

# Association of British Clinical Diabetologists (ABCD) position statement on the use of sodium-glucose cotransporter-2 inhibitors in type 1 diabetes (updated 2019)

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## Abstract

**SGLT-2 inhibitors may be increasingly used in people with type 1 diabetes as new licenses are obtained. These drugs have the potential to improve glycaemic control in people with type 1 diabetes with the added benefit of weight loss, better control of blood pressure and more time in optimal glucose range. SGLT-2 inhibitors are associated with higher incidence of diabetic ketoacidosis without significant hyperglycaemia. The present ABCD position statement is to mitigate this risk and other potential complications in people taking these drugs. Particular caution needs to be exercised in people who are at risk of diabetic ketoacidosis due to low calorie diet, illnesses, injuries, starvation, excessive exercise, excessive alcohol consumption and reduced insulin administration among other precipitating factors for diabetic ketoacidosis.**

*Br J Diabetes* 2019;**19**:66-72

**Key words:** SGLT-2 inhibitors, type 1 diabetes, ketoacidosis, position statement

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

- One of the SGLT-2 inhibitors (dapagliflozin) is now licensed in people with type 1 diabetes with BMI >27 in the UK and is currently going through a NICE technology appraisal. ABCD

supports the NICE guidelines for management of type 1 diabetes and this position statement will be updated as soon as the results of technology appraisal are published.<sup>1</sup>

- SGLT-2 inhibitor treatment may be a useful adjunct to achieve lower HbA<sub>1c</sub>, increased time in optimal glucose range and lower glucose variability with the added benefit of weight loss and lower insulin dose without increasing the incidence of hypoglycaemia in people with type 1 diabetes who are overweight and with poorly controlled diabetes.
- ABCD recommends that any use of SGLT-2 inhibitors in type 1 diabetes and in people with diabetes on insulin must be under regular supervision by a specialist clinician with careful monitoring and support from a diabetes team. ABCD supports the international consensus on risk management of diabetic ketoacidosis (DKA) in people with type 1 diabetes treated with SGLT-2 inhibitors.<sup>2</sup>
- All people with diabetes should receive adequate education about how to prevent, recognise and treat DKA reinforced with educational prompts (eg, wallet card, fridge magnets, etc).
- People with diabetes should be reminded of the precipitating factors for DKA – ie, excessive carbohydrate restriction, excessive alcohol, use of illicit drugs, surgical procedures, vigorous exercise, vomiting, acute medical illness including infections and infarctions, insulin pump failure, missed or reduced insulin doses, travel with disrupted insulin regimen/schedule.
- People with diabetes should be informed that DKA has been reported in about 4% per year in people with diabetes taking SGLT-2 inhibitors, particularly those in whom the insulin dose was reduced by more than 20%. Many of these people with diabetes had normal or only mildly raised blood glucose levels.
- ABCD recommends stopping or discontinuing SGLT-2 inhibitors before any surgical or medical procedures (ideally for 3 days), and in people with diabetes who are acutely ill, hospitalised, unable to eat or have any nausea, vomiting or abdominal discomfort.
- ABCD recommends withholding SGLT-2 inhibitors in people with diabetes whose insulin therapy is being changed (eg, injections to pump or manual mode to automode or automated insulin delivery).
- People with diabetes should be informed that higher amputation rates and fractures have been reported with one of the

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<https://doi.org/10.15277/bjd.2019.208>

SGLT-2 inhibitors (canagliflozin) in type 2 diabetes. SGLT-2 inhibitors should be used with caution in people with diabetes with peripheral vascular disease and stopped if any signs of peripheral vascular insufficiency are detected.

- Inform people with diabetes and educate all healthcare professionals that there have been six reports of Fournier's gangrene through the yellow card system until January 2019 in about 550,000 patient-years of treatment with SGLT-2 inhibitors in people with diabetes. This is a serious condition. Inform the patients to seek immediate medical attention if they experience pain, redness, swelling or discomfort in the perineal area. The treatment may include prompt antibiotics and may require surgical debridement.
- Inform people with diabetes that SGLT-2 inhibitors can cause mild diuresis and nocturia and the importance of maintaining adequate hydration to prevent dehydration which would increase the risk of hypovolaemia.
- The smallest possible dose of SGLT-2 inhibitors (eg, dapagliflozin 5 mg daily) should be used to minimise the risk of ketoacidosis.
- People with diabetes should be provided with a blood ketone monitor and trained to use it. Blood ketones should be checked if feeling unwell even when the capillary glucose levels are not particularly high. Blood ketones should also be measured with changes in diet, activity, insulin dose or events known to precipitate ketoacidosis such as infections, dehydration, surgery, injury, pump occlusion/malfunction or stress.
- ABCD recommends checking blood ketones before starting SGLT-2 inhibitors in type 1 diabetes. SGLT-2 inhibitors should be avoided if blood ketones are  $\geq 0.6$  mmol/L. Patients may become eligible if their ketone level reduces at a later date.
- If the ketones are above 0.6 mmol/L, SGLT-2 inhibitor should be discontinued if people with diabetes are already taking them. Additional insulin along with carbohydrate (15–30 g rapidly absorbed) and adequate oral hydration (300–500 ml/hourly) may avoid frank DKA and hospitalisation in people with diabetes with mild ketosis (0.6–1.5 mmol/L).
- People with diabetes with blood ketones above 1.6 mmol/L should seek medical attention. People with diabetes on an insulin pump should return to injectable insulin and trouble shoot the pump to ensure it is delivering insulin before restarting it. Some people with diabetes may require treatment with intravenous fluids and intravenous insulin.
- All people with diabetes should be issued a medical alert card and advised to carry it with them at all times. If the patient requires hospitalisation for treatment of ketoacidosis they should inform the medical personnel that they have type 1 diabetes, they are taking SGLT-2 inhibitors and they are at risk of DKA with normal glucose levels. There should be a low threshold for evaluation by blood gases, bicarbonate, anion gap and blood ketones.
- All healthcare professionals should be educated about the various SGLT-2 inhibitors, the risk of DKA associated with this class of medication even when the glucose levels are normal, and the need to treat them with glucose as well as insulin.
- In patients who are well controlled ( $HbA_{1c} < 58$  mmol/mol),

10–20% insulin dose reduction may be needed when SGLT-2 inhibitors are started but this should be accompanied by frequent capillary blood glucose monitoring or continuous glucose monitoring (CGM) along with easy access to a healthcare provider. Carbohydrate intake may need to be flexibly increased or decreased to avoid excessive or inadequate reduction in insulin dose.

- People with diabetes on very low insulin doses are not suitable for SGLT-2 inhibitors. ABCD suggests an insulin requirement of at least 0.5 IU/kg body weight before considering adjunct SGLT-2 inhibitors. Adjustment in insulin doses should be made every 24–48 hours.
- For people with diabetes who are less well controlled ( $HbA_{1c} \geq 58$  mmol/mol), no reduction in prandial or basal insulin may be necessary based on capillary blood glucose, CGM data, hypoglycaemia history and awareness.
- SGLT-2 inhibitors should not be used in pregnancy as pregnancy is associated with an increased risk of ketoacidosis which is known to be associated with a higher risk of fetal mortality.
- Insufficient data are currently available to advocate use in children and youths with type 1 diabetes <18 years of age and in people over 75 years of age.
- Some people with Latent Autoimmune Diabetes of Adulthood (LADA) may appear to have type 2 diabetes but may be quite insulin deficient and need to be treated with the same caution as people with type 1 diabetes.

### SGLT-2 inhibitors and current licensed indications

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. These drugs reduce blood glucose by preventing renal reabsorption of glucose, a mechanism which is insulin independent but glucose dependent.<sup>3</sup> An additional positive effect on lowering BP by natriuresis and weight loss might partly mediate the cardiovascular benefit recently observed in clinical trials in people with type 2 diabetes, although other mechanisms are possible.<sup>4–8</sup> 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 four SGLT-2 inhibitors licensed in the UK – dapagliflozin, canagliflozin, empagliflozin and ertugliflozin. Only dapagliflozin has obtained licence for type 1 diabetes in the UK. Sotagliflozin is a dual SGLT-1 and SGLT-2 inhibitor and will not be discussed in this article.

Ipragliflozin has recently been approved for use in Japan for adults with type 1 diabetes when co-administered with insulin.<sup>9</sup> There is increasing off-label use of these agents in type 1 diabetes, partly prompted by recent research studies. This has led to this revision of the 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 (ie,  $HbA_{1c} < 58$  mmol/mol (7.5%), BP <140/80

mmHg, cholesterol <5 mmol/L) is 29.9%, 74.8% and 70.3%, respectively. All three targets were achieved in only 18.6% of people with diabetes.<sup>1,10,11</sup>

There are considerable data showing higher cardiovascular<sup>12,13</sup> and renal risk<sup>14</sup> in people with type 1 diabetes. There is therefore scope for achieving tighter glycaemic control with appropriate insulin therapy as well as adjunct therapy for people with type 1 diabetes that may help improve risk factor control.

A previous ABCD position statement outlined the standards of care in people with type 1 diabetes.<sup>15</sup> 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.<sup>16</sup> This intensification, however, may increase the risk of hypoglycaemia, weight gain and associated adverse cardiovascular profile.<sup>17</sup>

Metformin is inexpensive and useful in some overweight people with type 1 diabetes but it does not improve HbA<sub>1c</sub> in the long term.<sup>18–20</sup> 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.<sup>21</sup> Dipeptidyl peptidase-4 (DPP4) inhibitors have not shown consistent positive effects on glycaemic control or glucose variability in people with type 1 diabetes.<sup>22</sup> By contrast, SGLT-2 inhibitors are oral glucose lowering drugs with potential in this group of people with diabetes and are being increasingly used off-label.<sup>23,24</sup>

### The evidence for SGLT-2 inhibitor use in type 1 diabetes

There is considerable emerging evidence for use of SGLT-2 inhibitors in type 1 diabetes, summarised in brief in Table 1.<sup>25–34</sup> A meta-analysis of three randomised controlled trials (RCTs) in people with type 1 diabetes on SGLT-2 inhibitors versus placebo added to insulin showed a significant reduction in fasting glucose (by 2.47 mmol/L) and insulin dose (–0.75 IU) without an increase in hypoglycaemia, infections or DKA in the SGLT-2 inhibitor group.<sup>35</sup> Another subgroup meta-analysis of RCTs in a similar group showed a significant reduction in HbA<sub>1c</sub> (–1.30%), weight (–1.3 kg) and insulin dose (–7.27 IU) without any increase in infections. DKA analysis was not performed.<sup>36</sup> The European Medicines Agency has accepted the application of a marketing authorisation variation for dapagliflozin 5 mg once daily for use as an oral adjunct treatment to insulin in people with type 1 diabetes who are overweight or obese.<sup>37</sup>

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.<sup>38</sup> In the dapagliflozin group HbA<sub>1c</sub> fell by nearly 8 mmol/mol from 62 mmol/mol with no change ( $p < 0.01$ ) in the placebo group in 12 weeks.

### Cautions in prescribing SGLT-2 inhibitors in type 1 diabetes

#### Risk of DKA

People with type 1 diabetes are characterised by their propensity to DKA in the absence of insulin. Insulin helps reduce blood glucose

but also prevents lipolysis. SGLT-2 inhibitors reduce glucose but have been associated with reports of ketoacidosis in people with type 1 and some people with type 2 diabetes through mechanisms which are not yet fully understood. The latest evidence is presented as follows.

A study based on the US Food and Drug Administration Adverse Event Reporting System (FAERS) showed that the proportional reporting ratio of DKA in people with diabetes on SGLT-2 inhibitors was 7.9, was higher for type 1 diabetes and women, in a wide range of age and body weight. Duration of treatment varied and death was reported in 37 individuals (1.54%).<sup>39</sup>

Peters *et al* reported a series of case reports of DKA in people with diabetes taking SGLT-2 inhibitors. Thirteen cases of DKA were observed in nine people with diabetes. Seven people had type 1 diabetes and two had type 2 diabetes. Four people with diabetes had repeat episodes.<sup>40</sup>

A post-hoc re-evaluation of 17,000 people with diabetes who participated in the Canagliflozin Development Programme in people with type 2 diabetes has been published. Twelve cases of unadjudicated 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. 50% of cases were reported to have either type 1 diabetes or Latent Autoimmune Diabetes of Adults (LADA).<sup>41</sup>

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 people with type 1 diabetes (5%) had symptomatic ketosis or DKA.<sup>42</sup> There have been other case reports of DKA in people with type 1 diabetes with SGLT-2 inhibitor use.<sup>43–45</sup>

#### Putative mechanism of ketogenesis

The cause of a small but significant rise in DKA in people taking SGLT-2 inhibitors is insufficiently understood. Several mechanisms have been suggested including excessive dose reduction of insulin, a shift in substrate metabolism with increased reliance on free fatty acids and ketone bodies rather than glucose and pyruvate.<sup>46</sup> Finally, there is a possibility that ketogenesis could occur due to direct action of SGLT-2 inhibitors on human pancreatic alpha cells increasing glucagon secretion.<sup>47,48</sup> SGLT-2 inhibitors are also thought to reduce renal clearance of ketone bodies.<sup>49</sup> The development of DKA is likely to be a combination of these.

The glucose concentration in a proportion of these people with diabetes with overt DKA can be close to target levels because of SGLT-2 inhibitor action.<sup>40,50</sup> The diagnosis of DKA can therefore be delayed or missed.

#### Effect of insulin dose reduction on ketosis

Insulin deficiency seems to be related to ketoacidosis in people with type 1 diabetes taking SGLT-2 inhibitors. A post hoc exploratory analysis of these people has shown that ketone formation is more when insulin dose reduction is >20% compared with when it is <20%.<sup>51</sup> Similarly, insulin pump failure and missed insulin doses were the most frequent risk factors in the cases of DKA seen in a recent study.<sup>27</sup> In another small study in

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

Author year	Age (years)	BMI, mean or range (kg/m <sup>2</sup> )	N	Type of study and duration	SGLT-2 inhibitor used vs. placebo plus insulin	Main results	DKA (where reported)
Henry <sup>25</sup> 2015	18–65	25.8	70	RCT (2 weeks)	Dapagliflozin 10 mg	↑ urine glucose (88 g/24 h). No increase in hypoglycaemia. 24-h daily average blood glucose (–2.29 vs. –1.13 mmol/L), mean amplitude of glucose excursion (–3.77 vs. –0.45 mmol/L) and mean change in daily insulin dose (–16.2% vs. –1.7%) was greater with dapagliflozin compared with placebo	None
Pieber <sup>26</sup> 2015	18–65	25.7	75	RCT (4 weeks)	Empagliflozin 25 mg	↓ insulin dose (–0.98 IU). No increase in hypoglycaemia. ↑ ketones in 2 people with diabetes	None
Dandona <sup>27</sup> 2017	18–75	28.3 and 28.1	833	RCT (24 weeks)	Dapagliflozin 5 and 10 mg	↓ HbA <sub>1c</sub> (–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%). Percentage of continuous glucose monitoring readings within range increased from 44.6% to 54.6% vs. no change in the placebo group	Similar in all groups 5 mg: 4 (due to insulin pump failure in 2, missed insulin dose in 1 and cause unidentified in 1) of 277 10 mg: 5 (due to insulin pump failure in 1, missed insulin dose in 3 and excessive alcohol intake in 1) of 296 Placebo: 3 (due to insulin pump failure in 1, missed insulin dose in 1 and stress in 1) of 260 In people with diabetes who had DKA insulin dose reduction vs. placebo in the above groups was –8.9%, –25.3% and –7.8% respectively at the time of DKA
Mathieu <sup>28</sup> 2018	18–75	27.3 and 27.8	813	RCT (24 weeks)	Dapagliflozin 5 and 10 mg	↓ HbA <sub>1c</sub> (–0.37% and 0.42%) ↓ insulin dose (–10.78% and 11.08%) ↓ body weight (–3.21% and 3.74%). No increase in hypoglycaemia. More CBG readings in target range	2.6% and 2.2% vs. 0% in placebo
Dandona <sup>29</sup> 2018	18–75	28.3 and 28.1	833	RCT (52 weeks)	Dapagliflozin 5 and 10 mg	↓ HbA <sub>1c</sub> (–0.33% and 0.36%) ↓ body weight (–2.95% and 4.54%). No increase in hypoglycaemia	DKA 4% and 3.4% vs. 1.9% in placebo
Rosenstock <sup>30</sup> 2018	Above 18	27.8 to 29.5	1707	RCT (26 to 52 weeks)	Empagliflozin 2.5, 10 and 25 mg	↓ HbA <sub>1c</sub> (–0.28%, 0.54% and 0.53%) ↓ insulin dose (–6.4%, 13.3% and 12.7%) ↓ body weight (–1.8, 3.0 and 3.4 kg). No increase in hypoglycaemia. ↑ glucose time in range	DKA 0.8%, 4.3% and 3.3% vs. 1.2% in placebo
Famulla <sup>31</sup> 2017	18–65	24.7, 27.4 and 25.4	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. ↑ time in target glucose range (3.9–10.0 mmol/L)	None
Rodbard <sup>32</sup> 2017	25–65	21–35	351	RCT (18 weeks)	Canagliflozin 100 and 300 mg	↓ mean glucose (–1.2, –0.7) and glucose variability with more time spent within target glucose range (3.9–10.0 mmol/L) than outside. Improved quality of life reported in canagliflozin group.	Not reported
Henry <sup>33</sup> 2015	25–65	28.0 and 28.1	351	RCT (18 weeks)	Canagliflozin 100 and 300 mg	↑ proportion of people with diabetes achieving HbA <sub>1c</sub> reduction of over 0.4% without any increase in body weight (36.9% and 41.4% vs. 4.5%)	↑ DKA (4.3% and 6% vs. 0% for placebo)
Biester <sup>34</sup> 2017	12–21	18–35	33	Randomised crossover single-dose study (24 hours)	Dapagliflozin 10 mg	↓ insulin dose (13.6%) and ↑ glucose excretion (610%) irrespective of baseline HbA <sub>1c</sub> .	None. 5 treated with dapagliflozin vs. 1 placebo treated patient had ↑ beta-hydroxybutyrate levels

CBG, capillary blood glucose; DKA, diabetic ketoacidosis; RCT, randomised controlled trial

people with type 1 diabetes using liraglutide and SGLT-2 inhibitors, two people developed DKA. Both of them had a reduction in insulin doses >20% and both events occurred within 48 hours of dose titration of dapagliflozin from 5 mg to 10 mg daily.<sup>38</sup> One patient had consumed a large amount of alcohol which was likely to be a precipitating factor in the development of euglycaemic ketoacidosis.

#### ***Effect of SGLT-2 inhibitor dose on ketosis***

Lower doses of SGLT-2 inhibitors are associated with reasonable efficacy but a lower incidence of DKA.<sup>27,28</sup> Empagliflozin 2.5 mg dose was associated with a DKA rate comparable to placebo.<sup>30</sup>

#### ***Ketone monitoring***

ABCD recommends capillary blood ketone monitoring by people with diabetes as a measure to diagnose early ketosis.<sup>52</sup> Urine ketone monitoring is not advisable due to the time lag between blood and urine ketone detection, possible difficulty in obtaining urine, and the fact that urine measures only acetoacetate (and not betahydroxybutyrate), which might paradoxically rise as betahydroxybutyrate, measured by capillary blood ketone, oxidises to acetoacetate, measured by urine ketone strips giving the false impression that the DKA is not resolving.<sup>53</sup> People with diabetes should not rely on a single measurement and should perform repeat testing for confirmation of evolution or resolution of ketosis.<sup>2</sup> ABCD recommends performing capillary blood ketone monitoring before starting any patient with type 1 diabetes on adjunctive treatment with SGLT-2 inhibitors, in situations that are known to precipitate DKA and in the presence of illness or symptoms of DKA. People with diabetes taking SGLT-2 inhibitors should be reminded to check their blood ketones irrespective of their blood glucose when they feel unwell as ketoacidosis can occur with normal glucose levels in this group.

#### ***Suspending SGLT-2 inhibitor treatment to reduce the risk of DKA***

ABCD recommends withholding SGLT-2 inhibitors in situations that are known to precipitate or worsen DKA (eg, starvation, alcohol, injury, infection, acute illness, inability to eat and drink, dehydration, elective or emergency surgery, missed or unavailable insulin, pump failure, change in insulin regimen or mode of delivery or a medical procedure) for as long as the precipitant is present. The restriction may typically last for 3–7 days and will need to be individualised based on the risk of DKA and the ongoing presence of any precipitant. It may be prudent to stop SGLT-2 inhibitors for 6 weeks or more in an occasional obese patient with type 1 diabetes who is being prepared for obesity surgery or is on a very low calorie diet.

#### ***Managing DKA in people with diabetes taking SGLT-2 inhibitors***

DKA should be suspected in any person with diabetes taking SGLT-2 inhibitors if they have symptoms like nausea, vomiting, excessive thirst, tiredness, loss of appetite, malaise, weakness and rapid breathing or difficulty breathing. Ketones should be measured in blood and urine ketone testing is not reliable. Blood



#### **Key messages**

- One of the drugs of the SGLT-2 inhibitor class (dapagliflozin) is now licensed for overweight people with type 1 diabetes and is currently going through a NICE technology appraisal
- While the management of type 1 diabetes requires insulin treatment, monitoring and education, SGLT-2 inhibitors may offer a potential adjunct to insulin treatment by improving glycaemic control with the additional benefits of weight loss, blood pressure and time in optimal glucose range
- SGLT-2 inhibitors may additionally 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 inhibitor use is associated with diabetic ketoacidosis without significant hyperglycaemia and certain circumstances increase this risk. Individuals should be counselled about this risk prior to initiation and at every other opportunity. These agents should be used with caution and with regular monitoring
- SGLT-2 inhibitors should be stopped in clinical situations which are known to induce ketoacidosis. These include (but are not limited to) starvation, very low calorie diets, acute illnesses (particularly infections, myocardial infarction and stroke), injury, planned surgery or procedure requiring starvation, missed meals, stress, vomiting, dehydration, excessive exercise, excessive alcohol consumption, use of illicit drugs, missed or significantly reduced insulin doses, insulin pump malfunction or occlusion
- Higher amputation rates and fractures have been reported with canagliflozin use in type 2 diabetes. Alternative agents should be considered in people with diabetes with peripheral vascular disease, foot ulcers, neuropathy or previous amputations and the drug stopped if there are signs of significant vascular insufficiency in lower limbs
- There have been some reports of Fournier's gangrene in people with diabetes taking SGLT-2 inhibitors. People with diabetes experiencing pain, redness and discomfort in the perineal area with fever and malaise should immediately seek medical attention. Fournier's gangrene should be treated promptly by antibiotics and surgical debridement

glucose levels can be normal in spite of DKA in people with diabetes taking SGLT-2 inhibitors because of renal excretion of glucose.<sup>54</sup> Local protocols such as stopping SGLT-2 inhibitors, injecting bolus insulin, consuming 30 g carbohydrates and

hydration (STICH) can help prevent deterioration in the clinical condition promptly.<sup>55</sup>

### Risk of amputation and stroke

The risk of amputation and stroke remains unclear with the available current evidence. Canagliflozin in people with type 2 diabetes was associated with a higher rate of lower limb amputations mainly at the level of the toes and metatarsals.<sup>6</sup> There was a higher rate of fractures in the CANVAS study but not in the CANVAS-R study.<sup>6</sup> A recent meta-analysis has confirmed an excess risk of amputations with canagliflozin but not with other SGLT-2 inhibitors.<sup>56</sup> Empagliflozin increased but canagliflozin reduced strokes in people with type 2 diabetes, although neither was significant in a subsequent meta-analysis.<sup>4,6,57</sup>

### 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 by individuals who are at risk of dehydration and acute kidney injury because of old age, illness or co-morbidities and co-prescription of diuretics.

### Conclusions

Dapagliflozin is now licensed in overweight or obese people with type 1 diabetes in the UK and is going through a NICE technology appraisal. SGLT-2 inhibitors may be an effective adjunct in improving glycaemic control in people with type 1 diabetes who are on insulin treatment.

As a class these drugs are usually tolerated well 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 precisely but may not be insignificant. People with type 1 diabetes taking SGLT-2 inhibitors must be advised 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). They should carry a medical alert card at all times. There should be prompts to identify people with diabetes attending Emergency Departments, Medical Admissions and Intensive Care Units who are prescribed SGLT-2 inhibitors to warn of the possibility of euglycaemic DKA where the patient may be in DKA despite relatively normal glucose levels. SGLT-2 inhibitors should be stopped in people with diabetes who are acutely ill or are admitted for elective surgery. SGLT-2 inhibitors should also be discontinued in people with diabetes who have developed DKA and should not be restarted unless a clear alternative cause of DKA is identified. Insulin doses should not be reduced by more than 20% when SGLT-2 inhibitors are prescribed.

ABCD recommends that regular monitoring of blood glucose and ketones should be undertaken in people with diabetes taking these drugs to avoid hypoglycaemia as well as ketosis.

**Conflict of interest** None declared.

**Funding** None.

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