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REVIEW ARTICLE

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# Sodium-glucose co-transporter inhibitors, their role in type 1 diabetes treatment and a risk mitigation strategy for preventing diabetic ketoacidosis: The STOP DKA Protocol

Ronald M. Goldenberg MD[1] | Jeremy D. Gilbert MD[2] | Irene M. Hramiak MD[3] | Vincent C. Woo MD[4] | Bernard Zinman MD[5]

[1]LMC Diabetes and Endocrinology, Concord, Ontario, Canada

[2]Division of Endocrinology and Metabolism, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

[3]Division of Endocrinology and Metabolism, St Joseph's Health Care London, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

[4]Section of Endocrinology and Metabolism, Health Sciences Centre, University of Manitoba, Winnipeg, Manitoba, Canada

[5]Lunenfeld-Tanenbaum Research Institute, Mt Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

**Correspondence**
Ronald M. Goldenberg, MD, LMC Diabetes and Endocrinology, 1600 Steeles Avenue West #5, Concord, Ontario, L4K 4M2, Canada.
Email: ronaldgoldenberg@gmail.com

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## Abstract

Recent phase 3 clinical trials have evaluated the impact of adding sodium-glucose co-transporter (SGLT) inhibitors to the type 1 diabetes armamentarium. These trials studied SGLT2 inhibitors (dapagliflozin and empagliflozin) and a dual SGLT1 and SGLT2 inhibitor (sotagliflozin), and demonstrated that these oral non-insulin antihyperglycaemic medications are able not only to improve glycaemic control, but also to reduce body weight and extend time in range without increasing rates of hypoglycaemia in type 1 diabetes. Diabetic ketoacidosis (DKA) is a feature of type 1 diabetes and the risk is increased when SGLT inhibitors are used in type 1 diabetes. To minimize the risk of DKA and still gain the multiple benefits, we developed the "STOP DKA Protocol ", an easily accessible and practical tool, that provides a risk mitigation strategy for reducing DKA in patients with type 1 diabetes being treated with SGLT inhibitors.

**KEYWORDS**
diabetic ketoacidosis, SGLT inhibitors, type 1 diabetes

## 1 | INTRODUCTION

The prevalence of type 1 diabetes is rising at a rate of ~3% per annum.[1,2] Complications associated with type 1 diabetes can be reduced by maintaining healthy behavioural habits, adhering to an intensive insulin regimen (multiple daily insulin injections [MDI] or insulin pump) and comprehensive monitoring of glucose levels,[3] but achieving and maintaining glycated haemoglobin (HbA1c) targets can be challenging, as evidenced by the less than optimal control and perhaps even worsening of control in some type 1 diabetes populations.[4,5] Since insulin-associated weight gain,[4] recurrent episodes of hypoglycaemia and risk of diabetic ketoacidosis (DKA) further complicate the day-to-day management of type 1 diabetes,[6-10] evaluations of adjunctive non-insulin therapies for type 1 diabetes are ongoing to address some of the challenges that arise from insulin monotherapy.[11]

The insulin-independent sodium-glucose co-transporter (SGLT) inhibitors may help fulfill an unmet therapeutic need in type 1 diabetes because they are associated with clinically impactful improvements in glycaemia, modest but beneficial weight loss and low hypoglycaemia risk. In March 2019, the SGLT2 inhibitor dapagliflozin received marketing approval in Europe and Japan for people with type 1 diabetes.[12,13] In April 2019, the European Medicines Agency granted marketing authorization for the dual SGLT1/SGLT2 inhibitor sotagliflozin in type 1 diabetes,[14] but the US Food and Drug Administration (FDA) has rejected sotagliflozin for the treatment of type 1 diabetes because of concerns about an increased risk of DKA.[15]

Given the likelihood that there will be increased use of SGLT inhibitors in type 1 diabetes, the present authors met in February 2019 to review the literature on SGLT inhibitor use in type 1 diabetes and the risk of SGLT inhibitor-associated DKA, with the goal of developing practical recommendations regarding a risk mitigation strategy for reducing DKA risk in these patients. Phase 3 randomized controlled trials with SGLT inhibitors in patients with type 1 diabetes and protocols focusing on prevention of DKA that were published in PubMed, or presented at professional conferences, or were in the public domain from January 1996 to February 2019, were reviewed by the authors independently and as a group. The recommendations detailed in the present paper were unanimously endorsed by the group.

### 1.1 | Search strategy and selection criteria

References for this review were identified through searches of PubMed for articles published from January 1996, to February 2019, by use of the terms "SGLT1/2 inhibitor", "SGLT2 inhibitor", "diabetic ketoacidosis", "ketosis", "canagliflozin", "dapagliflozin", "empagliflozin", "sotagliflozin", "Phase 3", "risk mitigation of diabetic ketoacidosis", "prevention of diabetic ketoacidosis", and "sick day management" in combination with the term "type 1 diabetes". Articles resulting from these searches and relevant references in the bibliographies of relevant papers were reviewed. Only articles published in English were included. Current product monographs of SGLT inhibitors, and relevant entries on the websites of the FDA Committee and the US National Library of Medicine ClinicalTrials.gov registry were also reviewed.

## 2 | MECHANISMS FOR DKA IN TYPE 1 DIABETES AND RISK ASSOCIATED WITH SGLT2 INHIBITION

Ketoacidosis can be a serious and life-threatening acute complication of type 1 diabetes and there are concerns that SGLT2 inhibition may magnify this risk. DKA encompasses acute metabolic decompensation that is characterized by hyperglycaemia, ketoacidosis, hypovolaemia and ketonuria.[16,17] It is often the first presentation of an undiagnosed type 1 diabetes state and is almost always triggered by a precipitant in known type 1 diabetes.[16] DKA is frequently caused by an excessive rise in glucagon levels in a milieu of absolute or relative insulin deficiency that in turn stimulates hepatic glycogenolysis. The resultant hyperglycaemic environment and osmotic diuresis promote a volume-depleted state that may progress to acute kidney injury. The lack of effective insulin fuels lipolysis, which provides a source of free fatty acids that are shunted through the ketosis pathway and converted into three different ketone bodies: the predominant β-hydroxybutyrate, its oxidized but less stable form acetoacetate, and acetone. The overwhelming build-up of glucose and ketone bodies in the presence of insulin deficiency culminates in elevated anion gap metabolic acidosis, with potentially fatal outcomes if DKA is not diagnosed and treated in a timely fashion.

Clinical signs and symptoms of DKA include polyuria, polydipsia, weakness, air hunger (Kussmaul breathing), nausea, vomiting, abdominal pain, shortness of breath, fruity (acetone) breath, and confusion.[16] From a biochemical standpoint, DKA is traditionally considered if test results report a pH ≤7.3, bicarbonate ≤15 mmol/L, an anion gap >12 mmol/L, positive serum or urine ketones, or a plasma glucose ≥14 mmol/L.[16] Some of the more common risk factors, and accordingly potential precipitants, for DKA are inappropriate insulin dose reduction or omission, diminished food and fluid consumption, low-carbohydrate diets, alcohol abuse, infection, abdominal crisis, thyrotoxicosis, myocardial infarction, trauma, surgery, and certain groups of pharmacotherapies.[16,17]

The SGLT inhibitors, as a result of their actions at the renal proximal tubules and the pancreatic α-cells, may, in the presence of insulin deficiency, increase the risk of ketosis or DKA (Figure 1). When the insulin dose is excessively downtitrated, SGLT2 inhibition, particularly in people with type 1 diabetes, may promote further ketogenesis and accordingly elevate the risk of developing DKA, especially during acute illness or the presence of known precipitants for ketosis or DKA. SGLT2 inhibition within the kidney can mitigate the marked hyperglycaemia of typical DKA, sometimes resulting in only moderate hyperglycaemia which can cause confusion for patients and healthcare providers, sometimes leading to missed diagnosis due to "euglycaemic" DKA where blood glucose is <14 mmol/L (Figure 1).[18]

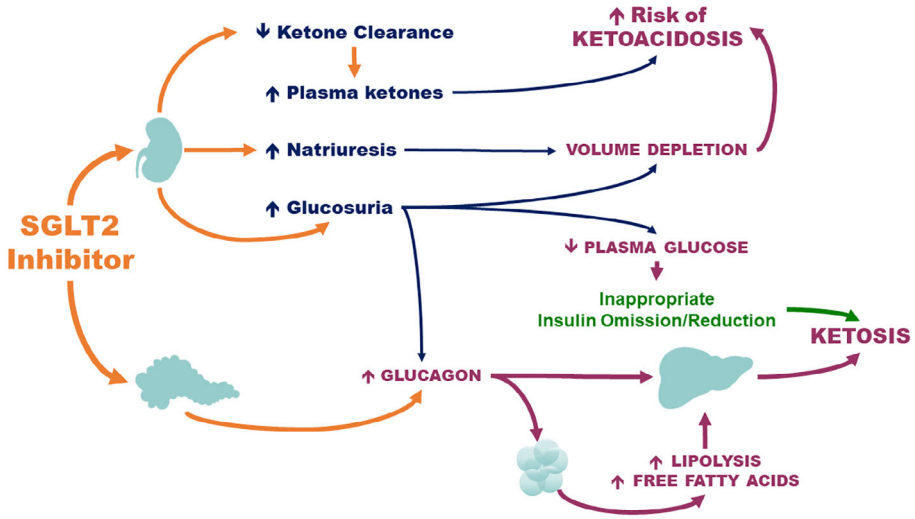



**FIGURE 1** Potential mechanisms for sodium-glucose co-transporter-2 (SGLT2) inhibitor-associated increased risk of diabetic ketoacidosis. Adapted from Priya et al. [18]

It should be emphasized that DKA, regardless of its origins, can be avoided and its complications mitigated with proper education, prompt treatment and avoidance of precipitating situations.[17] Sick-day protocols for type 1 diabetes have been used to help prevent DKA in type 1 diabetes by providing precise guidance regarding extra bolus insulin or carbohydrate as needed, depending on blood glucose and ketone levels.[19-21]

## 3 | PHASE 3 TRIALS OF SGLT INHIBITORS IN TYPE 1 DIABETES

With the overarching goal of expanding the type 1 diabetes toolbox beyond insulin, several multinational phase 3 trials in type 1 diabetes cohorts were conducted using the SGLT2 inhibitors dapagliflozin (DEPICT Programme)[22-24] and empagliflozin (EASE Programme),[25] as well as the dual SGLT1/2 inhibitor sotagliflozin (inTandem Programme). Given that the detailed results of these research programmes have already been published, only the salient points of each will be discussed. The baseline characteristics of the DEPICT, EASE and inTandem cohorts are summarized in Table S1, while the key efficacy and safety outcome measures are outlined in Tables 1 and 2, respectively.

### 3.1 | The DEPICT programme

The dapagliflozin-focused DEPICT phase 3 programme consisted of two studies: DEPICT-1 (24-wk short-term study +28-wk extension)[22,23] and DEPICT-2 (24 wk).[24] The populations of these two studies had comparable baseline age, duration of type 1 diabetes, and HbA1c levels (Table S1). While the DEPICT-1 participants were predominantly white (95%) with 60% of the cohort recruited in Europe and 27% in North America,[22] 78% of the DEPICT-2 population was white and 20% Asian, with approximately 34%, 35% and 19% of the group enrolled in Europe, North America and Japan, respectively.[24] The HbA1c entry criterion was ≥58 to ≤91 mmol/mol (≥7.5% to ≤10.5%) and approximately three-quarters of both cohorts had an HbA1c level ≥ 58 to <75 mmol/mol (≥7.5% to <9.0%) at randomization.[23,24] Only individuals with a calculated creatinine clearance of ≥60 mL/min/1.73$^2$ were included. Although the DEPICT-1 cohort used more insulin than the DEPICT-2 population, the ratio of participants using continuous subcutaneous insulin infusion (CSII) to MDI was similar in both groups with one in three using CSII and two in three using MDI.[22-24]

Both DEPICT trials included two dapagliflozin (5 and 10 mg) groups and a placebo arm.[22-24] Insulin titrations were left to the discretion of the investigators but reductions >20% were not recommended. Over 24 wk, clinically meaningful decreases in HbA1c, weight, and total daily insulin dose were observed in parallel with longer durations of time in range (Table 1). There was no clear dose dependence observed for the efficacy outcomes. While genital mycotic infections were more frequent with dapagliflozin, the incidence of hypoglycaemia and severe hypoglycaemia were balanced across the three study arms (Table 2). Compared with the placebo group, more participants in the dapagliflozin-allocated groups achieved a ≥ 0.5% HbA1c reduction without severe hypoglycaemia.

According to the protocol, all participants were advised on how to recognize potential signs and symptoms of DKA, how to manage them and how to use the blood glucose-ketone metres provided with specific instructions to contact their study site if their β-hydroxybutyrate reading was ≥0.6 mmol/L, irrespective of their glucose value. Although dapagliflozin assignment was associated with greater incidents of adjudicated DKA, no dose-related response was noted in either of the DEPICT studies (Table 2). Insulin pump failure and missed insulin injections were the predominant sources of "definite DKA" incidents.

### 3.2 | The EASE Programme

The empagliflozin-focused EASE (Empagliflozin as Adjunctive to inSulin thErapy) phase 3 programme comprised the EASE-2 (52 wk, primary endpoint at 26 wk) and EASE-3 (26 wk) trials.[25] Most of

**TABLE 1** Summary of efficacy results (over 24 to 26 weeks) from phase 3 SGLT inhibitor trials in type 1 diabetes cohorts

| | Dapagliflozin | | Empagliflozin | | Sotagliflozin | | |
|---|---|---|---|---|---|---|---|
| | DEPICT-1[22] | DEPICT-2[24] | EASE-2[25] | EASE-3[25] | inTandem1[26] | inTandem2[27] | inTandem3[28] |
| N | 778 | 813 | 730 | 975 | 793 | 782 | 1402 |
| Duration, weeks | 24 (28 extension) | 24 | 52 | 26 | 24 (28 extension) | 24 (28 extension) | 24 |
| Study arms | 5 mg | 5 mg | 10 mg | 2.5 mg | 200 mg | 200 mg | 400 mg |
| | 10 mg | 10 mg | 25 mg | 10 mg | 400 mg | 400 mg | |
| | | | | 25 mg | | | |
| | Placebo | Placebo | Placebo | Placebo | Placebo | Placebo | Placebo |
| Change in HbA1c [a], % | | | | 2.5 mg: −0.28* | | | |
| | 5 mg: −0.42* | 5 mg: −0.37* | 10 mg: −0.54* | 10 mg: −0.45* | 200 mg: −0.36† | 200 mg: −0.37† | 400 mg: −0.46† |
| | 10 mg: −0.45* | 10 mg: −0.42* | 25 mg: −0.53* | 25 mg: −0.52* | 400 mg: −0.41† | 400 mg: −0.35† | |
| Time in range (>3.9 to ≤10 mmol)[a], h/d | | | | 2.5 mg: NS | | | |
| | 5 mg: +2.2* | 5 mg: +2.2* | 10 mg: +2.9* | 10 mg: +2.6* | 200 mg: NS | 200 mg: +2.0§ | NR |
| | 10 mg: +2.6* | 10 mg: +2.6* | 25 mg: +3.1* | 25 mg: +1.8‡ | 400 mg: +2.5† | 400 mg: +3.2† | |
| Change in insulin dose[a], % | | | | 2.5 mg: −6.4* | | | |
| | 5 mg: −8.8* | 5 mg: −10.8* | 10 mg: --13.3* | 10 mg: −9.5* | 200 mg: −6.2† | 200 mg: −8.2† | 400 mg: −9.7† |
| | 10 mg: −13.2* | 10 mg: −11.1* | 25 mg: −12.7* | 25 mg: −12.6* | 400 mg: −9.7† | 400 mg: −9.5† | |
| Change in weight[a], kg (unless | | | | 2.5 mg: −1.8* | | | |
| | 5 mg: −3.0* | 5 mg: −3.2%* | 10 mg: −2.7* | 10 mg: −3.0* | 200 mg: −2.4† | 200 mg: −2.0† | 400 mg: −3.0† |
| Otherwise specified) | 10 mg: −3.7* | 10 mg: −3.7%* | 25 mg: −3.3* | 25 mg: −3.4* | 400 mg: −3.5† | 400 mg: −2.6† | |

Abbreviations: CSII, continuous subcutaneous insulin infusion; HbA1c, glycated haemoglobin; MDI, multiple daily insulin injections; NR, not reported; NS, not significant.

[a]Values shown are placebo-corrected.

*$P < 0.0001$.; †$P < 0.001$.

‡$P < 0.01$.

§$P < 0.044$.

the participants were white (EASE-2, 94%; EASE-3, 95%) and were recruited in either Europe (EASE-2, 54%; EASE-3, 63%) or North America (EASE-2, 39%; EASE-3, 25%). Although the durations of diabetes (EASE-2, 23 y; EASE-3, 21 y) and distributions of CSII to MDI users (two in five participants using CSII and three in five using MDI for EASE-2, and three in 10 using CSII and seven in 10 using MDI for EASE-3) were different, the overall baseline demographic and clinical characteristics of the two EASE trial populations were similar (Table S1). The HbA1c entry criterion of ≥58 to ≤86 mmol/mol (≥7.5% to ≤10.0%) was similar to that of the DEPICT programme. At baseline, 55% of the EASE-2 and 58% of the EASE-3 participants had an HbA1c ≥64 mmol/mol (≥8.0%). Notably, the EASE-2 and EASE-3 participants were required to also have an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m$^2$.

EASE-2 participants were randomized to one of two doses of empagliflozin (10 or 25 mg) or placebo, while EASE-3 participants were allocated one of three doses of empagliflozin (2.5, 10 or 25 mg) or placebo.[25] Insulin adjustments were left to the investigators' clinical judgement and local guideline recommendations with specific guidance to not lower insulin doses excessively. Empagliflozin use was associated with clinically significant HbA1c, weight and total daily insulin dose reductions as well as improved time in range (Table 1). Genital mycotic infections were more frequently reported in the empagliflozin vs placebo groups (Table 2). While patient-reported information, via the electronic diary entries, indicated significantly less symptomatic hypoglycaemia (<3 mmol/L) with 10 and 25 mg empagliflozin relative to placebo, pooled safety analyses of the EASE-2 and EASE-3 data suggest similar adjudicated severe hypoglycaemia rates between empagliflozin and placebo (Table 2).

Every participant was provided with a blood glucose-ketone meter and instructed to monitor ketone levels when they were feeling unwell and to seek medical care if their β-hydroxybutyrate levels exceeded 1.5 mmol/L. Notwithstanding, one DKA-related death occurred in the 25-mg empagliflozin group as a result of poor communication and delayed management despite β-hydroxybutyrate readings of up to 6.3 mmol/L, modest hyperglycaemia (blood glucose 10.5 mmol/L), flu-like symptoms, sinusitis, prolonged emesis, and abdominal pain. According to the pooled data, the 10 and 25 mg

**TABLE 2** Summary of safety results from phase 3 SGLT inhibitor trials in type 1 diabetes cohorts

| | Dapagliflozin | | Empagliflozin | | Sotagliflozin | | |
|---|---|---|---|---|---|---|---|
| | DEPICT-1[23] | DEPICT-2[24] | EASE-2/3[25] pooled | EASE-3[25] | inTandem1[26] | inTandem2[27] | inTandem3[28] |
| Genital mycotic infections, % | 5 mg: 15·5 | 5 mg: 10·0 | 10 mg: 12·8 | | 200 mg: 9·1 | 200 mg: 9·2 | |
| | 10 mg: 13·5 | 10 mg: 7·8 | 25 mg: 14·3 | | 400 mg: 13·0 | 400 mg: 11·0 | 400 mg: 6·4 |
| | | | | 2·5 mg: 5·4 | | | |
| | Placebo: 3·1 | Placebo: 1·8 | Placebo: 4·3 | Placebo: 2·5 | Placebo: 3·4 | Placebo: 2·3 | Placebo: 2·1 |
| Severe hypoglycaemia, % | 5 mg: 10·5 | 5 mg: 6·3 | 10 mg: 4·1 | | 200 mg: 6·5 | 200 mg: 5·0 | |
| | 10 mg: 8·4 | 10 mg: 8·5 | 25 mg: 2·7 | | 400 mg: 6·5 | 400 mg: 2·3 | 400 mg: 3·0 |
| | | | | 2·5 mg: 1·2 | | | |
| | Placebo: 11·5 | Placebo: 7·7 | Placebo: 3·1 | Placebo: 2·5 | Placebo: 9·7 | Placebo: 5·0 | Placebo: 2·4 |
| Adjudicated DKA, % | 5 mg: 4·0 | 5 mg: 2·6 | 10 mg: 4·3 | | 200 mg: 3·4 | 200 mg: 0 | |
| | 10 mg: 3·4 | 10 mg: 2·2 | 25 mg: 3·3 | | 400 mg: 4·2 | 400 mg: 1·5 | 400 mg: 3·0 |
| | | | | 2·5 mg: 0·8 | | | |
| | Placebo: 1·9 | Placebo: 0 | Placebo: 1·2 | Placebo: 1·2 | Placebo: 0·4 | Placebo: 0 | Placebo: 0·6 |
| % with DKA on CSII:MDI | | 5 mg: 86:14 | 10 mg: 67:33 | | 200 mg: 89:11 | 200 mg: 17:83 | |
| | | 10 mg: 50:50 | 25 mg: 56:44 | | 400 mg: 64:36 | 400 mg: 56:44 | 400 mg: 48:52 |
| | NR | | | 2·5 mg: 50:50 | | | |
| | | Placebo: NA | Placebo: 50:50 | Placebo: 33:67 | Placebo: 100:0 | Placebo: NA | Placebo: 29:71 |

Data include extension period where applicable.
Abbreviations: CSII, continuous subcutaneous insulin infusion; DKA, diabetic acidosis; MDI, multiple daily injections; NR, not reported.

empagliflozin groups had more "certain DKA" episodes than the corresponding placebo group (Table 2). Although the event rates were low, the 2.5 mg empagliflozin group (two events) had similar frequencies of "certain DKA" to the placebo group (three events) while benefiting from clinically meaningful reductions in HbA1c, weight and total daily insulin dose (Table 1). Of the 41 episodes of DKA that happened while taking empagliflozin, 15 had a blood glucose level < 13.9 mmol/L.[25] Notably, DKA occurrence was generally associated with inappropriate insulin dose reduction or at least one precipitating factor; female sex and insulin pump use were revealed as critical DKA risk factors.

## 3.3 | The inTandem Programme

Unlike the SGLT2 inhibitors canagliflozin, dapagliflozin and empagliflozin which are pharmacologically more selective for the SGLT2 protein,[26-28] sotagliflozin is a dual SGLT1/2 inhibitor.[29] It not only lowers circulating glucose levels by diminishing glucose reabsorption in the kidneys but also decreases postprandial glucose excursions by dampening and slowing intestinal glucose absorption.[30,31]

The sotagliflozin-focused inTandem phase 3 programme included the North America-based inTandem1 (24-wk core period, 28-wk extension),[32] Europe- and Israel-based inTandem2 (24-wk core period, 28-wk extension),[33] and inTandem3 (24 wk)[34] trials. White participants made up ~92%, 96% and 89% of the inTandem1,[32] inTandem2,[33] and inTandem3[28] cohorts; ≤1% of these study populations were Asian. The HbA1c entry range for the inTandem trials, at 7.0% to 11.0% (53 to 97 mmol/mol), was wider than those for the DEPICT and EASE phase III trials described above and this probably contributed to the <64 mmol/mol (<8.0%) mean baseline HbA1c values recorded for the inTandem1 and inTandem2 cohorts; the mean baseline HbA1c for the inTandem3 population was 66 mmol/mol (8.2%). The mandatory renal entry criterion was a baseline eGFR of ≥45 mL/min/1.73m$^2$. Amongst the inTandem populations at baseline, the inTandem1 participants had the longest type 1 diabetes duration, had the highest body mass index and had the lowest eGFR (Table S1). The CSII to MDI composition in the inTandem1, inTandem2, and inTandem3 cohorts were three in five to two in five, one in four to three in four, and three in five to two in five participants, respectively.

The inTandem1[32] and inTandem2[33] trials evaluated two doses of sotagliflozin (200 and 400 mg) alongside placebo, while the inTandem3 trial[34] was a two-arm (400 mg sotagliflozin vs placebo) study. Following the first dose of the study medication, insulin doses were titrated according to self-monitored blood glucose levels. Sotagliflozin was associated, across all three trials, with clinically relevant reductions in HbA1c, weight and total daily insulin dose (Table 1). Time in range was greater relative to that for the corresponding placebo group with sotagliflozin 400 mg in the inTandem1 trial and with both sotagliflozin 200 and 400 mg in the inTandem2 trial (Table 1). Genital mycotic infections (Table 2) and diarrhoea were more common in the sotagliflozin-assigned participants and dose-dependent relationships were noted for both side effects in inTandem1 and inTandem2. Documented episodes of

severe hypoglycaemia were comparable or less with sotagliflozin vs placebo in all three inTandem trials (Table 2).

All participants were provided with urine ketone strips as well as blood β-hydroxybutyrate meters and strips. They received instructions on detecting and treating ketosis and were told to contact their study site immediately if their β-hydroxybutyrate levels were > 0.6 mmol/L, regardless of their glucose readings. Significantly higher and dose-dependent rates of DKA were documented for sotagliflozin relative to placebo assignment (Table 2). Notably, mean β-hydroxybutyrate levels in the sotagliflozin groups of inTandem1 and inTandem2 rose ~0.1 mmol/L from baseline and, in each of these trials, ~60% of the sotagliflozin-associated DKA episodes presented at a blood glucose level > 13.9 mmol/L, with the remainder occurring within the blood glucose range of 8.3 to 13.9 mmol/L,[32,33] thereby underscoring that DKA can occur with only modest hyperglycaemia. Despite the heightened risk of DKA, sotagliflozin use was associated with more participants (relative to those allocated placebo) achieving an HbA1c level < 53 mmol/mol (<7.0%) in the absence of severe hypoglycaemia, DKA or weight gain.[32,33] This, coupled with patient-reported enhanced treatment satisfaction and diminished diabetes distress, suggests that there are significant merits in considering SGLT inhibitors as adjuncts to insulin therapy in type 1 diabetes.[32,33]

### 3.4 | Summary of results from phase 3 trials of SGLT inhibitors in type 1 diabetes

Taken together, the SGLT inhibitors have generally been associated with improved glycaemic control (placebo-corrected HbA1c reductions between 0.3% to 0.5%), weight loss (placebo-corrected weight differences of −2.0 to −3.5 kg), and increased time in range (placebo-corrected increases of between 2 to 3 h) in type 1 diabetes, with low risk of hypoglycaemia. Despite DKA risk mitigation strategies in the clinical trials, DKA rates in the groups assigned to an SGLT inhibitor were as high as 3% to 4%, while rates in the placebo group were no higher than 2%. Although SGLT inhibitor-associated efficacy, at current recommended doses, does not appear to follow a dose-dependent trend, it appears that the higher doses are on the flat part of the dose–response curve and lower doses provide reasonable efficacy. The data with the very low dose of empagliflozin (2.5 mg) suggest no increased risk of DKA, but the very low rates make these data inconclusive. Irrespective of this finding, an effective DKA risk mitigation strategy, if implemented concomitantly with the initiation of SGLT inhibitor therapy, may improve the benefit to risk relationship in the context of the observed DKA.

## 4 | USE OF SGLT INHIBITORS IN TYPE 1 DIABETES AND THE STOP DKA PROTOCOL RISK MITIGATION STRATEGY

Concerns around introducing SGLT inhibitors as an option for add-on therapy in type 1 diabetes persist given that DKA episodes have been shown to be greater with SGLT inhibitors relative to placebo even in tightly controlled randomized clinical trial settings. A meta-analysis conducted by the present author group revealed a 3.5-fold greater risk of DKA with SGLT inhibitors versus placebo (Figure 2). Nonetheless, the use of SGLT inhibitors in type 1 diabetes remains an attractive notion, given the potential to improve glycaemia, reduce weight, and lengthen time in range without increasing the risk of severe hypoglycaemia. Outcome measures, such as improved patient satisfaction and less diabetes distress, should also be taken into consideration.

In response to the increasing likelihood of SGLT inhibitor use in type 1 diabetes and recent approvals,[12-14,35,36] protocols and recommendations such as the STICH protocol[37] and an international consensus document[38] have been developed to provide guidance on how to effectively reduce the risk of ketosis and DKA. Although these as yet untested protocols represent an important step in proactive clinical care, they do not include pragmatic details which limits their use as "one-stop" documents that physicians, allied healthcare professionals, and patients can quickly access and refer to, especially during "sick-days". Specifically, these previously published protocols do not provide detailed recommendations on exactly how much extra bolus insulin and carbohydrate should be administered in response to specific levels of blood glucose and ketones as part of a DKA risk mitigation strategy,[37,38] despite the availability of traditional sick-day protocols for type 1 diabetes that provide such information.[19-21]

To try and bridge this care gap, we have developed the "STOP DKA Protocol" that includes a series of succinct directions with evidence-based recommendations and easy-to-follow directions. We submit that the safe use of SGLT inhibitors in type 1 diabetes begins with ensuring that only individuals with a key set of personal and clinical characteristics are prescribed these anti-hyperglycaemic agents (Figure 3). Important considerations aside from sub-optimal HbA1c control are diligent and appropriate use of insulin, ability to perform ketone monitoring every 2 to 4 h during acute illness, no recent DKA or decompensated diabetes, and no history of recurrent severe hypoglycaemia or hypoglycaemia unawareness. Given that these medications are not approved in pregnancy and that DKA during pregnancy can also be precipitated by factors such as emesis or infection[39] and can increase foetal risk,[40] SGLT inhibitors should not be prescribed to women of childbearing potential who are pregnant or planning pregnancy, or who are unwilling to use an appropriate family planning method. Furthermore, SGLT inhibitors should be discontinued as soon as an unplanned pregnancy is diagnosed. In consideration of all of these factors, we therefore recommend that only prescribers who have expertise in managing individuals with type 1 diabetes prescribe SGLT inhibitor treatment to such patients. We also suggest that insulin doses are cautiously adjusted during the initial phase of the SGLT inhibitor regimen according to current insulin: carbohydrate ratios and insulin sensitivity factors, and that basal insulin doses are modified based on glucose monitoring values (Figure 4). Finally, we encourage a comprehensive conversation with each patient on the precipitating causes of ketosis and the actions that should be taken during an acute illness if they suspect they are at imminent risk of DKA with symptoms that are suggestive of

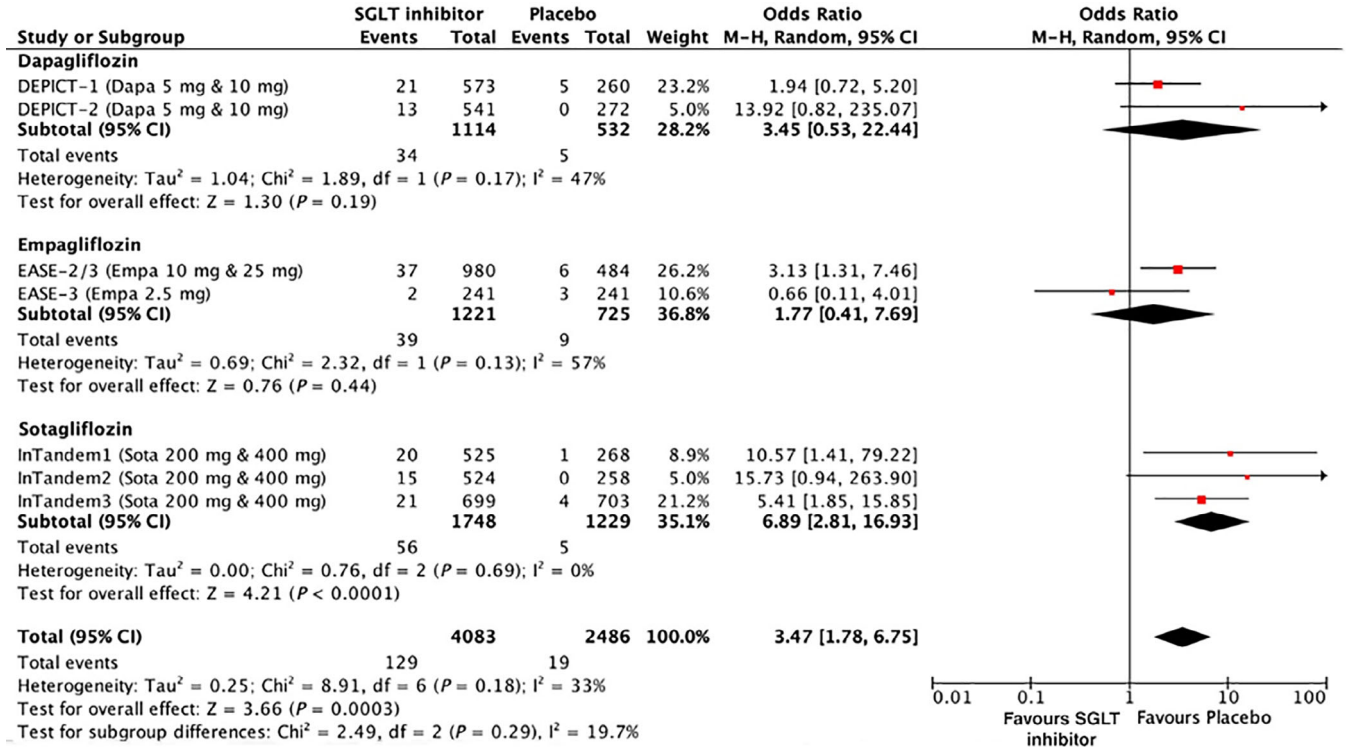



**FIGURE 2** Meta-analysis of sodium-glucose co-transporter (SGLT) inhibitors and diabetic ketoacidosis in type 1 diabetes T1D in phase 3 trials. CI, confidence interval

**Individuals with type 1 diabetes who are the most suitable candidates for an SGLT inhibitor as adjunctive therapy**

- Age ≥ 18 years
- Require HbA1C lowering and less glycaemic variability
- Adherent to monitoring and insulin administration
- No recent DKA or signs of decompensated diabetes
- No recurrent severe hypoglycaemia or hypoglycaemia unawareness
- Willing to avoid very low carbohydrates, ketogenic diets and excess alcohol consumption
- Females of childbearing potential should not be pregnant or planning pregnancy, and must be willing to use an appropriate family planning method
- Able to understand and implement a protocol with blood ketone and glucose testing for treating symptomatic ketosis (see **STOP DKA** protocol)
- Overweight or obese

**FIGURE 3** Place in therapy: Individuals with type 1 diabetes who are the most suitable candidates for sodium-glucose co-transporter (SGLT) inhibitor treatment. DKA, diabetic ketoacidosis. HbA1c, glycated haemoglobin

ketosis/DKA (Figure 5). Critical steps to follow when symptoms of DKA develop include never stopping insulin, stopping the SGLT inhibitor, keeping hydrated and taking supplemental insulin and carbohydrates every 2 to 4 h according to blood ketone and glucose levels as per the STOP DKA table (Figure 6B).

The STOP DKA Protocol has many recommendations that align with those in previously published DKA risk mitigation documents.[19-21,25,32-34,37,38] One of the unique features of the STOP DKA Protocol is that it emphasizes a stepwise approach that takes its cue from the patient's glycaemia and ketone status. Notably, the blood ketone categories for assessing ketosis in the STOP DKA Protocol have been adapted from those typically used in sick-day protocols for type 1 diabetes (Figure 6B).[20] Specifically, the "normal" category has been renamed "normal or mild" and is defined by blood ketone levels <1.0 mmol/L, the "moderate" category is defined as levels 1.0 to 1.4 mmol/L, while the other two more concerning categories, high (1.5 to 2.9 mmol/L) and extreme (≥3.0 mmol/L), retain the same boundaries. The premise for the modifications is the relatively high rate of asymptomatic ketosis (≥0.6 mmol/L) observed in the SGLT inhibitor trials in type 1 diabetes cohorts (17% to 46% at some point over 52 weeks)[25,26] and the ≥1.0 mmol/L threshold that some type 1 diabetes sick-day

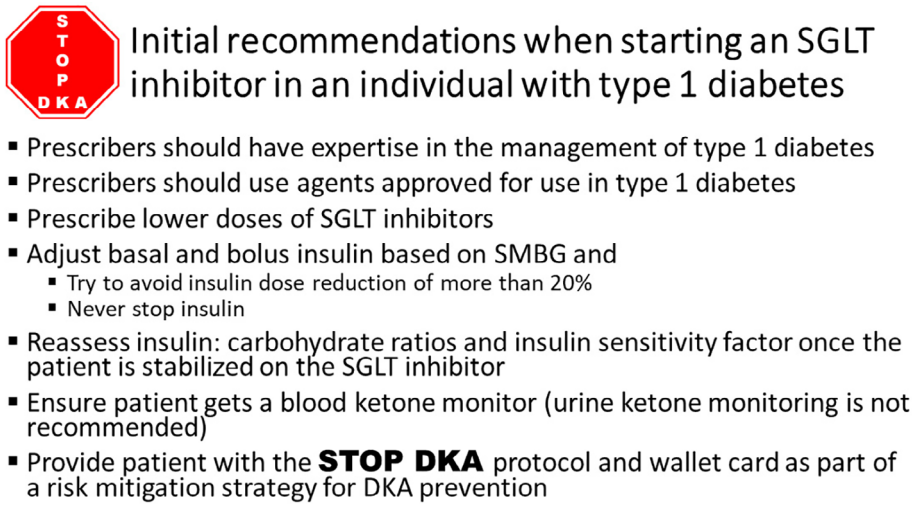



**FIGURE 4** The recommendations of the STOP DKA protocol when initiating treatment with a sodium-glucose co-transporter (SGLT) inhibitor in an individual with type 1 diabetes. DKA, diabetic ketoacidosis; SMBG, self-monitoring of blood glucose

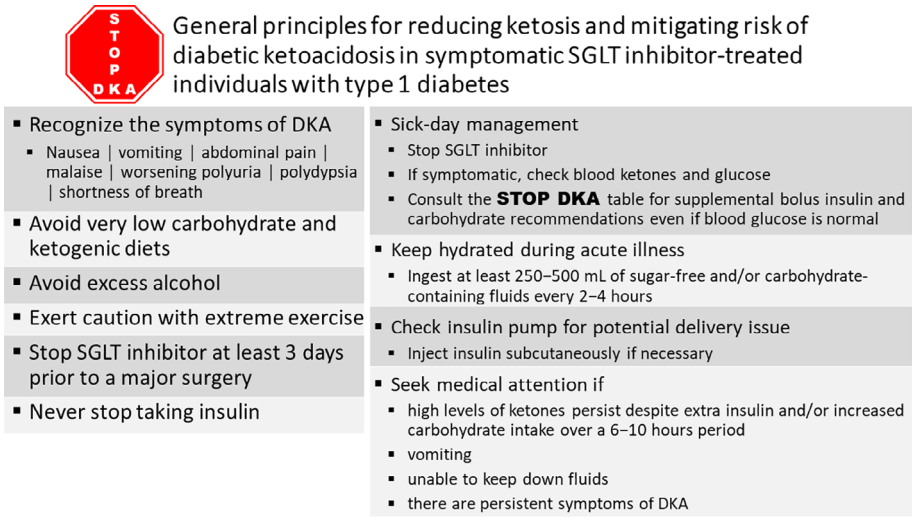



**FIGURE 5** General principles of the STOP DKA protocol for reducing ketosis and mitigating the risk of diabetic ketoacidosis in symptomatic sodium-glucose co-transporter (SGLT) inhibitor-treated individuals with type 1 diabetes. DKA, diabetic ketoacidosis

protocols use.[19] Glucose thresholds for intervention in the STOP DKA Protocol extend into the normal range (Figure 6) in recognition that DKA can occur in individuals treated with SGLT inhibitors in the absence of hyperglycaemia.

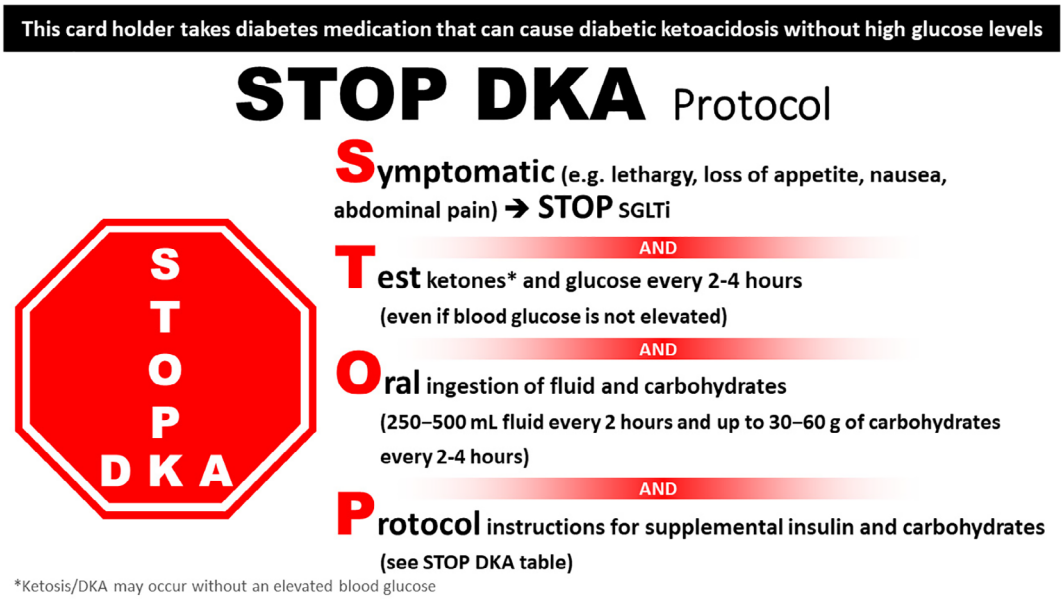
Despite the price differential which is often an important consideration, we recommend avoiding urine ketone monitoring and relying only on blood ketone monitoring for the following reasons[41]:

- Unlike blood ketone monitoring which measures β-hydroxybutyrate, urine ketone monitoring only measures acetoacetate which is unstable and unreliable for DKA diagnosis (see below)
- Unlike urine ketone monitoring, blood ketone monitoring has better sensitivity and specificity for DKA; acetoacetate levels rise with the duration of DKA and may be undetectable in urine samples during the early phases of DKA
- There is poor correlation between urine ketone and plasma ketone levels; notably, ketone estimates from urine samples represent bladder ketone levels since the last void and not current urine ketone levels
- Resolution of DKA may be missed since treatment-triggered β-hydroxybutyrate oxidation would elevate urine acetoacetate levels and present a false-positive signal indicating persistent DKA

In short, we recommend that all individuals with type 1 diabetes who are being treated with an SGLT inhibitor use blood ketone monitoring kits when checking ketone status to ensure accurate diagnosis of ketosis status.

The STOP DKA Protocol recommends a tiered approach for supplemental insulin for those with symptoms of ketosis/DKA (Figure 6B). Extra bolus insulin every 2 to 4 h based on blood ketones and glucose can be calculated based on total daily insulin dose[20] or by adjusting usual correction boluses.[21] Extra carbohydrate should be ingested when extra bolus insulin is administered, especially when blood glucose is ≤14 mmol/L (Figure 6B). To optimize the practicality of the STOP DKA Protocol, we have included a list of sugar-free fluid

(A)




(B)

**STOP DKA Considerations for Bolus Insulin and Carbohydrates**

(for moderate or higher ketones, consider increasing basal insulin by 20%–50% until ketones return to normal)

| KETONE level (mmol/L) and category (check every 2—4 h) | BLOOD GLUCOSE* (check every 2—4 h) 4·0—8·0 mmol/L (70—150 mg/dL) | 8·1—14·0 mmol/L (151—250 mg/dL) | >14 mmol/L (>250 mg/dL) |
|---|---|---|---|
| <1.0 Normal or Mild | • No extra insulin<br>• Give usual bolus to cover carbohydrates plus usual correction | • No extra insulin<br>• Give usual bolus to cover carbohydrates plus usual correction | • 5–10% TDD supplemental insulin or usual correction bolus plus usual bolus to cover carbohydrates |
| 1·0–1·4 Moderate | • 5% TDD supplemental insulin plus usual bolus to cover carbohydrates<br>• 30–45 g carbohydrates every 2–4 h | • 10% TDD supplemental insulin or 1.5x correction bolus plus usual bolus to cover carbohydrates<br>• 30 g carbohydrates every 2–4 h | • 10% TDD supplemental insulin or 1.5x correction bolus plus usual bolus to cover carbohydrates every 2-4h |
| 1·5–2·9 High | • 10% TDD supplemental insulin plus usual bolus to cover carbohydrates<br>• 30–45 g carbohydrates every 2–4 h | • 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates<br>• 30–45 g carbohydrates every 2–4 h | • 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates every 2-4 h |
| ≥3·0 Extreme | • 10% TDD supplemental insulin plus usual bolus to cover carbohydrates<br>• 45–60 g carbohydrates every 2–4 h | • 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates<br>• 30–45 g carbohydrates every 2–4 h | • 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates every 2-4 h |

**DKA is likely if ketones remain ≥3 mmol/L despite supplemental insulin**
**If symptoms are ongoing and/or you are unable to ingest fluids, go directly to the emergency department**

*Glucose values in mg/dL are not exact conversions from those in mmol/L to allow for round numbers. TDD=total daily insulin dose; usual bolus=usual bolus using insulin:carbohydrate ratio without correction. If supplemental insulin is calculated by both TDD and correction bolus methods, administer the amount that provides the higher dose of insulin.

**Sources of 15 g Simple Carbohydrates (Fluid)**

- 150 mL (2/3 cup) regular soft drink
- 250 mL (1 cup) of sports drink
- 150 mL (~2/3 cup) of juice
- 125 mL (1/2 cup) of regular gelatin dessert
- 125 mL (1/2 cup) of apple sauce
- 75 mL (1 stick) of popsicle

**Sources of Sugar-free Fluids**

- Water
- Low or zero calorie drink mix
- Diet soft drink
- Tea
- Clear soup or broth

**FIGURE 6** STOP DKA wallet or electronic card. **A**, front of card. **B**, Back of card. Adapted from the Australian diabetes educators association clinical guiding principles for sick day Management of Adults with type 1 and type 2 Diabetes,[19] ISPAD clinical practice consensus Guidelines,[20] and Seattle Children's hospital insulin sick day Management for Diabetes (non-DKA) Pathway[21]

sources that may be used to counteract the hypovolaemic state and recommended fluid sources of carbohydrate replenishments with the corresponding volumes to obtain the necessary amount of carbohydrate. Given the utility of the EASE[25] and inTandem[32-34] wallet cards, we have designed a two-sided wallet card, which we believe will serve as a compact and useful reference guide for both patients and healthcare providers (Figure 6). A PDF version of the STOP DKA Protocol wallet card may be downloaded at http://www.innovativetherapeutics.org/wp-content/uploads/2016/01/STOP-DKA-Card-Innovative-Therapeutics.pdf.

## 5 | FUTURE RESEARCH ON SGLT INHIBITORS IN TYPE 1 DIABETES

Ongoing education is necessary for both patients and healthcare providers to ensure the safe use of SGLT inhibitors in type 1 diabetes, especially for reducing the risk of DKA; however, further insights into how we can safely and maximally realize the potential of SGLT inhibitors in type 1 diabetes is still needed. Accordingly, we propose the following as potential directions for future investigations: initiatives that examine the efficacy of a risk evaluation and mitigation strategy for

DKA prevention such as the STOP DKA Protocol; mechanistic inquiries to gain an accurate perspective of the risk of DKA; clinical trials and real-world surveys to document long-term efficacy and safety data, as well as patient satisfaction; and clinical studies to assess the practicality of prescribing lower doses of SGLT inhibitors, measure cardio-renal outcomes, and test the feasibility of use in individuals with renal insufficiency.

## 6 | SUMMARY

The SGLT2 inhibitors have been valuable agents for managing type 2 diabetes. The mechanisms and sites of action of SGLT inhibitors support the concept that they may help fulfill an unmet therapeutic need in type 1 diabetes. This is now well supported by the overall efficacy data that have emerged from phase 3 trials in type 1 diabetes: lower $HbA_{1c}$ levels, weight loss, and improved time in range with low hypoglycaemia risk. However, the SGLT inhibitors must be used safely and appropriately in type 1 diabetes and the safe use of the class is strongly dependent on using them in the right patients at the right time (Figure 3). Implementing a practical risk mitigation strategy for DKA such as the STOP DKA Protocol should help in reducing the risk of DKA. In brief, adherence to these general principles should result in an acceptable risk of DKA while retaining the advantages associated with SGLT inhibitor use in many individuals with type 1 diabetes.

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## CONFLICT OF INTEREST

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## AUTHOR CONTRIBUTIONS

R.M.G. conceived the work, prepared the literature search, and drafted the original versions of the tables, figures, and text. R.M.G., J.D.G., I.M.H., V.C.W. and B.Z. contributed substantially to the development of the recommendations as well as to the critical revision of the manuscript. The final version of the manuscript was reviewed and approved by every author, all of whom agree to act as guarantors of the work.

## ORCID

*Ronald M. Goldenberg* https://orcid.org/0000-0002-1788-3255
*Bernard Zinman* https://orcid.org/0000-0002-0041-1876

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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