

Association of British Clinical Diabetologists (ABCD) position statement on the use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors in type 1 diabetes

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Abstract

SGLT-2 inhibitors are currently neither licensed nor recommended in people with type 1 diabetes. The management of type 1 diabetes consists essentially of insulin treatment, monitoring and education. SGLT-2 inhibitors can be a useful adjunct to insulin treatment in improving glycaemic control. They may also potentially be helpful in reducing cardiovascular and renal complications in people with type 1 diabetes. However, further studies will be needed to establish this. SGLT-2 inhibitors can cause diabetic ketoacidosis and certain circumstances appear to increase this risk. They should therefore be used with caution all the time and only under specialist supervision. Higher amputation rates have been reported with some SGLT-2 inhibitors and hence they should be used with caution in patients with peripheral vascular disease.

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ABCD recommendations for use of SGLT-2 inhibitors in type 1 diabetes

- SGLT-2 inhibitors are currently not licensed in people with type 1 diabetes. ABCD supports the NICE guidelines for management of type 1 diabetes.¹
- SGLT-2 inhibitor treatment is not currently recommended in people with type 1 diabetes but may be a useful adjunct to

achieve better glycaemic control with added benefit of weight loss in patients who are inadequately controlled.

- ABCD recommends that any use of SGLT-2 inhibitors in type 1 diabetes patients on insulin must be under regular supervision by a specialist clinician with careful monitoring and support from a diabetes team.
- Patients should be informed that diabetic ketoacidosis has been reported in patients taking SGLT-2 inhibitors, particularly those in whom the insulin dose was reduced by more than 20%. Patients should be reminded of the precipitating factors for diabetic ketoacidosis (ie, excessive carbohydrate restriction, excessive alcohol, infections, surgical procedures and acute medical illness).
- As diabetes control improves with SGLT-2 inhibitors, the insulin dose may have to be reduced. Such reduction should be gradual and not exceed 10% of the dose at a time. Patients should have access to a blood ketone monitor and appropriate training in using it. Blood ketones should be checked if feeling unwell even when the capillary glucose levels are not particularly high. If the ketones are above 0.6 mmol/L, medical help should be sought as the patient may require additional advice to prevent ketoacidosis and/or treatment with intravenous fluids and insulin.
- ABCD recommends stopping SGLT-2 inhibitors before major surgical procedures and in patients who are acutely ill. Patients should be informed that higher amputation rates and fractures have been reported in one trial with one of the SGLT-2 inhibitors (ie, canagliflozin) in type 2 diabetes.
- SGLT-2 inhibitors should be used with caution in patients with peripheral vascular disease and stopped if any signs of peripheral vascular insufficiency are detected.
- Patients should be informed that SGLT-2 inhibitors can cause mild diuresis and nocturia and they should maintain adequate hydration to prevent the effects of dehydration.

SGLT-2 inhibitors and their current licensed indications

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are an established class of drugs which effectively lower glucose levels in people with type 2 diabetes, with additional cardiac and renal benefits in the Cardiovascular Outcome Trials. These drugs reduce blood glucose by preventing renal reabsorption of glucose, a mechanism

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which is insulin independent but glucose dependent.² Additional positive effects on lowering blood pressure by natriuresis and weight loss might partly mediate the cardiovascular benefit recently observed in clinical trials in patients with type 2 diabetes, although other mechanisms are possible.³⁻⁶ Dapagliflozin was the first SGLT-2 inhibitor to be approved for use in Europe in 2011 and in the UK in 2012. There are currently three SGLT-2 inhibitors licensed in the UK: dapagliflozin, canagliflozin and empagliflozin. Sotagliflozin is a dual SGLT inhibitor and will not be discussed in this article.

Currently, SGLT-2 inhibitors are licensed in people with type 2 diabetes but are neither licensed nor recommended in type 1 diabetes. Nevertheless, there is increasing off-label use of these agents in type 1 diabetes. This has prompted development of the following ABCD position statement on the use of SGLT-2 inhibitors in type 1 diabetes.

Potential role in type 1 diabetes

Optimal management of type 1 diabetes remains a challenge in the UK. Recent data show that the percentage of people achieving the National Institute for Health and Care Excellence (NICE) recommended targets i.e. HbA_{1c} <58 mmol/mol (7.5%), BP <140/80 mm of Hg, cholesterol <5mmol/l is 30.2%, 75.8% & 69.3% respectively. All three targets were achieved only in 18.9% of the patients.^{1,7,8}

There are considerable data showing a higher cardiovascular^{9,10} and renal risk¹¹ in people with type 1 diabetes. There is therefore scope for improving risk factor control by tighter glycaemic control with appropriate insulin therapy aided by potential adjunct therapy for people with type 1 diabetes. Extrapolating from the recent data in type 2 diabetes, SGLT-2 inhibitors may potentially be helpful in reducing cardiovascular and renal complications in people with type 1 diabetes. However, outcome studies will be needed to establish this.

The ABCD position statement outlines the standards of care in people with type 1 diabetes.¹² Intensified insulin therapy is often used to control hyperglycaemia in type 1 diabetes on the basis of studies which showed a link between hyperglycaemia and micro and macrovascular complications of diabetes.¹³ This intensification, however, may increase the risk of hypoglycaemia, weight gain and associated adverse cardiovascular profile.¹⁴

Metformin is inexpensive and useful in some overweight people with type 1 diabetes but it does not improve HbA_{1c} in the long term.^{15,16} Glucagon-like peptide-1 (GLP-1) analogues and receptor agonists may be helpful in subgroups of people with type 1 diabetes but the data are limited.¹⁷ Dipeptidyl peptidase-4 (DPP4) inhibitors have not shown any consistent effect on glycaemic control or glucose variability in patients with type 1 diabetes.¹⁸ In contrast, SGLT-2 inhibitors are oral glucose-lowering drugs with potential in this group of patients.¹⁹

Evidence for SGLT-2 inhibitors in type 1 diabetes

There is considerable emerging evidence for the use of SGLT-2 inhibitors in type 1 diabetes, which is summarised in brief in Table 1.²⁰⁻²⁶ A meta-analysis of three randomised controlled trials (RCTs) in patients with type 1 diabetes treated with SGLT-2 inhibitors versus placebo added to insulin showed significant reductions in fasting glucose (by 2.47 mmol/L) and insulin dose

(−0.75 IU) without any increase in hypoglycaemia, infections or diabetic ketoacidosis (DKA) in the SGLT-2 inhibitor group.²⁷ Another subgroup meta-analysis of RCTs in a similar group showed significant reductions in HbA_{1c} (−1.30%), weight (−1.3 kg) and insulin dose (−7.27 IU) without any increase in infections. DKA analysis was not performed.²⁸ In a further RCT from a single centre, 30 patients with type 1 diabetes on liraglutide and insulin were put on additional dapagliflozin or placebo.²⁹ In the dapagliflozin group HbA_{1c} fell by 0.66% from 7.8% (p<0.01), with no change in the placebo group after 12 weeks.

The European Medicines Agency has accepted the application of a marketing authorisation variation for dapagliflozin for use as an oral adjunct treatment to insulin in people with type 1 diabetes.³⁰

Cautions in prescribing SGLT-2 inhibitors in type 1 diabetes

Risk of diabetic ketoacidosis (DKA)

People with type 1 diabetes are characterised by their propensity to DKA in the absence of insulin. Insulin helps reduce glucose but also prevents lipolysis. SGLT-2 inhibitors reduce glucose but have been associated with reports of ketoacidosis in people with type 1 diabetes and some people with type 2 diabetes through mechanisms which are not yet fully understood. The current evidence is presented below.

A study based on the US Food and Drug Administration Adverse Event Reporting System (FAERS) showed that the proportional reporting ratio of DKA in patients on SGLT-2 inhibitors was 7.9, was higher for type 1 diabetes and in women, with a wide range of age and body weight. Duration of treatment varied and death was reported in 37 individuals (1.54%).³¹

Peters *et al* reported a series of case reports of DKA in patients taking SGLT-2 inhibitors. Thirteen cases of DKA were observed in nine patients (seven with type 1 diabetes and two with type 2 diabetes). Four patients had recurrent episodes.³²

A post hoc re-evaluation of 17,000 patients who participated in the canagliflozin development programme has been reported. Twelve cases of DKA were reported, four (0.07%) in the canagliflozin 100 mg group, six (0.11%) in the canagliflozin 300 mg group and two (0.03%) in the placebo comparator group. Six of the participants (50%) were reported to have either type 1 diabetes or latent autoimmune diabetes of adults (LADA).³³

Another study by Perkins *et al* is an eight-week open-label proof of concept trial using SGLT-2 inhibitors in type 1 diabetes. Two of the 40 patients with type 1 diabetes (5%) had symptomatic ketosis or DKA.³⁴ There have been a few other case reports of DKA in patients with type 1 diabetes who took SGLT-2 inhibitors.³⁵⁻³⁷

Putative mechanism of ketogenesis

The reason for the small but not insignificant rise in DKA in people taking SGLT-2 inhibitors is poorly understood. Several mechanisms have been suggested including excessive dose reduction of insulin, a tendency towards ketosis, a shift in substrate metabolism with increased reliance on free fatty acids and ketone bodies rather than glucose and pyruvate.³⁸ Finally there is a

Table 1 Summary of evidence for SGLT-2 inhibitors in type 1 diabetes

Author (year)	Patient features: age (years), BMI (kg/m ²), n	Type of study and duration	SGLT-2 inhibitor used vs. placebo plus insulin	Results	DKA (where reported)
Henry (2015) ²⁰	Age 18–65, BMI 24.8 (n=70)	RCT (2 weeks)	Dapagliflozin 10 mg	↑ urine glucose (109.10 g/24 h). No increase in hypoglycaemia	None
Pieber (2015) ²¹	Age 18–65, BMI 25.7 (n=75)	RCT (4 weeks)	Empagliflozin 25 mg	↓ insulin dose (−0.98 IU). No increase in hypoglycaemia. ↑ ketones in 2 patients (not an adverse event)	None
Dandona (2017) ²²	Age 18–75, BMI 28.3 (n=833)	RCT (24 weeks)	Dapagliflozin 5 and 10 mg	↓ HbA _{1c} (−0.42% and −0.45%). ↓ insulin dose (−8.8% and 13.2%). ↓ body weight (−2.96% and 3.72%). No increase in hypoglycaemia (79%, 79% and 80%)	Similar in all groups 5 mg: 4 of 277 10 mg: 5 of 296 Placebo: 3 of 260 In patients who had DKA, insulin dose reduction vs. placebo in the above groups was −8.9%, −25.3% and −7.8% at the time of DKA
Famulla (2017) ²³	Age 18–65, BMI 18.5–35 (n=75)	RCT (4 weeks)	Empagliflozin 2.5, 10 and 25 mg	↓ mean glucose under the median continuous glucose monitoring curve (−12.2, −30.3 and −33.0 mg/dL.h). ↓ glucose variability	None
Rodbard (2017) ²⁴	Age 25–65, BMI 21–35 (n=351)	RCT (18 weeks)	Canagliflozin 100 and 300 mg	↓ mean glucose (−1.2, −0.7) with more time spent within target glucose range than outside	None
Henry (2015) ²⁵	Age 25–65, BMI 21–35 (n=351)	RCT (18 weeks)	Canagliflozin 100 and 300 mg	↑ proportion of patients achieving HbA _{1c} reduction of >0.4% without any increase in body weight (36.9% and 41.4% vs. 4.5%)	↑ DKA (4.3% and 6% vs. 0)
Biester (2017) ²⁶	Age 12–21, BMI 18–35 (n=33)	Randomised crossover single dose study (24 hours)	Dapagliflozin 10 mg	↓ insulin dose (13.6%) and ↑ glucose excretion (610%) irrespective of baseline HbA _{1c}	None; 5 treated with dapagliflozin vs. 1 placebo treated patient had increase in betahydroxybutyrate levels

possibility that ketogenesis could occur due to the direct action of SGLT-2 inhibitors on human pancreatic alpha cells increasing glucagon secretion.^{39,40} As the glucose concentrations in some of these patients can be close to target levels, the diagnosis of DKA can be delayed or missed.

Effect of insulin dose reduction on ketosis

Insulin deficiency seems to be related to ketoacidosis in patients with type 1 diabetes taking SGLT-2 inhibitors. A post hoc exploratory analysis of these patients has shown that ketone formation is greater when the insulin dose reduction is >20% compared with an insulin dose reduction of <20%.⁴¹ Similarly, insulin pump failure and missed insulin doses were the most frequent risk factors in the cases of DKA seen in the most recent study.²² In another small study in patients with type 1 diabetes using liraglutide and SGLT-2 inhibitors, two patients developed DKA. Both patients had a reduction in insulin doses of >20% and both events occurred within 48 hours of dose titration of dapagliflozin from 5 mg to 10 mg daily.³⁰ In addition, one patient had consumed a large amount of alcohol which is likely to be a factor in the development of euglycaemic ketoacidosis.

Risk of amputations and stroke

The risk of amputations and stroke remains unclear with the available current evidence. Canagliflozin in people with type 2 diabetes was associated with a higher rate of amputations mainly at the level of the toe and metatarsals.⁵ There was a higher rate of fractures in the CANVAS study but not in the CANVAS-R study.⁵ A recent meta-analysis has confirmed an excess risk of amputations with canagliflozin but not with other SGLT-2 inhibitors.⁴² Numerically, empagliflozin increased but canagliflozin reduced strokes in patients with type 2 diabetes, although both numbers were not significant and a subsequent meta-analysis is reassuring.^{3,5,43}

Risk of dehydration

As the mechanism of action of SGLT-2 inhibitors leads to glycosuria, they act as mild diuretics. Precautions should therefore be taken in individuals who are at risk of dehydration and acute kidney injury because of old age or co-morbidities.

Conclusions

SGLT-2 inhibitors are currently not licensed or recommended in people with type 1 diabetes. However, they may be an effective adjunct



Key messages

- SGLT-2 inhibitors are currently neither licensed nor recommended in people with type 1 diabetes.
- While the management of type 1 diabetes requires insulin treatment, monitoring and education, SGLT-2 inhibitors may be a potential adjunct in improving glycaemic control with the additional benefit of weight loss.
- SGLT-2 inhibitors may be associated with diabetic ketoacidosis and certain circumstances appear to increase this risk. SGLT-2 inhibitors should therefore be used with caution and with regular monitoring.
- Higher amputation rates and fractures have been reported in one SGLT-2 inhibitor outcome trial and hence these drugs should be used with caution in patients with peripheral vascular disease, foot ulcers or previous amputations and stopped if there are any signs of vascular insufficiency in the lower limbs.

in improving glycaemic control in people with type 1 diabetes who are on insulin treatment.

SGLT-2 inhibitors are well tolerated with very few side effects including urinary and genital infections, dehydration and DKA. In general, the rate and prevalence of DKA in people with type 1 diabetes taking SGLT-2 inhibitors is too low to quantify exactly but may not be insignificant. In patients with type 1 diabetes taking SGLT-2 inhibitors, it would make pragmatic sense to anticipate and monitor for possible DKA in situations known to precipitate metabolic decompensation (injury, infections, myocardial infarction, stroke, insulin deficiency, other stressful events and catabolic states). There should be prompts to identify patients attending emergency departments or medical admissions units who are prescribed SGLT-2 inhibitors to warn of the possibility of euglycaemic DKA where the patient may be in DKA despite normal glucose levels. SGLT-2 inhibitors should be stopped in patients who are acutely ill or are admitted for elective surgery. SGLT-2 inhibitors should also be discontinued in patients who have developed DKA and should not be re-challenged unless a clear alternative cause of DKA is identified. Insulin doses should not be reduced >20% if SGLT-2 inhibitors are added to insulin regimens.

ABCD recommends that regular monitoring of blood glucose and ketones should be undertaken in patients taking these drugs to avoid hypoglycaemia as well as ketosis. The ABCD position statement may need revision after further results of the Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes trials (DEPICT 1 and 2) become available. DEPICT 1 was a double-blind, randomised, parallel-controlled, three-arm, phase 3 multicentre study carried out at 143 sites in 17 countries and reported results at 24 weeks. DEPICT 2 will provide safety and efficacy data at 52 weeks.⁴⁴

Conflict of interest None.

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