SGLT inhibitors for people with type 1 diabetes

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Abstract
Despite significant advances in insulin therapy and monitoring technology, many with type 1 diabetes (T1DM) fail to achieve satisfactory glycaemic control and it remains a disease associated with significant morbidity and a reduced life expectancy. Adjunctive therapies which improve glycaemic control while reducing the risk of hypoglycaemia and weight gain are needed, and SGLT inhibitors have emerged as a potential candidate by virtue of their unique insulin-independent mechanism of action. There is now substantial evidence for their efficacy in T1DM, but with an increased risk of diabetic ketoacidosis. Dapagliflozin and sotagliflozin have recently been approved for use in Europe for type 1 diabetes. SGLT inhibitors will not be suitable for all with T1DM so careful selection of individuals who may benefit is important, with strategies in place to mitigate the risk of ketoacidosis. Copyright © 2019 John Wiley & Sons.

Key words
type 1 diabetes; SGLT inhibitors

Introduction
While significant advances have been made since insulin became available to treat type 1 diabetes (T1DM), it remains a disease associated with significant morbidity and reduced life expectancy.1 The mainstay of treatment is insulin replacement therapy yet despite the availability of analogue insulins, structured education and new technologies, many fail to achieve satisfactory glycaemic control.2 Data from the Scottish Diabetes Survey from 2017 show that only a quarter of people with T1DM have an HbA1c below the recommended target of 58mmol/mol; 42% are between 58–74mmol/mol and 33% are greater than 75mmol/mol.3 Furthermore, targets recommended by the National Institute for Health and Care Excellence (NICE) and the American Diabetes Association (ADA) are even more stringent; NICE recommends an HbA1c of 48mmol/mol,4 the Scottish Intercollegiate Guidelines Network (SIGN) and the ADA recommend 53mmol/mol where possible, so a substantial number with T1DM are not at target.5,6

What are the barriers to satisfactory glycaemia control in T1DM?
The Diabetes Control and Complications Trial (DCCT)7,8 and its follow up study, Epidemiology of Diabetes Interventions and Complications (EDIC),9 demonstrated that strict glycaemic control in patients with T1DM reduced the risk of microvascular and cardiovascular complications. In the DCCT, for every 10% reduction in HbA1c, there was a 35–40% reduction in the risk of microvascular complications. DCCT/EDIC also found that intensive glycaemic control early in the disease has beneficial durable effects both in terms of microvascular and cardiovascular complications, a phenomenon which has been termed as metabolic memory or glycaemic legacy.10 However, intensive insulin therapy was often associated with adverse effects of increased hypoglycaemia and weight gain.

Hypoglycaemia is common with insulin therapy and presents a major barrier to achieving glycaemic control.11 People with T1DM experience, on average, two episodes of hypoglycaemia per week, and the annual prevalence of severe hypoglycaemia per week, and the annual prevalence of severe hypoglycaemia is reported to be between 30–40%.12 In addition to its acute physiological effects, hypoglycaemia can have a significant psychological impact with anxiety and fear of episodes, which in turn can result in less tight glycaemic control in order to avoid hypoglycaemia. Hypoglycaemia is also estimated to account for between 6–10% of all diabetes-related mortality,13 and
may be associated with increased cardiovascular risk.\textsuperscript{14} Intensive insulin therapy is also associated with excess weight gain: an important issue given the increasing prevalence of obesity and over-weight in people with T1DM.\textsuperscript{15} In Scotland, 63\% of people with T1DM are overweight or obese\textsuperscript{6} with similar figures found in cohort studies elsewhere.\textsuperscript{15} This in part reflects the trend seen in the general population and is a consequence not only of factors such as high-calorie diets and sedentary lifestyles but also the effect of intensive insulin therapy. Obesity is associated with a multitude of adverse outcomes including cardiovascular disease, cancer, depression and poor quality of life. Weight gain is also associated with insulin resistance which can result in the development of so-called ‘double diabetes’ as well as causing endothelial dysfunction, oxidative stress and increased cardiovascular risk.\textsuperscript{16}

**Adjunctive therapies in T1DM**

There is a need for possible adjunctive therapies in the management of T1DM. Such therapies should improve glycaemic control while reducing adverse effects such as weight gain and hypoglycaemia. Several potential adjuncts have been investigated to date but have been associated with significant side effects such as gastrointestinal upset or hypoglycaemia, or have had minimal effect on HbA1c.

Pramlintide, a synthetic amylin analogue, is licensed in the US for use in T1DM in addition to a basal bolus regimen. Amylin is co-released with insulin from beta cells and slows gastric emptying and reduces glucagon levels. It results in a reduction in post-prandial hyperglycaemia with a consequent moderate reduction in HbA1c and has some effect on satiety which can result in weight loss. The clinical use of pramlintide is limited and has some effect on satiety.\textsuperscript{17–19} The use: they should only be used in patients with control of blood glucose levels and increased GLP-1 levels. When maintained on a glucose diet, they had lost weight, reduced oral intake and poor weight gain. However, mice heterozygous for the SGLT-1 mutation had a normal weight and oral intake but demonstrated an increase in GLP-1 in response to a glucose-containing meal. This work suggested that partial SGLT-1 inhibition may have some therapeutic benefit in improving glycaemic control without causing the gastrointestinal upset typically associated with SGLT-1 inhibition.\textsuperscript{29}

**SGLT inhibitors as adjunctive therapy**

Several of the currently licensed SGLT-2 inhibitors have completed clinical trials in T1DM and are summarised in Table 1. In February 2019, dapagliflozin became the first SGLT-2 inhibitor to gain approval from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) for use in combination with insulin for the treatment of T1DM.\textsuperscript{30} Shortly after, sotagliflozin was also given a positive opinion from the EMA CHMP.\textsuperscript{31} By contrast, the US Food and Drug Administration (FDA) rejected a submission for the use of sotagliflozin in T1DM.\textsuperscript{32} The approval for use of dapagliflozin and sotagliflozin is accompanied by strict criteria regarding the intended use: they should only be used in those with a BMI above 27kg/m\textsuperscript{2} and must be initiated and supervised by specialist physicians.\textsuperscript{30,31}

**Studies in T1DM**

The safety and efficacy of dapagliflozin in adults with T1DM has been investigated in two large randomised controlled phase 3 trials: DEPICT-I
and DEPICT-2 (Dapagliflozin evaluation in patients with inadequately controlled type 1 diabetes). These were both 24-week studies which evaluated doses of 5mg and 10mg dapagliflozin on HbA1c, total insulin dose, body weight and safety (Table 1).33,34

The EASE (Empagliflozin as adjunctive to insulin therapy) programme, which included a phase 2 study as well as two double-blind, placebo-controlled phase 3 trials, evaluated the safety and efficacy of empagliflozin as adjunctive therapy in T1DM. Standard doses of 10mg and 25mg were investigated as well as a lower 2.5mg dose. EASE-3 also included a continuous glucose monitoring substudy.35,36

The safety and efficacy of sotagliflozin in T1DM was assessed in the inTANDEM-1–3 studies (detailed in Table 1). inTANDEM-1 was a 52-week trial which randomised North American adults with T1DM to placebo, 200mg sotagliflozin or 400mg sotagliflozin after six weeks of insulin optimisation.37 inTANDEM-2 was its European counterpart and inTANDEM-3 was a double-blind trial where participants were randomised to placebo or 400mg sotagliflozin for 24 weeks.38,39

Canagliflozin has not been studied in T1DM as extensively as other SGLT-2 inhibitors. There has been one large-scale, randomised double-blind controlled trial where a total of 351 patients were randomised to 100mg or 300mg canagliflozin or placebo in combination with insulin.40

Diabetic ketoacidosis
Ketoacidosis is an important safety concern associated with the use of SGLT inhibitors. Post-marketing surveillance revealed several cases of DKA associated with SGLT-2 inhibitors in patients with T2DM

<table>
<thead>
<tr>
<th>Trial name/drug</th>
<th>No.</th>
<th>Study duration (weeks)</th>
<th>Treatment groups</th>
<th>Change in HbA1c (%)</th>
<th>Change in insulin dose (%)</th>
<th>Change in body weight (kg)</th>
<th>Hypoglycaemia (total no. of events)</th>
<th>Severe hypoglycaemia (no. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEPICT-133 dapagliflozin</td>
<td>833</td>
<td>24</td>
<td>5mg 10mg Placebo</td>
<td>-0.48 -0.46</td>
<td>-5.5 -9.8</td>
<td>-2.29 -2.98</td>
<td>220 (79%) 235 (79%) 207 (80%)</td>
<td>21 (8%) 19 (6%) 19 (7%)</td>
</tr>
<tr>
<td>DEPICT-234 dapagliflozin</td>
<td>815</td>
<td>24</td>
<td>5mg 10mg Placebo</td>
<td>-0.37 -0.42</td>
<td>-10.8 -11.1</td>
<td>-3.21 -3.74</td>
<td>227 (81.9%) 241 (81.4%) 212 (81.5%)</td>
<td>29 (10.5%) 25 (8.4%) 30 (11.5%)</td>
</tr>
<tr>
<td>EASE-135 empagliflozin</td>
<td>75</td>
<td>28 days</td>
<td>2.5mg 10mg 25mg Placebo</td>
<td>-0.35 -0.36 -0.49</td>
<td>-0.074 -0.094 -0.084</td>
<td>-1.5 -1.8 -1.9</td>
<td>16 (84.2%) 13 (68.4%) 17 (94.4%) 17 (89.5%)</td>
<td>0* 0 0</td>
</tr>
<tr>
<td>EASE-236 empagliflozin</td>
<td>730</td>
<td>52</td>
<td>10mg 25mg Placebo</td>
<td>-0.37 -0.45</td>
<td>-12 -12.9</td>
<td>-3.2 -3.6</td>
<td>223 (100%) 239 (96%) 238 (97.9%)</td>
<td>20 (4.1%) † 13 (2.7%) 15 (3.1%)</td>
</tr>
<tr>
<td>EASE-336 empagliflozin</td>
<td>975</td>
<td>26</td>
<td>2.5mg 10mg 25mg Placebo</td>
<td>-0.27 -0.44 -0.50</td>
<td>-6.4 -9.5 -12.6</td>
<td>-1.8 -3.0 -3.4</td>
<td>237 (98.3%) 241 (97.1%) 237 (96.7%) 235 (97.5%)</td>
<td>3 (1.2%) NR NR 6 (2.5%)</td>
</tr>
<tr>
<td>TANDEM-137 sotagliflozin (US)</td>
<td>793</td>
<td>52</td>
<td>200mg 400mg Placebo</td>
<td>-0.25 -0.31</td>
<td>-8.0 -12.6</td>
<td>-3.14 -4.32</td>
<td>260 (98.9%) 258 (98.5%) 266 (99.3%)</td>
<td>17 (6.5%) 17 (6.5%) 26 (9.7%)</td>
</tr>
<tr>
<td>TANDEM-238 sotagliflozin (Europe)</td>
<td>782</td>
<td>52</td>
<td>200mg 400mg Placebo</td>
<td>-0.37 -0.35</td>
<td>-6.3 -8.2</td>
<td>-2.18 -2.92</td>
<td>255 (97.7%) 260 (98.9%) 252 (97.7%)</td>
<td>13 (5.0%) 6 (2.3%) 13 (5.0%)</td>
</tr>
<tr>
<td>TANDEM-339 sotagliflozin</td>
<td>1402</td>
<td>24</td>
<td>400mg Placebo</td>
<td>-0.46</td>
<td>-9.7</td>
<td>-2.98</td>
<td>673 (96.3%) 570 (95.3%)</td>
<td>21 (3%) 17 (2.4%)</td>
</tr>
<tr>
<td>Canagliflozin NCT02139943 phase 2 trial</td>
<td>351</td>
<td>18</td>
<td>100mg 300mg Placebo</td>
<td>-0.29 -0.25</td>
<td>8.9 12.9</td>
<td>-2.6 -4.2</td>
<td>115 (98.3%) 116 (99.1%) 113 (96.6%)</td>
<td>3 (2.6%) 8 (6.8%) 2 (1.7%)</td>
</tr>
</tbody>
</table>

*For EASE-1, data reported as rates of hypoglycaemic episodes. †Individual data not provided: pooled EASE-2 and EASE-3 data. ‡Reported as units/kg.

Table 1. Summary of the main findings from clinical trials of canagliflozin, empagliflozin, dapagliflozin and sotagliflozin.
SGLT inhibitors for people with type 1 diabetes

Box 1. Practical considerations

- SGLT inhibitors should not be used in patients who are poorly compliant with insulin therapy and have had previous episodes of diabetic ketoacidosis (DKA).
- Patients should monitor capillary blood glucose and ketones regularly and understand how to recognise DKA.
- Use lowest dose of SGLT inhibitor.
- Reduce prandial insulin by 10–20% initially and adjust doses of prandial and basal insulin based on frequent pre- and post-prandial glucose monitoring.
- Reassess insulin:carbohydrate ratios once established on SGLT inhibitor.
- Advise withholding SGLT inhibitor during intercurrent illness, and increase frequency of glucose and ketone monitoring.

Box 2. The STICH protocol for people with T1DM using SGLT inhibitors

1. Confirm ketosis.
2. Identify and address cause(s) of ketosis.
3. Apply STICH protocol:
   - a. Stop the SGLT inhibitor
   - b. Inject bolus insulin
   - c. Consume 30–60g carbohydrates
   - d. Hydrate
4. Recheck ketones every 3–4 hours.
5. Seek medical advice if ketosis does not improve or if symptoms of diabetic ketoacidosis appear.

and, consequently, both the FDA and EMA have published safety warnings of an increased risk of DKA in those being treated with this class of drug. Factors noted to predispose to DKA include intercurrent illness, reduction or withdrawal of insulin doses, and poor nutrition. 41,42 In individuals with T1DM, this may occur due to a lowering of insulin levels below those needed to suppress lipolysis and ketogenesis and reduced renal clearance of ketone bodies normally mediated by SGLT-2 receptors. As such, an important safety outcome in phase 3 trials in those with T1DM has been the occurrence of DKA.

DKA appears to occur more frequently in trial participants who have suffered intercurrent illness and in those using insulin pumps, most likely a consequence of infusion site failure. It has also been suggested that the increased risk of DKA in those with T1DM treated with SGLT inhibitors is because it can occur at lower glucose levels (11–12mmol/mol) preventing recognition of early metabolic decompensation from blood glucose measurements alone. 43

All trials have demonstrated a significant reduction in the total daily insulin requirements with the use of SGLT inhibitors in T1DM. In order to minimise the risk of DKA associated with a reduction in insulin, DEPICT studies recommended reducing insulin by up to 20% following the first dose, and subsequently up-titrating to baseline where possible. 33,34 In the EASE studies, the insulin regimen was to be kept stable during the first seven days of treatment and was then adjustable. 35,36 inTANDEM participants were asked to reduce prandial insulin by 30% with the first dose, then readjust according to capillary blood glucose. 35-39

In DEPICT-1, DKA occurred in four (1%) and five (2%) participants on 5mg and 10mg dapagliflozin, respectively; and in three (1%) participants on placebo. 33 In DEPICT-2, there were seven (2.6%), six (2.2%) and no (0%) cases of DKA in participants receiving 5mg dapagliflozin, 10mg dapagliflozin and placebo, respectively. 34

EASE-1 reported no cases of DKA and rates of hypoglycaemic episodes were similar between placebo and treatment groups. 38 In EASE-2 and 3, the pooled number of cases of DKA were 21, 18 and 6 for 10mg and 25mg empagliflozin and placebo, respectively. EASE-3 investigated a lower dose of 2.5mg and reported two and three cases of DKA for placebo and empagliflozin, respectively. 36

DKA occurred in nine (3.4%) and 11 (4.2%) participants receiving sotagliflozin 200 and 400mg, respectively; and in one (0.4%) receiving placebo in inTANDEM-1. 37 In inTANDEM-2 reported that 15 out of 782 (1.9%) had at least one episode of DKA compared to none in the placebo group. 38 inTANDEM-3 reported rates of DKA in the sotagliflozin and placebo groups of 3.0% (21 patients) and 0.6% (four), respectively. 39

In summary, the risk of DKA is small but significant and, despite encouraging safety data, it is important to be aware that the nature of clinical trials may not fully represent DKA in the general population. This risk may be higher, as clinical trials excluded those with a previous diagnosis of DKA and measures to mitigate the risk of DKA were used (participants were counselled with regard to: the risk of ketoacidosis; how to recognise DKA signs and symptoms; regular ketone testing etc) which may not be easily replicated in clinical practice. Real-world experience may yield different outcomes or greater numbers of DKA.

Practical aspects in the use of SGLT2 inhibitors in T1DM

Not all individuals with T1DM will benefit from treatment with SGLT inhibitors and the small but clinically significant risk of DKA is an important consideration. Mitigation strategies to reduce the risk of DKA will form an important part of their use. 44 DKA is more likely to occur in those with poor glycaemia control or with recurrent episodes of DKA, and SGLT inhibitors should not be used in this group. Individuals considered for this treatment option will need to be able to monitor blood glucose and capillary blood ketones regularly, and should be educated on how to monitor rising levels of each, in addition to recognising DKA. Using the lowest dose of SGLT inhibitor and reducing prandial insulin will minimise the risk of hypoglycaemia, and close attention to insulin to carbohydrate ratios after commencement will be required. These practical considerations are summarised in Box 1.

Minimising the risk of DKA

Education of both the individual being treated (and carers if relevant) and health care professionals will play an important role in reducing the risk of DKA associated with SGLT inhibitor use. This will include the provision of detailed written materials for both. Those treated should be encouraged to carry an
alert card to show to health care professionals at the time of illness. They should avoid situations likely to increase ketosis such as low carbohydrate diets, and should increase the frequency of ketone monitoring during periods of metabolic stress. It is important for both the individual being treated and health care professionals to be aware that DKA associated with the use of SGLT inhibitors may not present typically, and that glucose levels may remain within the normal range because SGLT inhibitors promote urinary excretion of glucose. DKA should be considered if the individual develops nausea, vomiting, abdominal pain or fatigue.

The STICH protocol has been proposed by Garg et al. as a means to mitigate the harm of DKA if it occurs during treatment with an SGLT2 inhibitor,45 (shown in Box 2). If ketosis is present, the individual on treatment should: (1) Stop SGLT inhibitor; (2) Inject insulin bolus; (3) Consume 30–60g carbohydrates; and (4) Hydrate with 200–500ml of fluid.45 Comprehensive guidance with regard to the safe use of SGLT inhibitors in T1DM has also been produced and covers patient selection, insulin dose adjustments, and initiation and discontinuation of SGLT inhibitors.44

Conclusions

Many with T1DM do not achieve their glycaemic targets and are limited by factors associated with intensive insulin therapy such as hypoglycaemia and weight gain. Recently, several agents have been investigated as potential adjunct therapies and SGLT inhibitors have shown great promise in clinical trials with positive effects in terms of HbA1c reduction and body weight. There remains an important concern regarding the small but significant risk of DKA and patient characteristics should be considered when initiating an SGLT inhibitor. Education of both the individual being treated and health care professionals will be important, using strategies such as STICH to minimise the risk of DKA. Dapagliflozin and sitagliptin have recently gained approval by the EMA for use as an adjunct to insulin in T1DM patients. Post-marketing surveillance will be critical in determining the real-world effects of SGLT inhibitors in this population.

Declaration of interests

Professor McKay has received honoraria for talks, advisory boards and support for attendance at conferences from: AstraZeneca, Boehringer Ingelheim, Napp, and Sanofi. Professor Fisher has received honoraria for talks, advisory boards and support for attendance at conferences from: AstraZeneca, Boehringer Ingelheim, Napp, and Sanofi. Dr Llano has no conflicts of interest to declare.

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