



# Optimising the Benefits of SGLT2 Inhibitors for Type 1 Diabetes

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## ABSTRACT

Sodium-glucose cotransporter 2 (SGLT2) inhibitor clinical studies in type 1 diabetes mellitus (T1DM) have demonstrated reduced HbA1c and lower glucose variability with increased time in optimal glucose range as well as additional benefits of reductions in weight and insulin dose without increasing the incidence of

hypoglycaemia. However, the appropriate use of SGLT2 inhibitor therapies within clinical practise to treat people with T1DM remains unclear. In this article we have used consensus expert opinion alongside the available evidence, product indication and most recent clinical guidance to provide support for the diabetes healthcare community regarding the appropriate use of SGLT2 inhibitors, focussing on specific considerations for appropriate prescribing of dapagliflozin within the T1DM management pathway. Its purpose is to provide awareness of the issues surrounding treatment with dapagliflozin in T1DM as well as offer practical guidance that also includes a checklist tool for appropriate dapagliflozin prescribing. The checklist aims to support clinicians in identifying those people with T1DM most likely to benefit from dapagliflozin treatment as well as situations where caution may be required.

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## INTRODUCTION

Globally, the annual incidence of type 1 diabetes mellitus (T1DM) is increasing by approximately 2–3% per year [1, 2]. T1DM is a consequence of the autoimmune or non-immune destruction of insulin-producing pancreatic  $\beta$ -cells and results in an increase in glycated haemoglobin (HbA1c) [3–5]. Strict glycaemic control in people with T1DM has been shown to reduce the risk of microvascular (e.g. diabetic retinopathy, nephropathy and neuropathy) and macrovascular (e.g. coronary artery disease and peripheral vascular disease) complications [6–8].

Optimal glycaemic control requires administration of insulin that simulates physiological insulin secretion and typically involves one or two subcutaneous injections of basal insulin daily to control glycaemia between meals and overnight and subcutaneous injections of prandial insulin at mealtime to control glycaemia following meals [9]. Improvements in therapeutic approaches, such as insulin pumps, continuous glucose monitoring (CGM) and hybrid closed-loop systems, are now also increasingly used [10]. These advances in diabetes technology have improved glycaemic control and resulted in overall decreases in the rates of hypoglycaemia and weight gain that were highlighted as major side effects of intensive insulin therapy in the landmark Diabetes Control and Complications Trial (DCCT) [11–13]. However, despite the improvements, hypoglycaemia and weight gain remain significant adverse events associated with insulin therapy [14, 15]. Furthermore, the vast majority of people with T1DM still do not achieve recommended glycaemic targets; only 29.9% of people with T1DM achieved HbA1c levels  $\leq 58$  nmol/mol (7.5%) in England and Wales, 2017–2018 [16]. Thus, there is an unmet need, and great interest within the diabetes care community, regarding adjunct therapies to improve glycaemic control without increasing the risk of hypoglycaemia and weight gain.

Until recently there have been no licensed treatment options available in the UK for people with T1DM that are inadequately controlled by insulin alone. Whilst unlicensed use of metformin occurs in clinical practice, results of the REMOVAL trial (a double-blind, placebo-controlled multicentre trial assessing the long-term effects of metformin added to insulin therapy in people with T1DM), although demonstrating a benefit in terms of weight loss, did not support a role for metformin to improve glycaemic control or to reduce insulin dose [17]. Furthermore, a meta-analysis of 13 randomised controlled trials (RCTs) demonstrated that metformin has not consistently shown glycaemic benefits in T1DM [18].

A number of studies have investigated the effect of alpha-glucosidase inhibitors, pioglitazone, glucagon-like peptide (GLP)-1 receptor agonists or dipeptidyl peptidase (DPP)-4 inhibitors in T1DM [19–26], but the inconsistent results have not supported the use of these treatments in clinical practise. For example, the DPP-4 inhibitor sitagliptin has been shown to reduce insulin requirements and improve metabolic control without increasing the risk of hypoglycaemia in people with T1DM in some studies [27, 28], whilst no major benefit has been observed in other studies [29, 30].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are particularly attractive for adjunctive use in T1DM, as they are oral agents that reduce the reabsorption of glucose in the kidney and increase its excretion via the urine, a mechanism that is independent of islet cell functionality [31–33]. SGLT2 inhibitor clinical studies, conducted in people with T1DM, have demonstrated reduced HbA1c and lower glucose variability with increased time in optimal glucose range [i.e. glucose levels 70–180 mg/dl (3.9–10 mmol/l)] as well as additional benefits of reductions in weight and insulin dose without increasing the incidence of hypoglycaemia [34–41]. However, SGLT2 inhibitors are not deemed suitable for everyone with T1DM and so careful selection of appropriate people, with the development and dissemination of appropriate strategies to minimise the risk of adverse events, is essential and has already been the

focus of activity within the diabetes care specialist community [42, 43].

Recently, there has been a growing literature base, including review articles and expert consensus guidance, focussing on the role of SGLT2 inhibitors in T1DM. However, the guidance provided is often conflicting and many of the recommendations may not accurately reflect current licence indications. As a consequence, there is uncertainty in the clinical community regarding the efficacy, safety and appropriate use of SGLT2 inhibitors for T1DM. We have therefore sought to contextualise the available SGLT2 inhibitor data, examine the risk-benefit profile and provide guidance on selecting appropriate people for SGLT2 inhibitor treatment and practical approaches for healthcare professionals who care for people with T1DM, focussing on specific considerations for appropriate SGLT2 inhibitor prescribing within the T1DM management pathway in the UK.

US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval has been granted to four SGLT2 inhibitors to date—canagliflozin, dapagliflozin, empagliflozin and ertugliflozin (the dual SGLT1/SGLT2 inhibitor sotagliflozin also has EMA approval), and in Japan, three other SGLT2 inhibitors—ipragliflozin, luseogliflozin and tofogliflozin—have been approved [44]. All of these approvals are for the treatment of type 2 diabetes mellitus (T2DM). Dapagliflozin is the first SGLT2 inhibitor to have its marketing authorisation extended to T1DM [45]. Furthermore, it also has approval from the National Institute for Health and Care Excellence (NICE) for T1DM, in which dapagliflozin was found to be a highly cost-effective treatment option in people with T1DM inadequately controlled by insulin alone, with an incremental cost-effectiveness ratio (ICER) of £13,775 per quality-adjusted life year (QALY) gained for dapagliflozin 5 mg compared with standard of care [46]. Following the positive NICE guidance, the Scottish Medicines Consortium (SMC) has recommended dapagliflozin for patients with inadequately controlled T1DM in Scotland. This positive decision means that appropriate patients with uncontrolled T1DM in Scotland will have access to dapagliflozin, as an adjunct to insulin, through the NHS with

funding expected to be available from November 2019 [47].

The guidance provided in this article is based on the available evidence, as well as from consensus expert opinion, in accordance with the label indication for dapagliflozin. The guidance aims to be of value to a wide audience of healthcare professionals working in the management of T1DM. Its purpose is to provide awareness of the issues concerning SGLT2 inhibitor therapy in T1DM as well as practical guidance that also includes a checklist tool to support clinicians in identifying those people with T1DM most likely to benefit from dapagliflozin treatment as well as situations where caution may be required.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## EFFICACY AND SAFETY OF SGLT2 INHIBITORS IN PEOPLE WITH T1DM

Several SGLT2 inhibitors have completed phase 3 clinical trials to evaluate the efficacy and safety of their use as adjunctive therapy in T1DM (Table 1). The empagliflozin-focussed EASE (Empagliflozin as Adjunctive to inSulin therapy) programme comprised the EASE2 (52 weeks) and EASE3 (26 weeks) trials [34]. EASE2 participants were randomised to one of two doses of empagliflozin (10 or 25 mg) or placebo while EASE3 participants were randomised to one of three doses of empagliflozin (2.5, 10 or 25 mg) or placebo. In EASE2, in the empagliflozin 10 and 25 mg groups the placebo-adjusted changes in HbA1c were  $-0.39$  and  $-0.45\%$  and the placebo-adjusted changes in body weight were  $-3.2$  and  $-3.6$  kg. In EASE3, in the empagliflozin 2.5, 10 and 25 mg groups the placebo-adjusted changes in HbA1c were  $-0.28$ ,  $-0.45$  and  $-0.52\%$  and the placebo-adjusted changes in body weight were  $-1.8$ ,  $-3.0$  and  $-3.4$  kg. All placebo-adjusted changes in HbA1c and body weight for both EASE2 and EASE3 were statistically significant with  $p < 0.0001$  (Table 1). In a pooled analysis of adverse events, an important finding was the

**Table 1** Phase 3 SGLT2 inhibitor clinical trials in T1DM

| Trial          | <i>N</i> | Study duration (weeks) | Treatment            | Insulin dose change vs. placebo (%) | HbA1c change vs. placebo (%) | Body weight change vs. placebo (kg) | Incidence DKA (%) |
|----------------|----------|------------------------|----------------------|-------------------------------------|------------------------------|-------------------------------------|-------------------|
| DEPICT1 [39]   | 833      | 52                     | Dapagliflozin 5 mg   | – 8.8 <sup>a</sup>                  | – 0.33                       | – 2.56                              | 4.0               |
|                |          |                        | Dapagliflozin 10 mg  | – 13.2 <sup>a</sup>                 | – 0.36                       | – 3.90                              | 3.4               |
|                |          |                        | Placebo              |                                     |                              |                                     | 1.9               |
| DEPICT2 [40]   | 815      | 24                     | Dapagliflozin 5 mg   | – 10.8                              | – 0.37                       | – 3.21                              | 2.6               |
|                |          |                        | Dapagliflozin 10 mg  | – 11.1                              | – 0.42                       | – 3.74                              | 2.2               |
|                |          |                        | Placebo              |                                     |                              |                                     | 0                 |
| EASE2 [34]     | 730      | 52                     | Empagliflozin 10 mg  | – 12.0                              | – 0.39                       | – 3.2                               | 4.3 <sup>b</sup>  |
|                |          |                        | Empagliflozin 25 mg  | – 12.9                              | – 0.45                       | – 3.6                               | 3.3 <sup>b</sup>  |
|                |          |                        | Placebo              |                                     |                              |                                     | 1.2               |
| EASE3 [34]     | 975      | 26                     | Empagliflozin 2.5 mg | – 6.4                               | – 0.28                       | – 1.8                               | 0.8               |
|                |          |                        | Empagliflozin 10 mg  | – 9.5                               | – 0.45                       | – 3.0                               | 4.3 <sup>b</sup>  |
|                |          |                        | Empagliflozin 25 mg  | – 12.6                              | – 0.52                       | – 3.4                               | 3.3 <sup>b</sup>  |
|                |          |                        | Placebo              |                                     |                              |                                     | 1.2               |
| inTANDEM1 [35] | 793      | 52                     | Sotagliflozin 200 mg | – 8.0                               | – 0.25                       | – 3.14                              | 3.4               |
|                |          |                        | Sotagliflozin 400 mg | – 12.6                              | – 0.31                       | – 4.32                              | 4.2               |
|                |          |                        | Placebo              |                                     |                              |                                     | 0.4               |
| inTANDEM2 [36] | 782      | 52                     | Sotagliflozin 200 mg | – 6.3                               | – 0.37                       | – 2.18                              | 2.3               |
|                |          |                        | Sotagliflozin 400 mg | – 8.2                               | – 0.35                       | – 2.92                              | 3.4               |
|                |          |                        | Placebo              |                                     |                              |                                     | 0                 |

**Table 1** continued

| Trial          | N    | Study duration (weeks) | Treatment            | Insulin dose change vs. placebo (%) | HbA1c change vs. placebo (%) | Body weight change vs. placebo (kg) | Incidence DKA (%) |
|----------------|------|------------------------|----------------------|-------------------------------------|------------------------------|-------------------------------------|-------------------|
| inTANDEM3 [37] | 1402 | 24                     | Sotagliflozin 400 mg | − 9.7                               | − 0.46                       | − 2.98                              | 3.0               |
|                |      |                        | Placebo              |                                     |                              |                                     | 0.6               |

<sup>a</sup> DEPICT1 24-week data

<sup>b</sup> Pooled EASE2 and EASE3 data

higher incidence of diabetic ketoacidosis (DKA) in the empagliflozin groups: 25 mg, 3.3%; 10 mg, 4.3%; placebo, 1.2%. Most cases of DKA were associated with a precipitating factor such as infection or reduced insulin dose. For both EASE2 and EASE3 CGM-derived glucose time in range [70–180 mg/dl (3.9–10 mmol/l)] significantly increased by approximately 3 h a day with empagliflozin compared with placebo; placebo-adjusted change (hours/day) from baseline of + 3.0 for empagliflozin 25 mg and + 2.9 for empagliflozin 10 mg in EASE2 and + 2.6 for empagliflozin 25 mg + 1.8 for empagliflozin 10 mg and + 1.0 for empagliflozin 2.5 mg in EASE3.

Sotagliflozin is a dual SGLT1/2 inhibitor and reduces glucose reabsorption in the kidneys through SGLT2 inhibition as well as delaying dietary glucose absorption through SGLT1 inhibition in the intestinal tract. The safety and efficacy of sotagliflozin in T1DM were assessed in the inTANDEM1-3 studies. The inTandem1 [35] and inTandem2 [36] trials evaluated two doses of sotagliflozin (200 and 400 mg) alongside placebo while the inTandem3 trial [37] was a two-arm (400 mg sotagliflozin vs. placebo) study. Sotagliflozin was associated, across all three trials, with statistically significant ( $p < 0.001$ ) reductions in HbA1c, weight and total daily insulin dose (Table 1). The primary end point for the inTandem3 trial, the proportion of participants achieving HbA1c  $\leq 53$  mmol/mol (7.0%) without severe hypoglycaemia or DKA at the end of the study, was met by a significantly higher proportion of people in the sotagliflozin arm compared with placebo (28.6% vs. 15.2%;  $p < 0.001$ ). Incidence of DKA was consistently higher in

people receiving sotagliflozin compared with placebo across the three trials: 400 mg, 3.0–4.2%; 200 mg, 2.3–3.4%; placebo, 0–0.6%. In pooled analyses of CGM data from inTandem1 and inTandem2, compared with placebo an additional time in range of 1.3 h/day was demonstrated with sotagliflozin 200 mg and 2.8 h/day with sotagliflozin 400 mg [48].

The safety and efficacy of dapagliflozin in T1DM were investigated in the Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT) clinical trial programme, which comprised two studies—DEPICT1 (24-week short term plus 28 week extension) [38, 39] and DEPICT2 (24 weeks) [40]. Both DEPICT trials included two dapagliflozin groups (5 and 10 mg) and a placebo arm. Both trials demonstrated statistically significant ( $p < 0.0001$ ) decreases in HbA1c, weight and total daily insulin dose. At week 52 in DEPICT1, the placebo-adjusted changes in HbA1c and weight in the dapagliflozin 5 and 10 mg groups, respectively, were: HbA1c − 0.33 and − 0.36%; weight − 2.95 and − 4.5 kg. At week 24 in DEPICT2, the placebo-adjusted changes in HbA1c and weight in the dapagliflozin 5 and 10 mg groups were similar to those reported in DEPICT1 (Table 1). An important finding was the higher incidence of DKA in the dapagliflozin groups compared with placebo for both DEPICT trials: 10 mg, 2.2–3.4%; 5 mg, 2.6–4.0%; placebo, 0–1.9%. The majority of the cases were a result of insulin pump failure or missed insulin dose and one case was as a consequence of excessive alcohol intake. All were resolved with standard of care. In pooled analyses of 24-week CGM data from DEPICT1 and

DEPICT2, those receiving dapagliflozin 5 mg or 10 mg both spent more time in range over 24 h than those receiving the placebo; the adjusted mean change from baseline at week 24 was 6.5% with dapagliflozin 5 mg, 8.1% with dapagliflozin 10 mg and – 2.6% with placebo [41].

Based on the positive results from the DEPICT studies dapagliflozin 5 mg received marketing approval in Europe in March 2019 as an adjunct to insulin in people with T1DM with a body mass index (BMI)  $\geq 27$  kg/m<sup>2</sup> (the BMI restriction reflects safety concerns around DKA risk in those with a lower BMI), when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy [45, 49]. It has also recently received SMC approval [47], and additionally has NICE approval following health economic analysis, which demonstrated the value of dapagliflozin as an adjunct treatment for people with T1DM at cost-effectiveness thresholds conventionally applied in the UK, with an estimated ICER per QALY gained (with the QALY gains being largely driven by the improved quality of life associated with weight reduction as opposed to the HbA1c reductions observed in the DEPICT studies) of between £6385 and £19,122 [46]. The impact of additional parameters, such as an increased time in range, on these estimations remains uncertain, even though there is a growing awareness that even small increments (5%) in time in range, as measured by CGM and not necessarily reflected by significant changes in glycated haemoglobin levels, may have beneficial effects [50].

## BENEFIT-RISK PROFILE OF DAPAGLIFLOZIN

The DEPICT trial results demonstrated a significant reduction in HbA1c from baseline in people in the dapagliflozin arm compared with those in the placebo arm. In addition, participants receiving dapagliflozin lost more weight than those in the placebo group. The reduction of weight is likely to be of importance for many people with T1DM and also has the potential to limit later cardiovascular risk. SGLT2 inhibitors have demonstrated a proven benefit for cardio-

renal outcomes in T2DM. It remains unclear whether or not these benefits would be replicated in people with T1DM as the pathophysiology of cardiorenal disease may be different in T1DM. Therefore, despite the potential for cardio-renal benefits with SGLT2 inhibitors in T1DM, further evidence is required to verify this.

The overall adverse event profile for dapagliflozin use in people with T1DM was similar to dapagliflozin use in people with T2DM. The most common side effects reported with dapagliflozin 5 mg across the DEPCIT clinical trial programme for T1DM were an increased incidence of genital mycotic infections (10–16% compared with 2–3% for placebo) and urinary tract infections (UTIs) (7–12% compared with 4–8% for placebo). The increased risk of genital mycotic infections associated with SGLT2 inhibitors has also been reported in a real-world setting [51]. Although these infections have the potential to significantly impact quality of life, most are mild-to-moderate infections that can be easily managed and do not necessitate dapagliflozin discontinuation.

SGLT2 inhibitors are associated with an increased risk for Fournier's gangrene, an extremely rare but serious and potentially life-threatening bacterial infection of the external genitalia, perineum and perianal region. Between March 2013 and January 2019, 55 cases of Fournier's gangrene have been reported in people receiving SGLT2 inhibitors (16 of which were on dapagliflozin) compared with 19 cases reported over 35 years in people taking other diabetes drugs [52].

Another serious complication associated with SGLT2 inhibitors is DKA—a medical emergency that occurs when a severe lack of insulin leads to the use of alternative energy sources such as fat, resulting in the production of acidic ketone bodies. Despite DKA risk mitigation strategies in DEPICT, DKA rates in people receiving dapagliflozin were as high as 3–4% while rates in the placebo group were < 2%. The risk of DKA may be even higher in routine clinical settings where monitoring is likely to be less stringent than in clinical trials. It has been suggested that the increased risk of DKA is predominantly due to the failure of people

receiving an SGLT2 inhibitor to promptly recognise early metabolic decompensation, which occurs at lower than usual glucose levels [53]. Also, the reduction in insulin dose may trigger ketogenesis in some people. Important strategies in mitigating DKA risk with an SGLT2 inhibitor include appropriate education of both people with T1DM and healthcare professionals, concerning the risk of DKA and how to minimise this risk, and the selection of appropriate people for treatment.

## APPROPRIATE PRESCRIBING OF DAPAGLIFLOZIN IN T1DM

Selecting appropriate people with T1DM for SGLT2 inhibitor treatment is critical for minimising the risks and maximising the potential benefits associated with this treatment. Yet, there is confusion surrounding which people with T1DM are most suitable.

The NICE guidance identifies dapagliflozin as a treatment with both clinical and economic value in people with T1DM [46]. Furthermore, the guidance provides recommendations for when prescribing of dapagliflozin would be appropriate in T1DM. Dapagliflozin with insulin is recommended for adults with T1DM with a BMI of  $\geq 27$  kg/m<sup>2</sup>, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy, only if they are on insulin doses of  $> 0.5$  units/kg of body weight/day (the insulin dose restriction reflects safety concerns around DKA risk in those with lower insulin needs) and they have completed a structured education programme (including information about the risk of DKA, how to recognise risk factors for DKA and its signs and symptoms, how and when to monitor blood ketone levels, what actions to take for elevated blood ketones) and treatment is started and supervised in a hospital diabetes clinic. Within this guidance, it is suggested that HbA1c levels should be measured after 6 months and regularly after this. Treatment with dapagliflozin in combination with insulin compared with insulin alone in people with T1DM remains cost effective (ICER per QALY gain  $< \pounds 20,000$ ) even in a scenario of no significant improvement in

glucose control, largely driven by reductions in insulin dose and body weight. However, in the absence of any sustained improvement in blood glucose control (defined as a fall in HbA1c level of  $\geq 0.3\%$ ), the current NICE guidance recommends that dapagliflozin should be discontinued, as the harms (risk of DKA) outweigh the benefits in this situation.




The SMC guidance applies to the full dapagliflozin marketing authorisation and does not include a restriction to patients with insulin needs  $> 0.5$  units/kg per day. It also does not apply to the stopping rules that are recommended in the NICE guidance. Analysis of data from DEPICT suggests that the majority of patients in practice are on insulin doses  $> 0.5$  units/kg per day, and most patients treated with dapagliflozin will achieve an HbA1c reduction of  $\geq 0.3\%$  at 6 months. Therefore, the differences in recommendation wording between NICE and SMC are not expected to lead to substantial inequality of access among England, Wales and Scotland.

Based on the DEPICT data and the current label indication for dapagliflozin as well as recent clinical guidance, we have formed consensus regarding appropriate prescribing of dapagliflozin in T1DM and developed a checklist that offers a quick reference guide for clinicians to identify the people most likely to benefit from dapagliflozin treatment as well as situations where caution may be required (Fig. 1). The checklist follows a traffic light system whereby we recommend that clinicians should consider prescribing dapagliflozin for people in the green section, not consider prescribing dapagliflozin for people in the red section and possibly consider prescribing dapagliflozin with caution for people in the amber section.

### Consider Prescribing Dapagliflozin

People most suitable for dapagliflozin in T1DM are likely to be those with a BMI  $\geq 27$  kg/m<sup>2</sup>, established on stable optimised insulin therapy (i.e. not recently diagnosed) and with high insulin needs (i.e.  $> 0.5$  units/kg of body weight/day).

One of the most important criteria for determining if someone is suitable for

|   | Consider prescribing   | Tick box |
|---|--|----------|
|  | BMI $\geq 27$ kg/m <sup>2</sup>  |          |
|   | Established on stable optimised insulin therapy                                |          |
|   | Insulin dose $> 0.5$ units/kg of body weight/day                               |          |
|   | Presentation with ketone levels $< 0.6$ nmol/L                                 |          |
|   | Willing and able to perform regular and frequent glucose and ketone monitoring |          |
|   | GFR $> 60$ ml/min/1.73 m <sup>2</sup>  |          |
|   | Age 18–74  |          |
|   | Possibly consider prescribing with caution                                     |          |
|  | History of DKA within the last 2 years   |          |
|   | Prior history of excess alcohol consumption                                    |          |
|   | Steroid therapy  |          |
|   | Insulin-titrating / changing insulin regimen / commencing on a pump            |          |
|   | Secondary insulin requiring diabetes   |          |
|   | Do not consider prescribing  |          |
|  | BMI $< 27$ kg/m <sup>2</sup>   |          |
|   | Insulin dose $< 0.5$ units/kg of body weight/day                               |          |
|   | History of poor treatment adherence  |          |
|   | History of DKA in last 12 months   |          |
|   | Recurrent severe genital mycotic infections                                    |          |
|   | Unwilling/unable to perform routine glucose and ketone monitoring              |          |
|   | Actively reducing weight e.g., low carbohydrate or ketogenic diet              |          |
|   | Excessive alcohol use  |          |
|   | Illicit drug use   |          |
|   | Females with childbearing potential who are pregnant or planning pregnancy     |          |
|   | GFR $< 60$ ml/min/1.73 m <sup>2</sup>  |          |
|   | Age $< 18$ or $\geq 75$  |          |

**Fig. 1** Checklist for appropriate prescribing of dapagliflozin in T1DM. *BMI* body mass index, *DKA* diabetic ketoacidosis, *GFR* glomerular filtration rate

dapagliflozin treatment is normal blood ketone levels ( $< 0.6$  mmol/l). Urine ketone monitoring is not advisable as it is not deemed to be as accurate as blood ketone testing, since urine test results are indicative of blood ketone levels in the past, and accuracy is also affected by hydration levels and kidney function [54]. The willingness/ability to follow prescribed regimens for monitoring ketones and responding appropriately to elevated ketone levels must also be considered.

Additional criteria for which people with T1DM should be prescribed dapagliflozin include glomerular filtration rate (GFR)  $> 60$  ml/min/1.73 m<sup>2</sup> (as dapagliflozin efficacy is dependent on renal function) and age 18–74 years (as the DEPICT clinical trial programme was conducted in this age group).

### Possibly Consider Prescribing Dapagliflozin with Caution

There are a number of groups of people for which dapagliflozin probably should not be

prescribed. However, the available data are unclear, and we would suggest proceeding on an individual basis with caution for people that fall into these categories. People with T1DM that should be prescribed dapagliflozin with caution include those with a prior history of DKA (i.e. within the last 2 years), prior history of excess alcohol consumption or currently prescribed steroid therapy. Clinicians should also proceed with caution if prescribing dapagliflozin to people with T1DM who are currently insulin-titrating, changing their insulin regimen or commencing on an insulin pump. There is some evidence from the clinical trials to suggest that SGLT2 inhibitor-related DKA may occur more frequently in people who are pump-treated compared with those treated with insulin injections. For example, in the sotagliflozin 400 mg arm of inTANDEM1, inTANDEM2 and inTANDEM3, DKA occurred in 4, 5 and 4% of people who were pump-treated compared with 2, 1 and 3% of people who received insulin by injection [35–37]. In most cases DKA will be accompanied by high glucose levels; however, it is not unusual for people on insulin pumps to



develop DKA despite having low or normal blood glucose levels.

Secondary insulin-requiring diabetes (diabetes that results as a consequence of another medication, endocrine disease or hereditary disease, e.g. pancreatic diabetes, which results in insulin deficiency following pancreatitis or pancreatectomy) has not been represented in the SGLT2 inhibitor clinical trial programmes. Therefore, as the role of dapagliflozin in this subgroup is uncertain we suggest proceeding with caution in such situations, but applying the same caveats as in those individuals with T1DM.

### Do Not Consider Prescribing Dapagliflozin

In line with the label indication for dapagliflozin we do not recommend that dapagliflozin be prescribed to people with T1DM with BMI  $< 27 \text{ kg/m}^2$  or those with low insulin needs ( $< 0.5$  units/kg of body weight/day). The aim of both these criteria is to manage the safety concerns of an increased risk of DKA associated with dapagliflozin in these subgroups. Based on available data as well as consensus we have developed further criteria to define additional groups that should not be offered treatment with dapagliflozin.

People with T1DM who have a history of poor treatment adherence such as missed insulin doses, have a history of DKA within the last 12 months, have had recurrent severe genital mycotic infections or display low engagement with their diabetes regimen (i.e. unwilling/unable to perform routine glucose and ketone monitoring) are at high risk of DKA when on SGLT2 inhibitor therapy and should not be prescribed dapagliflozin treatment. Also, people with certain lifestyle behaviours that increase DKA risk, such as actively reducing body weight by for example following a low carbohydrate restriction or ketogenic diet or engaging in the use of excessive alcohol (i.e. drinking more than the current UK guidelines of 14 units a week) and/or illicit drugs, should not receive dapagliflozin.

Given that SGLT2 inhibitors are not approved in pregnancy and that DKA during pregnancy is associated with significant

maternal and foetal mortality [55, 56], dapagliflozin should not be prescribed to females with T1DM who are pregnant or planning pregnancy or who are unwilling to use appropriate contraceptives to avoid pregnancy.

Dapagliflozin should not be prescribed to people with T1DM with GFR  $< 60 \text{ ml/min/1.73 m}^2$ . This recommendation is not based on concerns of safety but due to the efficacy of dapagliflozin, which has not been demonstrated in those with poor renal function.

As there are limited data on the use of SGLT2 inhibitors in those  $< 18$  years or  $\geq 75$  years we do not recommend dapagliflozin in these age groups.

## APPROACHES IN ROUTINE CLINICAL PRACTICE

When using dapagliflozin in routine clinical practise there are a number of issues to consider to mitigate the risks associated with this treatment.

Education regarding the risks of minor adverse events such as mycotic genital infections and UTIs should be provided to people with T1DM when initiating dapagliflozin treatment. This may encourage people to self-monitor treatment efficacy and adverse effects and help them manage these infections. People should also be made aware of the risk of Fournier's gangrene, a rare but serious and potentially life-threatening infection, which has been associated with the use of SGLT2 inhibitors, and they should be informed of additional risk factors that may increase their risk of this infection, including for example poor personal hygiene, alcohol abuse and obesity [57, 58]. People should be advised to seek urgent medical attention if they experience severe pain, tenderness, erythema or swelling in the genital or perineal area, accompanied by fever or malaise. If Fournier's gangrene is suspected, clinicians are advised to stop dapagliflozin and urgently start appropriate treatment, including the administration of broad-spectrum intravenous antibiotics and surgical removal of extensive areas of necrosis.

An increased risk of DKA has been associated with the use of dapagliflozin, with inadequate

insulin dose being reported as the most common risk factor. Therefore, individuals who are relatively insulin deficient, have sudden reductions in insulin dose or have an increased requirement for insulin (due to illness, surgery or alcohol abuse) should be closely monitored. Education of both people with T1DM and healthcare professionals will play a crucial role in reducing the risk of DKA associated with dapagliflozin use. This should include the provision of relevant information in both oral and written forms. A person-centred information leaflet covering the key messages should be provided for the person to take away and refer to when needed. It is important for those with T1DM as well as healthcare professionals to be aware that DKA associated with the use of dapagliflozin may not present typically and that glucose levels may be relatively normal, a condition referred to as normoglycemic DKA or euglycemic DKA [59]. Thus, we recommend testing for raised blood ketone levels when DKA symptoms are present, or during bouts of minor illness, even if blood glucose levels are within the normal range.

Prior to initiation with dapagliflozin people with T1DM should be re-educated on their condition and should also undergo formal structured education focussed on mitigating the risk of DKA. An example of a healthcare professional checklist that may be used in relation to the use of dapagliflozin in people with T1DM, and which advises on information to be included in an education session, is provided in the Appendix in the electronic supplementary material. The risks associated with dapagliflozin treatment should be fully explained, but balanced against the positive impact on HbA1c, weight and time in optimal glucose range. People should be informed of the symptoms of DKA (rapid weight loss, nausea or vomiting, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat), emphasising that DKA may occur even if blood glucose levels are within the normal range. Information should also be provided regarding DKA risk factors and the importance of ketone monitoring.

Very-low-calorie diets and ketogenic diets are increasingly popular dietary approaches to induce rapid weight loss, but are associated with an increased risk of DKA in people with T1DM. Therefore, anyone commencing on dapagliflozin should be strongly advised against such weight loss strategies and should also be educated regarding the importance of avoiding other important pro-ketogenic factors such as missed insulin doses.

People should also be educated on the management of blood glucose during periods of illness ('sick-day management'). This should include specific information regarding the frequency of blood glucose monitoring, blood glucose targets, blood ketone monitoring, appropriate adjustment of insulin doses and identifying early signs and symptoms of DKA. To complement the education, people with T1DM should be provided with the TREND-UK patient information leaflet 'Type 1 diabetes: What to do when you are ill' [60]. People should be reminded of the seriousness of DKA and advised to discontinue dapagliflozin and call their GP or diabetes team, or go to the nearest accident and emergency (A&E) hospital, if they develop any DKA symptoms.

Education to support healthcare professionals to understand and manage the risk of DKA in people with T1DM and in helping people to recognise and respond appropriately to symptoms is important. Even though initiation of dapagliflozin treatment is by specialists, ongoing prescribing and monitoring will be performed in the community. Hence GPs, A&E staff and specialist healthcare professionals should all receive dapagliflozin education. Considerations such as blood ketone monitoring, sick-day rules, mycotic genital infection/UTI risk, DKA advice and appropriate reductions in insulin dose will be important education topics. An information leaflet for healthcare professionals similar to TREND-UKs 'Appropriate use of SGLT2 inhibitors in type 2 diabetes: right person, right medication, right time' [61] but focussed on T1DM would be considered a useful resource.

Regarding blood ketone monitoring, for the first week following dapagliflozin initiation monitoring should be once a day then the

frequency of routine monitoring should be individualised based on specific risk factors. Blood ketone levels should also be checked in situations that may increase the risk of DKA, and people with T1DM and healthcare staff should be advised regarding actions to be taken in cases of raised ketone levels. The STOP DKA protocol is considered a useful strategy if ketone levels become increased during treatment with dapagliflozin and to prevent progression to DKA [62]. The protocol builds on the STICH protocol [63] and provides a risk mitigation strategy to follow when symptoms of DKA develop, which includes never stopping insulin, stopping the SGLT inhibitor, keeping hydrated and taking supplemental insulin and carbohydrates every 2–4 h according to blood ketone and glucose levels as per the STOP DKA table. Blood ketone levels should be reassessed and emergency medical care sought if ketones levels remain increased or if DKA symptoms present.

## PRACTICAL APPROACHES FOR DAPAGLIFLOZIN TREATMENT IN T1DM

People with T1DM considered eligible for dapagliflozin treatment (those meeting the criteria listed in the green section of Fig. 1) should undergo routine safety and efficacy monitoring following dapagliflozin initiation. We suggest that this includes hypoglycaemia frequency, insulin dose requirement, weight change and Hb1Ac. HbA1c provides only an approximate measure of glucose control and does not address glucose fluctuations. The introduction of CGM has enabled a more relevant end point for assessing glycaemic control to be recorded, i.e. time in range [the percentage of time a person's glucose level is within 70–180 mg/dl (3.9–10 mmol/l)] [64–66]. Time in range is inversely correlated to the risk of developing micro- and macrovascular complications and quality of life [67]. Therefore, we also recommend that time in range is recorded, using either CGM systems or frequent capillary blood glucose monitoring, for people with T1DM receiving dapagliflozin treatment.

When initiating dapagliflozin treatment we recommend insulin dose reduction, basal or

prandial, based on an assessment of an individual's glucose monitoring data. If there are concerns around nocturnal hypoglycaemia basal insulin should be reduced, whilst meal-time insulin should be reduced if there are concerns around post prandial hypoglycaemia. Insulin dose reduction should not exceed 20% to avoid DKA.

In cases of acute illness (with the exception of minor illnesses such as colds), injury, planned medical or surgical procedures requiring starvation, very low calorie diets, missed meals, stress, excessive exercise (long duration and/or high intensity exercise sessions), dehydration, missed or significantly reduced insulin dose, insulin pump malfunction or occlusion, and use of illicit drugs or excessive alcohol, dapagliflozin should be discontinued until the person's condition has stabilised and ketone levels are consistently < 0.6 mmol/l.

Anyone on dapagliflozin who presents with symptoms suggestive of DKA should have their blood ketone concentrations checked regardless of their blood glucose concentration. Dapagliflozin should be discontinued immediately if DKA is suspected or diagnosed. The management of DKA involves administering intravenous fluids to correct dehydration and to replace any salts that may be lost during ketoacidosis through passing excessive quantities of urine [68]. Insulin is also required to suppress the ketone bodies. People should be monitored for complications of DKA and its treatment, for example cerebral oedema, hypokalaemia, hyperkalaemia and hypoglycaemia. Dapagliflozin should not be restarted in those who experienced DKA during use, unless another cause for DKA is identified and resolved.

## SUMMARY

Whilst insulin remains the mainstay of treatment for T1DM, many people with T1DM are unable to meet their glycaemic targets with insulin treatment alone. Results from the DEPICT clinical trial programme have demonstrated the SGLT2 inhibitor dapagliflozin to be an effective adjunct therapy with the potential

to enable more people with T1DM to achieve their glycaemic goals. These results have led to dapagliflozin being the first oral treatment approved in Europe and having NICE and SMC approval as an adjunct to insulin for people with T1DM whose glucose levels are not adequately controlled with insulin alone. However, not all people with T1DM are suitable for dapagliflozin treatment and individual characteristics need to be considered when initiating dapagliflozin to mitigate DKA risk. To aid clinicians in selecting appropriate people for dapagliflozin treatment we have developed a traffic light system checklist. Those most likely to benefit from dapagliflozin treatment include overweight/obese people, established on stable optimised insulin therapy, with a low DKA risk profile, that have demonstrated adherence to their insulin regimen and the ability to understand and utilise relevant education relating to DKA risk and risk mitigation strategies. Dapagliflozin should be avoided in people with T1DM with low insulin needs, who are at high risk of DKA, have difficulty adhering to their insulin regimen or have difficulty understanding and following treatment instructions.

The guidance presented here provides a valuable reference for healthcare professionals contributing to diabetes treatment and care in the UK, offering expert consensus advice regarding appropriate prescribing, as well as approaches in routine clinical practice and practical approaches, for dapagliflozin treatment in T1DM.

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