SGLT inhibitor adjunct therapy in type 1 diabetes

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Abstract
Non-insulin adjunct therapies in type 1 diabetes have been proposed as a means of improving glycaemic control and reducing risk of hypoglycaemia. Evidence to support this approach is, however, scant and few pharmacological agents have proved effective enough to become part of routine clinical care. Recent short-term Phase II trials and 24 week Phase III trials provide initial support for the use of sodium–glucose cotransporter (SGLT) inhibitors in type 1 diabetes. Two international, multicentre, randomised, controlled clinical trials, Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT-1) and inTandem3, have reported that SGLT inhibition with dapagliflozin and sotagliflozin, respectively, confer additional benefits in terms of a 5–6 mmol/mol (0.4–0.5%) reduction in HbA1c accompanied by weight loss and reductions in total daily insulin doses. The reduction in HbA1c does not come with a significantly increased risk of hypoglycaemia but does carry an increased risk of diabetic ketoacidosis and mycotic infections. These results suggest that SGLT inhibition will have a place in the management of type 1 diabetes. Longer-term clinical trials (≥52 weeks) and observational cohort studies are needed to determine any additional benefits or adverse effects of this adjunct therapy and to determine which group of patients may benefit most from this approach. In addition, use of SGLT inhibitors in routine type 1 diabetes care will require specific patient and healthcare professional educational packages to ensure patient safety and to minimise risk.

Keywords  Clinical trials · Diabetic ketoacidosis · GLP-1 receptor agonist · HbA1c · Hypoglycaemia · Insulin · Review · Sodium–glucose cotransporter inhibitors · Type 1 diabetes · Weight

Introduction
Chronic exposure to hyperglycaemia in type 1 diabetes carries an increased risk of microvascular [1] and macrovascular disease [2]. Intensive insulin therapy aimed at optimal glucose control can largely prevent or minimise these complications, especially when combined with appropriate blood pressure control and lipid-lowering therapy [1, 2]. Current insulin delivery systems are limited by peripheral drug delivery and lack of feedback inhibition. This, together with the impaired response to hypoglycaemia in type 1 diabetes, means that intensive insulin therapy is associated with increased glucose variability, weight gain and severe hypoglycaemia [3–5]. Hence, most individuals with type 1 diabetes do not achieve recommended glycaemic targets [6, 7] and overall life expectancy is still substantially lower than in the non-diabetic population [8]. Meeting the twin challenges of hyperglycaemia and hypoglycaemia in type 1 diabetes may require additional adjunct pharmacotherapies to complement insulin replacement [9].
Adjunct non-insulin pharmacological interventions in type 1 diabetes

Initial trials of adjunct therapy in type 1 diabetes were small, short-term and generally had unimpressive outcomes [9]. Pramlintide, currently licensed only in the USA, was one of few agents shown to be effective, but its beneficial effects on HbA1c and weight were small and the risk of hypoglycaemia was increased [10]. Of the dipeptidyl peptidase-4 inhibitors, sitagliptin is the most widely studied as adjunct therapy in type 1 diabetes, but no major benefit was seen in three 52 week RCTs [11–13]. More recently, two large multicentre RCTs, ADJUNCT ONE (N = 1400) [14] and REMOVAL (REducing with MetfOrmin Vascular Adverse Lesions; N = 428) [15], examined the effectiveness of the glucagon-like peptide-1 receptor agonist lixisenatide (1.2 mg and 1.8 mg doses) and metformin, respectively, as adjuncts to insulin therapy in type 1 diabetes. In ADJUNCT ONE, lixisenatide showed significant benefits over placebo in terms of HbA1c, weight and total insulin dose reduction. However, the impact on HbA1c was not impressive (mean 0.15–0.2% reduction) and the rates of symptomatic hypoglycaemia and hyperglycaemia with ketosis increased significantly. Accordingly, Novo Nordisk, the sponsor of the ADJUNCT trials, did not pursue a label indication for lixisenatide in type 1 diabetes. Similarly, despite the frequent off-label use of metformin in type 1 diabetes [9, 16], in the REMOVAL study it failed to significantly reduce carotid intima–media thickness (the primary endpoint) and early small reductions in HbA1c and body weight were not sustained [15].

In summary, while the rationale for adjunct therapy in type 1 diabetes is clear, there is little robust evidence to support the adjunctive use of currently available therapies.

Phase II clinical trials of SGLT inhibition in type 1 diabetes

Sodium–glucose cotransporters (SGLTs) are found predominantly in the mucosa of the small intestine (SGLT1) and the proximal tubules of the kidney (SGLT2 and SGLT1) [13]. SGLT2 inhibition reduces glucose reabsorption in the renal tubule, leading to increased glucose excretion. SGLT1 inhibition reduces dietary glucose and galactose absorption in the intestine and augments the release of gastrointestinal incretins. Selective SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin) or dual SGLT1/SGLT2 inhibitors (sitagliptin/empagliflozin) are therefore an attractive therapeutic proposition for diabetes because increased urinary glucose excretion will reduce hyperglycaemia and, through loss of energy (each gram of glucose lost is equivalent to 16.7 kJ [4 cal]), facilitate weight loss [17]. While there is an obvious place for such a therapy in type 2 diabetes, pre-clinical research in rodent models also suggest that these agents may be beneficial as an adjunct therapy in type 1 diabetes (e.g. [18, 19]).

In an open-label, proof-of-concept trial in 40 young adults with long-duration type 1 diabetes, Perkins et al reported on the effects of empagliflozin 25 mg once daily for 8 weeks. Participants were asked to reduce prandial and basal insulin by 30% on initiation of treatment [20], with further dose adjustments being made based on capillary glucose measures. Empagliflozin co-therapy reduced HbA1c by 4 ± 5 mmol/mol (0.3 ± 0.4%; mean ± SD) and total daily insulin requirements were decreased, largely as a result of a reduction in basal insulin (from 25.7 ± 10.6 to 19.5 ± 7.9 U/day, p < 0.0001) [20]. Mean body weight also decreased (from 72.6 ± 12.7 to 70.0 ± 12.3 kg, p < 0.0001) and, despite the fall in HbA1c, symptomatic hypoglycaemia <3.0 mmol/l and all hypoglycaemia <3.9 mmol/l measured using continuous glucose monitoring (CGM) were less frequent compared with baseline. Two participants withdrew early because of diabetic ketoacidosis (DKA) (associated with severe gastroenteritis in one and pump failure in the other).

In a placebo-controlled, double-blind, parallel-group study using empagliflozin 2.5 mg, 10 mg or 25 mg daily with insulin for 4 weeks, Pieber et al [21] found benefits in terms of HbA1c (4–5 mmol/mol [0.4%] reduction), total insulin dose (0.07–0.09 U/kg reduction) and weight (1.5–1.9 kg reduction) (all p < 0.05). Similarly, Henry et al randomly assigned 70 adults with type 1 diabetes (HbA1c 53–86 mmol/mol [7–10%]), stabilised on insulin, to receive dapagliflozin (1, 2.5, 5 or 10 mg) or placebo over 2 weeks [22]. Insulin doses were not proactively reduced but were adjusted based on capillary blood glucose for safety. Dapagliflozin increased glucosuria dose-dependently, with the highest dose (10 mg) resulting in a urinary glucose excretion of 88 g/24 h (95% CI 55, 121) [22]. This dose reduced 24 h average glucose (−2.29 mmol/l [95% CI −3.71, −0.87]) and mean amplitude of glycaemic excursion (−3.77 mmol/l [95% CI −6.09, −1.45]), both assessed by CGM. Total daily insulin dose was reduced by 16.2% (95% CI 0.5, 29.4) [22].

An 18 week, double-blind, Phase II randomised study involving 315 adults with long-duration type 1 diabetes assessed the effect of canagliflozin 100 mg or 300 mg daily vs placebo as adjunct therapy [23]. Participants initially down-titrated insulin doses by 10–20% (based on baseline HbA1c), followed by dose adjustments according to capillary blood glucose. Significant improvements in the following variables were produced by canagliflozin 100 mg and 300 mg, respectively (placebo-subtracted least mean squares differences from baseline): HbA1c (mean change −3.2 mmol/mol [−0.3%] and −2.7 mmol/mol [−0.3%]); body weight (mean change −3.4% and −5.3%); and total insulin dose (absolute mean change in total insulin dose −4.1 U/day [−8.9%] and −7.6 U/day [−12.9%]). The latter was largely driven by reductions in basal insulin. In this trial, DKA was experienced by 5.1% and 9.4% of the participants receiving canagliflozin 100 mg and
300 mg, respectively, and by none in the placebo arm. Rates of hypoglycaemia were broadly similar across all groups, although more episodes of severe hypoglycaemia occurred with canagliflozin 300 mg [23]. Based on these findings, further development of the programme for canagliflozin in type 1 diabetes was stopped.

Finally, in a 4 week randomised, placebo-controlled, double-blind trial in 33 adults with long-duration type 1 diabetes, Sands et al [24] studied the effect of the dual SGLT1/2 inhibitor sotagliflozin. Compared with placebo, HbA1c decreased by 5.3 mmol/mol (0.5%) (p ≤ 0.01) from baseline, as did total insulin daily dose (approximately 15%; p < 0.05). In contrast to selective SGLT2 inhibitors, this dual inhibitor was primarily associated with reduced bolus insulin (~26%, p < 0.01). Post-meal AUC for glucose and mean amplitude of glycaemic excursion were also significantly reduced, as was body weight (~1.7 kg vs -0.5 kg, p < 0.01). There was no increase in the rate of hypoglycaemia, although two participants experienced DKA, possibly due to pump failure [24].

### Phase III clinical trials with SGLT inhibitors in type 1 diabetes

The first two Phase III trials of SGLT inhibitors in type 1 diabetes were published in September 2017. In inTandem3 [25], a 24 week double-blind, placebo-controlled RCT, 1402 people with type 1 diabetes were randomised to receive either sotagliflozin (400 mg/day) or placebo after a 2 week single-blind run-in period (Table 1). Based on lessons learned from the Phase II studies, participants were instructed to reduce meal-time insulin by 30% with the first dose of study drug and then subsequently adjust insulin based on capillary blood glucose. Participants received information on the detection and treatment of DKA and were provided with blood ketone meters. The cohorts were well-matched at baseline and were mostly (88%) white adults (aged 42 ± 14 years) with long-duration type 1 diabetes (20 ± 12 years) and an average baseline HbA1c of 66 ± 10 mmol/mol (8.2 ± 0.9%) [21]. Sixty per cent of the participants were on multi-dose insulin (MDI) and 40% were on insulin-pump therapy. The pre-specified composite endpoint (HbA1c <53 mmol/mol [7.0%] at week 24, with no episodes of severe hypoglycaemia or DKA) was achieved in significantly more participants taking sotagliflozin (48 participants [6.9%] vs 23 [3.3%]) (Table 3). Documented hypoglycaemia and hypoglycaemia event rates were similar in both groups, although sotagliflozin-treated participants had a significantly lower event rate of hypoglycaemia <3.1 mmol/l. As expected, general mycotic infections and diarrhoea occurred more frequently with sotagliflozin vs placebo and a greater proportion of participants experienced one or more episodes of DKA (3.0% vs 0.6%) [21].

The 24 week data from two further ongoing clinical trials (inTandem1 and inTandem2) have been published as abstracts [26, 27] (Tables 1–3). Placebo-adjusted effects of sotagliflozin 200 mg and 400 mg in these two RCTs after 24 weeks were similar to those reported in inTandem3.

The second Phase III trial was the Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT-1) trial [28], a double-blind, parallel-controlled, three-arm, 24 week study in 833 individuals with type 1 diabetes, in which participants were randomised to receive dapagliflozin 5 mg or 10 mg or placebo (Table 1) after a run-in period of 8 weeks to optimise glycaemic control. Participants were asked to reduce both basal and bolus insulin by up to 20% on the day of study drug initiation and to adjust subsequent doses based on self-monitoring of blood glucose four to six times daily. Two periods (each lasting 2 weeks) of blinded CGM were also included. Participants received education on DKA and were provided with blood ketone meters. As in inTandem3, most participants were white, with a mean age of 42.5 (±13.9) years and a duration of type 1 diabetes of 20.3 (±11.8) years (Table 1) [28]. In this trial, the addition of dapagliflozin (5 mg or 10 mg) vs placebo to type 1 diabetes therapy resulted in a significant reduction HbA1c (mean change from baseline at week 24−5 mmol/mol [−0.42%] [95% CI −0.56, −0.28] and −4 mmol/mol [−0.45%] [95% CI −0.58, −0.31] for dapagliflozin 5 mg and 10 mg, respectively, both p < 0.0001 vs placebo) (Table 2). This improvement in HbA1c was accompanied by significant reductions in body weight (mean change at week 24 was −2.98 kg, p < 0.001) and a reduction in placebo-corrected alterations in the mean daily total, bolus and basal doses of insulin (difference −5.3 U/day [−9.7%], −2.8 U/day [−12.3%] and −2.6 U/day [−9.9%], respectively, p < 0.001 for all comparisons). In participants with a baseline systolic blood pressure (SBP) of >130 mmHg, the reduction in SBP by week 16 was greater with sotagliflozin (difference −3.5 mmHg, p = 0.002 vs placebo) (Table 2). Dapagliflozin 400 mg daily was relatively well tolerated compared with placebo (overall rate of any adverse event was 52–55%), although serious adverse events were more common with sotagliflozin (48 participants [6.9%] vs 23 [3.3%]) (Table 3). Documented hypoglycaemia and hypoglycaemia event rates were similar in both groups, although sotagliflozin-treated participants had a significantly lower event rate of hypoglycaemia <3.1 mmol/l. As expected, general mycotic infections and diarrhoea occurred more frequently with sotagliflozin vs placebo and a greater proportion of participants experienced one or more episodes of DKA (3.0% vs 0.6%) [21].
### Table 1  Summary of trial design, duration, primary and secondary endpoints and participant baseline characteristics in currently available literature on Phase III studies involving SGLT inhibitor adjunct therapy in type 1 diabetes

<table>
<thead>
<tr>
<th>Study detail</th>
<th>Dapagliflozin</th>
<th>Sotagliflozin</th>
<th>InTandem2</th>
<th>InTandem3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study name</td>
<td>DEPICT-1</td>
<td>InTandem1</td>
<td>InTandem2</td>
<td>InTandem3</td>
</tr>
<tr>
<td>Design</td>
<td>Optimise diabetes management</td>
<td>Optimise insulin</td>
<td>Optimise insulin</td>
<td>Standard of care insulin</td>
</tr>
<tr>
<td>Study arms</td>
<td>Three (PBO, DAPA 5 mg, DAPA 10 mg)</td>
<td>Three (PBO, SOTA 200 mg, SOTA 400 mg)</td>
<td>As for InTandem1</td>
<td>Two (PBO, SOTA 400 mg)</td>
</tr>
<tr>
<td>Total N</td>
<td>833</td>
<td>793</td>
<td>782</td>
<td>1402</td>
</tr>
<tr>
<td>Study duration</td>
<td>52 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
<td>52 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
<td>52 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>HbA&lt;sub&gt;1c&lt;/sub&gt; change from baseline at week 24</td>
<td>Reduction in HbA&lt;sub&gt;1c&lt;/sub&gt; vs PBO on optimised insulin (24 weeks)</td>
<td>As for InTandem1</td>
<td>Proportion with HbA&lt;sub&gt;1c&lt;/sub&gt; &lt; 53 mmol/mol (&lt;7.0%) no SH and no DKA (24 weeks)</td>
</tr>
<tr>
<td>Secondary key endpoints</td>
<td>Proportion with HbA&lt;sub&gt;1c&lt;/sub&gt; decrease of ≥6 mmol/mol (≥0.5%) without SH at 24 weeks; % change in total daily insulin; % change in body weight; CGM change in mean 24 h glucose, MAG, % 24 h readings within target range</td>
<td>Proportion with HbA&lt;sub&gt;1c&lt;/sub&gt; &lt; 53 mmol/mol (&lt;7.0%), no SH, and no DKA; body weight, bolus insulin dose, FPG, DTSQ, DDS2</td>
<td>As for InTandem1</td>
<td>HbA&lt;sub&gt;1c&lt;/sub&gt;, body weight, SBP, bolus insulin dose</td>
</tr>
<tr>
<td>Mean age of participants</td>
<td>42 years</td>
<td>46 years</td>
<td>41 years</td>
<td>42 years</td>
</tr>
<tr>
<td>Mean duration of type 1 diabetes</td>
<td>20 years</td>
<td>24 years</td>
<td>18 years</td>
<td>20 years</td>
</tr>
<tr>
<td>Method of insulin delivery</td>
<td>40% CSII; 60% MDI</td>
<td>60% CSII; 40% MDI</td>
<td>26% CSII; 74% MDI</td>
<td>40% CSII; 60% MDI</td>
</tr>
<tr>
<td>Mean BMI at baseline</td>
<td>28 kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>30 kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>28 kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>28 kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean HbA&lt;sub&gt;1c&lt;/sub&gt; at screening</td>
<td>73 mmol/mol (8.8%)</td>
<td>66 mmol/mol (8.2%)</td>
<td>68 mmol/mol (8.4%)</td>
<td>68 mmol/mol (8.4%)</td>
</tr>
<tr>
<td>Mean HbA&lt;sub&gt;1c&lt;/sub&gt; at baseline</td>
<td>69 mmol/mol (8.5%; after 8 weeks' lead-in)</td>
<td>60 mmol/mol (7.6%; after 6 weeks' optimisation)</td>
<td>61 mmol/mol (7.7%; after 6 weeks' optimisation)</td>
<td>66 mmol/mol (8.2%)</td>
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<tr>
<td>Mean baseline SBP</td>
<td>Not reported</td>
<td>120 mmHg</td>
<td>123 mmHg</td>
<td>122 mmHg</td>
</tr>
<tr>
<td>eGFR inclusion criteria</td>
<td>Not reported</td>
<td>≥45 ml min&lt;sup&gt;-1&lt;/sup&gt; [1.73 m]&lt;sup&gt;2&lt;/sup&gt;</td>
<td>≥45 ml min&lt;sup&gt;-1&lt;/sup&gt; [1.73 m]&lt;sup&gt;2&lt;/sup&gt;</td>
<td>≥45 ml min&lt;sup&gt;-1&lt;/sup&gt; [1.73 m]&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

These are not head-to-head studies

<sup>a</sup> This table shows 24 week data from DEPICT, InTandem1 and InTandem2

CSII, Continuous subcutaneous insulin infusion (pump); DAPA, dapagliflozin; DDS2, Diabetes Distress Scale 2; DTSQ, Diabetes Treatment Satisfaction Questionnaire; FPG, fasting plasma glucose; MAG, mean absolute glucose change; PBO, placebo; SH, severe hypoglycaemia; SOTA, sotagliflozin
<table>
<thead>
<tr>
<th>Efficacy measure (PBO adjusted)</th>
<th>Dapagliflozin DEPICT-1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sotagliflozin inTandem1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>inTandem2&lt;sup&gt;a&lt;/sup&gt;</th>
<th>inTandem3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA₁c change</strong></td>
<td>DAPA 5 mg: −4.6 mmol/mol (&lt;−0.42%) (p &lt; 0.0001)</td>
<td>SOTA 200 mg: −4.0 mmol/mol (&lt;−0.36%) (p &lt; 0.001)</td>
<td>SOTA 200 mg: −4.0 mmol/mol (&lt;−0.36%) (p &lt; 0.001)</td>
<td>SOTA 400 mg: −5.1 mmol/mol (&lt;−0.46%) (p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>DAPA 10 mg: −5.0 mmol/mol (&lt;−0.45%) (p &lt; 0.0001)</td>
<td>SOTA 400 mg: −4.5 mmol/mol (&lt;−0.41%) (p &lt; 0.001)</td>
<td>SOTA 400 mg: −3.9 mmol/mol (&lt;−0.35%) (p &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary (composite) endpoint and percent achieving this</strong></td>
<td>HbA₁c &lt; 53 mmol/mol (&lt;7.0%), no SH, no DKA</td>
<td>PBO: 22%</td>
<td>PBO: 15%</td>
<td>PBO: 15.2%</td>
</tr>
<tr>
<td></td>
<td>SOTA 200 mg: 34%</td>
<td>SOTA 200 mg: 31%</td>
<td>SOTA 400 mg: 32%</td>
<td>SOTA 400 mg: 28.6%</td>
</tr>
<tr>
<td></td>
<td>SOTA 400 mg: &lt;53 mmol/mol (&lt;7.0%), no SH, no DKA</td>
<td></td>
<td></td>
<td>HbA₁c reduction ≥6 mmol/mol (≥0.5%) without SH</td>
</tr>
<tr>
<td></td>
<td>PBO: 25%</td>
<td>SOTA 200 mg: 34%</td>
<td>SOTA 200 mg: 31%</td>
<td>PBO: 36.7%</td>
</tr>
<tr>
<td></td>
<td>DAPA 5 mg: 50%</td>
<td>SOTA 400 mg: 32%</td>
<td></td>
<td>SOTA 400 mg: 60.9%</td>
</tr>
<tr>
<td></td>
<td>DAPA 10 mg: 51%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Change from baseline in total insulin dose (%)</strong></td>
<td>DAPA 5 mg: −8.8% (p &lt; 0.0001)</td>
<td>NA</td>
<td>NA</td>
<td>SOTA 400 mg: −9.71% (p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>DAPA 10 mg: −13.2% (p &lt; 0.0001)</td>
<td>SOTA 200 mg: −5.4 mmHg (p = 0.017)</td>
<td>SOTA 400 mg: −3.5 mmHg (p = 0.002)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean change in SBP</strong></td>
<td>NA</td>
<td>SOTA 400 mg: −6.6 mmHg (p = 0.003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean change from baseline in body weight</strong></td>
<td>DAPA 5 mg: −2.96% (p &lt; 0.0001)</td>
<td>SOTA 200 mg: −2.4 kg (p &lt; 0.001)</td>
<td>SOTA 200 mg: −2.0 kg (p &lt; 0.001)</td>
<td>SOTA 400 mg: −3.0 kg (p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>DAPA 10 mg: −3.72% (p &lt; 0.0001)</td>
<td>SOTA 400 mg: −3.5 kg (p &lt; 0.001)</td>
<td>SOTA 400 mg: −2.6 kg (p &lt; 0.001)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>This table shows 24 week data from DEPICT, inTandem1 and inTandem2

DAPA, dapagliflozin; NA, data not publicly available; PBO, placebo; SH, severe hypoglycaemia; SOTA, sotagliflozin
reduction for each of the dapagliflozin doses. CGM revealed modest but significant reductions in glucose variability with both doses of dapagliflozin. For instance, the time spent in the target glucose range (>3.9 mmol/l to <10.0 mmol/l) was increased from 43.2 ± 12.4% to 52.3 ± 14.8% (p < 0.05) after 24 weeks of dapagliflozin 10 mg. Again, adverse events were not uncommon, with more genital infections occurring with dapagliflozin vs placebo (Table 3). Hypoglycaemia (all categories) did not occur more frequently with dapagliflozin. DKA was infrequent in all groups (1–2%) and was not increased significantly by dapagliflozin [28]. However, adjudication of suspected DKA differed between the DEPICT-1 and inTandem3 trials and rates of DKA would have been similar had both trials adopted the same criteria (2.5% increase with treatment vs placebo groups) [29].

Summary

Most people with type 1 diabetes do not achieve recommended glycaemic targets. Adjunct therapy may complement insulin replacement and enable more people to achieve their glycaemic goals but there has been limited evidence to support this approach. Two recent RCTs, inTandem3 and DEPICT-1, suggest that SGLT inhibition may prove to be a viable and effective adjunct therapy in type 1 diabetes [25, 28]. Considering the Phase II and III trials together, on average, addition of SGLT inhibitors to insulin replacement in type 1 diabetes resulted in a 5–6 mmol/mol (0.4–0.5%) reduction in HbA1c, a 3–4 kg weight loss and a 10–15% reduction in total daily insulin dose. The glucose-lowering effect of SGLT inhibitors is insulin independent and glucose dependent and is accompanied by reduced glucose variability. Hypoglycaemia rates are not increased by SGLT inhibition but there is an associated increased risk of DKA.

DKA seems to occur more frequently in pump-treated patients; the use of rapid-acting insulin alone in pumps means there is no basal insulin back-up as in MDI treatment. An elegant study by Patel et al [30] suggests that the increased risk of DKA is predominantly due to the failure of type 1 diabetes patients on SGLTI to promptly recognise early metabolic decompensation, which occurs at lower than usual glucose levels, rather than being due to any acceleration in the rate of ketogenesis following the interruption of basal insulin infusion. Most healthcare organisations advocate blood ketone testing if capillary glucose is >16.7 mmol/l (<300 mg/dl) or persistently >13 mmol/l (235 mg/dl) and an individual is feeling unwell. However,
capillary glucose may not rise above 11–12 mmol/l (200–215 mg/dl) despite significant ketosis in individuals with type 1 diabetes receiving SGLT inhibitor treatment [30]. Education of patients concerning the risk of DKA at lower than expected glucose levels is therefore crucial, together with advice on sick-day rules and routine provision of a blood ketone meter (see Text Box). Clinicians should consider whether it is safe to prescribe SGLT2 inhibitors for individuals who are poorly compliant, whose blood glucose is poorly controlled (HbA1c >75 mmol/mol [9%]) and who are most at risk for hospitalisation from DKA [31]. It may also be advisable to limit SGLT inhibition to those on MDI rather than insulin pump, unless steps can be taken to minimise the risk of pump failure, which would result in abrupt discontinuation of insulin. In addition, using the lowest available dose of SGLT inhibitor may reduce the risks of DKA and other adverse events. Education of patients should include revision of insulin:carbohydrate ratios for calculating bolus insulin, perhaps by accounting for predicted glucose loss in the urine, and to ensure total insulin dose (especially basal) is not reduced by more than 10–15%.

It remains to be clarified whether dual SGLT1/2 inhibition, which in the short-term appears to have a greater effect on postprandial glucose control, confers additional benefits in terms of HbA1c or other outcomes over the longer term. Upcoming results from 52 week RCT trials (DEPICT-2, inTandem1, inTandem2, Empagliflozin as Adjunctive to inSulin thErapy Over 52 Weeks in Patients with Type 1 Diabetes Mellitus [EASE-2]) will help to determine whether SGLT inhibitor adjunct therapy has sustained benefits in terms of HbA1c, weight and total insulin dose reduction and determine its impact on rates of DKA and severe hypoglycaemia. Data on long-term clinical efficacy, safety (especially less-common adverse events), survival, health-related quality of life, patient-reported outcomes and resource requirements will require longer-term observational cohort studies. Future trials might determine whether the beneficial effects of SGLT inhibition on blood pressure [25] and arterial stiffness [32] translate into improved cardiovascular outcomes (still a major cause of increased morbidity and mortality in type 1 diabetes [8]), whether SGLT inhibitors have a renoprotective effect in type 1 diabetes (as in type 2 diabetes [33]) and does dual SGLT1/2 inhibition have additional benefits in those with impaired renal function because of the reduction in gastrointestinal glucose uptake. Alternatively, will early animal data showing these compounds can increase renal excretion of calcium [34], and results from CANVAS indicating higher fractures rates in participants with type 2 diabetes taking canagliflozin [35], translate into an already increased risk of bone fractures in type 1 diabetes?

Taken together, early data are promising but further research is needed to define clearly the cohort of people with type 1 diabetes who will benefit most from SGLT inhibitor co-prescription as well as to obtain more data on safety and persistence of benefit in the longer term. SGLT inhibitors are not currently approved by the US Food and Drug Administration or the European Medicines Agency for use in type 1 diabetes but they may become a therapeutic option in the future. Education of patients and healthcare professionals will be of paramount importance if SGLT inhibitors are to be introduced safely into routine clinical care of type 1 diabetes.

**Recommendations for patients with type 1 diabetes initiated on SGLT inhibitor adjunct therapy**

- Not recommended for poorly compliant patients with HbA1c >75 mmol/mol (9%) and history of DKA
- Consider increased DKA risk in patients on insulin-pump therapy
- Use lowest available dose of SGLT inhibitor required to achieve clinical benefit
- Reduce prandial insulin by 10–20% initially and adjust doses of prandial and basal insulin based on frequent pre- and postprandial glucose monitoring
- Reassess insulin:carbohydrate ratios once established on SGLT inhibitor
- Provide blood ketone meter and advise on DKA diagnosis and management
- Advise blood ketone testing if patient is feeling sick and blood glucose >9 mmol/l
- Advise stopping SGLT inhibitor during intercurrent illness or conditions where there is fluid loss or reduced fluid intake
- Advise about increased risk of genital mycotic infections and/or diarrhoea

**Funding** RJM is supported by funding from the Medical Research Council, Diabetes UK, JDRF, British Heart Foundation and Chief Scientist Office.

**Duality of interest** RJM has received honoraria for educational talks and advisory activity from Sanofi, Novo Nordisk and Eli Lilly. RRH has received research funding from Abbott, AstaMed, Eli Lilly, Hitachi, Novo Nordisk, Sanofi-lexicon and ViaCyte and has been a consultant/advisory panel member for Abbott, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Elcelyx, Intarcia, Ionis, Janssen/Johnson & Johnson, Ligand, Merck, Regeneron and Sanofi-Aventis.

**Contribution statement** RJM and RRH wrote and edited the manuscript and are responsible for its content.

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