 28 kg/m^2) and using lower doses of the SGLT inhibitor (e.g., dapagliflozin 5 mg). Real-world data to date fails to show dramatic increases in DKA in Europe, despite the availability of these agents for use in T1DM. Monitoring of the field in the coming years will provide evidence of the safety of the introduction of SGLTi in T1DM.

Author contribution(s)

Birgit Janssens: Conceptualization; Project administration; Writing-original draft; Writing-review & editing.

Simon Caerels: Conceptualization; Project administration; Supervision; Writing-original draft; Writing-review & editing.

Chantal Mathieu: Conceptualization; Resources; Supervision; Validation; Writing-original draft; Writing-review & editing.

Conflict of interest statement

BJ and SC declare no conflicts of interest. CM serves, or has served, on the advisory panel for Novo Nordisk, Sanofi, Merck Sharp and Dohme Ltd., Eli Lilly and Company, Novartis,

AstraZeneca, Boehringer Ingelheim, Hanmi Pharmaceuticals, Roche, Medtronic, ActoBio Therapeutics, Pfizer, Dianax, and UCB. Financial compensation for these activities has been received by KU Leuven; KU Leuven has received research support for CM from Medtronic, Novo Nordisk, Sanofi, Merck Sharp and Dohme Ltd., Eli Lilly and Company, Roche, Abbott, ActoBio Therapeutics, and Novartis; CM serves, or has served, on the speakers bureau for Novo Nordisk, Sanofi, Merck Sharp and Dohme, Eli Lilly and Company, Boehringer Ingelheim, Astra Zeneca, and Novartis. Financial compensation for these activities has been received by KU Leuven. CM was an investigator in the EASE, inTandem and DEPICT trials. She is an author on DEPICT manuscripts.

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References

1. Foster NC, Beck RW, Miller KM, *et al.* State of type 1 diabetes management and outcomes from the T1D exchange in 2016–2018. *Diabetes Technol Ther* 2019; 21: 66–72.
2. Gubitosi-Klug RA, Braffett BH, White NH, *et al.* Risk of severe hypoglycemia in type 1 diabetes over 30 years of follow-up in the DCCT/EDIC study. *Diabetes Care* 2017; 40: 1010–1016.
3. Centers for Disease Control and Prevenion. *National diabetes statistics report, 2020*. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services, 2020.
4. Bayona Cebada A, Nattero-Chavez L, Alonso Diaz S, *et al.* Efficacy and safety of SGLT2 inhibitors in type 1 diabetes after the introduction of an off-label use protocol for clinical practice. *Diabetes Technol Ther* 2020; 22: 208–215.
5. Cuypers J, Mathieu C and Benhalima K. SGLT2-inhibitors: a novel class for the treatment of type 2 diabetes introduction of SGLT2-inhibitors in clinical practice. *Acta Clin Belg* 2013; 68: 287–293.
6. Dorsey-Trevino EG, Gonzalez-Gonzalez JG, Alvarez-Villalobos N, *et al.* Sodium-glucose cotransporter 2 (SGLT-2) inhibitors and microvascular outcomes in patients with type 2 diabetes: systematic review and meta-analysis. *J Endocrinol Invest* 2020; 43: 289–304.
7. Giugliano D, Longo M, Ida Maiorino M, *et al.* Efficacy of SGLT-2 inhibitors in older adults with diabetes: systematic review with meta-analysis of cardiovascular outcome trials. *Diabetes Res Clin Pract* 2020; 162: 108114.
8. Perkovic V, Jardine MJ, Neal B, *et al.* Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380: 2295–2306.
9. Buse JB, Wexler DJ, Tsapas A, *et al.* 2019 Update to: management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2020; 63: 221–228.
10. National Institute for Health and Care Excellence. Sotagliflozin with insulin for treating type 1 diabetes [Internet]. Technology appraisal guidance (TA622). NICE, www.nice.org.uk/guidance/ta622 (2020, accessed May 2020).
11. National Institute for Health and Care Excellence. Dapagliflozin with insulin for treating type 1 diabetes [Internet]. Technology appraisal guidance (TA597). NICE, www.nice.org.uk/guidance/ta597 (2019, accessed May 2020).
12. Dashora U, Dipesh CP, Gregory R, *et al.* Association of British Clinical Diabetologist (ABCD) position statement on the use of sodium-glucose cotransporter-2 inhibitors in type 1 diabetes (updated 2019). *Br J Diabetes* 2019; 19: 66–72.
13. Buse JB, Garg SK, Rosenstock J, *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.
14. Danne T, Cariou B, Banks P, *et al.* 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* 2018; 41: 1981–1990.
15. Garg SK, Henry RR, Banks P, *et al.* Effects of sotagliflozin added to insulin in patients with type 1 diabetes. *N Engl J Med* 2017; 377: 2337–2348.
16. Danne T, Cariou B, Buse JB, *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.

17. Dandona P, Mathieu C, Phillip M, *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. *Lancet Diabetes Endocrinol* 2017; 5: 864–876.
18. Dandona P, Mathieu C, Phillip M, *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.
19. Mathieu C, Dandona P, Gillard P, *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.
20. Mathieu C, Dandona P, Philip M, *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.
21. Mathieu C, Rudofsky G, Phillip M, *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 Obes Metab*. Epub ahead of print 20 April 2020. DOI: 10.1111/dom.14060.
22. Rosenstock J, Marquard J, Laffel LM, *et al.* Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the EASE trials. *Diabetes Care* 2018; 41: 2560–2569.
23. Henry RR, Payal T, Cindy T, *et al.* 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.
24. Pieber TR, Famulla S, Eilbracht J, *et al.* Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). *Diabetes Obes Metab* 2015; 17: 928–935.
25. Hampp C, Swain RS, Horgan C, *et al.* Use of sodium–glucose cotransporter 2 inhibitors in patients with type 1 diabetes and rates of diabetic ketoacidosis. *Diabetes Care* 2020; 43: 90–97.
26. Danne T, Pettus J, Giaccari A, *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 Technol Ther* 2019; 21: 471–477.
27. Musso G, Gambino R, Cassader M, *et al.* Efficacy and safety of dual SGLT 1/2 inhibitor sotagliflozin in type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ* 2019; 365: I1328.
28. Yamada T, Shojima N and Noma H. 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 Obes Metab* 2018; 20: 1755–1761.
29. Lu J, Tang L, Meng H, *et al.* 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 Metab Res Rev* 2019; 35: e3169.
30. Danne T, Garg S, Peters AL, *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.
31. Goldenberg RM, Gilbert JD, Hramiak IM, *et al.* Sodium-glucose co-transporter inhibitors, their role in type 1 diabetes treatment and a risk mitigation strategy for preventing diabetic ketoacidosis: the STOP DKA protocol. *Diabetes Obes Metab* 2019; 21: 2192–2202.
32. Garg SK, Peters AL, Buse JB, *et al.* Strategy for mitigating DKA risk in patients with type 1 diabetes on adjunctive treatment with SGLT inhibitors: a STICH protocol. *Diabetes Technol Ther* 2018; 20: 571–575.
33. Macfarlane J and 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 Clin Proc* 2019; 94: 1909–1910.
34. Peters AL, Robert RH, Thakkar P, *et al.* Diabetic ketoacidosis with canagliflozin, a sodium–glucose cotransporter 2 inhibitor, in patients with type 1 diabetes. *Diabetes Care* 2016; 39: 532–538.
35. Benoit SR, Zhang Y, Geiss LS, *et al.* Trends in diabetic ketoacidosis hospitalizations and in-hospital mortality—United States, 2000–2014. *MMWR Morb Mortal Wkly Rep* 2018; 67: 362–365.
36. Taylor SI, Blau JE, Rother KI, *et al.* SGLT2 inhibitors as adjunctive therapy for type 1 diabetes: balancing benefits and risks. *Lancet Diabetes Endocrinol* 2019; 7: 949–958.

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