



# International Consensus on Risk Management of Diabetic Ketoacidosis in Patients With Type 1 Diabetes Treated With Sodium–Glucose Cotransporter (SGLT) Inhibitors

*Diabetes Care* 2019;42:1147–1154 | <https://doi.org/10.2337/dc18-2316>

Thomas Danne,<sup>1</sup> Satish Garg,<sup>2</sup>  
Anne L. Peters,<sup>3</sup> John B. Buse,<sup>4</sup>  
Chantal Mathieu,<sup>5</sup> Jeremy H. Pettus,<sup>6</sup>  
Charles M. Alexander,<sup>7</sup> Tadej Battelino,<sup>8</sup>  
F. Javier Ampudia-Blasco,<sup>9</sup>  
Bruce W. Bode,<sup>10</sup> Bertrand Cariou,<sup>11</sup>  
Kelly L. Close,<sup>12</sup> Paresh Dandona,<sup>13</sup>  
Sanjoy Dutta,<sup>14</sup> Ele Ferrannini,<sup>15</sup>  
Spiros Fournelos,<sup>16</sup> George Grunberger,<sup>17</sup>  
Simon R. Heller,<sup>18</sup> Robert R. Henry,<sup>6</sup>  
Martin J. Kurian,<sup>19</sup> Jake A. Kushner,<sup>20</sup>  
Tal Oron,<sup>21,22</sup> Christopher G. Parkin,<sup>23</sup>  
Thomas R. Pieber,<sup>24</sup> Helena W. Rodbard,<sup>25</sup>  
Desmond Schatz,<sup>26</sup> Jay S. Skyler,<sup>27</sup>  
William V. Tamborlane,<sup>28</sup>  
Koutaro Yokote,<sup>29</sup> and Moshe Phillip<sup>21,22</sup>

**Sodium–glucose cotransporter (SGLT) inhibitors are new oral antidiabetes medications shown to effectively reduce glycosylated hemoglobin (A1C) and glycemic variability, blood pressure, and body weight without intrinsic properties to cause hypoglycemia in people with type 1 diabetes. However, recent studies, particularly in individuals with type 1 diabetes, have demonstrated increases in the absolute risk of diabetic ketoacidosis (DKA). Some cases presented with near-normal blood glucose levels or mild hyperglycemia, complicating the recognition/diagnosis of DKA and potentially delaying treatment. Several SGLT inhibitors are currently under review by the U.S. Food and Drug Administration and European regulatory agencies as adjuncts to insulin therapy in people with type 1 diabetes. Strategies must be developed and disseminated to the medical community to mitigate the associated DKA risk. This Consensus Report reviews current data regarding SGLT inhibitor use and provides recommendations to enhance the safety of SGLT inhibitors in people with type 1 diabetes.**

Intensive insulin management remains the only option for effective treatment of type 1 diabetes. However, fear of hypoglycemia (1–3) and weight gain (4) are often barriers to optimal use of insulin therapy. Consequently, there exist an unmet need and great patient interest in adjunct therapies of type 1 diabetes to improve glycemic control without increasing the risk of hypoglycemia and weight gain. Most noninsulin adjunctive therapies approved for type 2 diabetes are not effective in type 1 diabetes. The only one approved in the U.S. is pramlintide, and it is not used much clinically owing to its limited efficacy and unfavorable side effects. One novel strategy studied to improve outcomes in patients with type 1 diabetes is the addition of sodium–glucose cotransporter (SGLT) inhibitors as an adjunct to insulin therapy.

SGLT2 inhibitors block the SGLT2 transporter in the proximal tubule of the kidney resulting in glycosuria and natriuresis. SGLT1+2 inhibitors have the additional effect of locally inhibiting SGLT1 in the gastrointestinal tract, delaying absorption of glucose and galactose from the intestinal tract. The use of SGLT2 inhibitors in the setting of type 2 diabetes is now recommended (5) to prevent major adverse cardiovascular events (including mortality and hospitalizations for heart failure) in patients with

<sup>1</sup>Diabetes Centre for Children and Adolescents, Kinder- und Jugendkrankenhaus Auf der Bult, Hannover, Germany

<sup>2</sup>University of Colorado Denver and Barbara Davis Center for Diabetes, Aurora, CO

<sup>3</sup>Keck School of Medicine of the University of Southern California, Los Angeles, CA

<sup>4</sup>University of North Carolina School of Medicine, Chapel Hill, NC

<sup>5</sup>Department of Endocrinology, UZ Gasthuisberg, KU Leuven, Leuven, Belgium

<sup>6</sup>Division of Endocrinology and Metabolism, Department of Medicine, University of California, San Diego, San Diego, CA

<sup>7</sup>Alexander Associates LLC, Gwynedd Valley, PA

<sup>8</sup>Department of Pediatric Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, University Medical Centre Ljubljana, and Faculty of Medicine, University of Ljubljana, Slovenia

<sup>9</sup>Clinic University Hospital of Valencia, Valencia, Spain

<sup>10</sup>Atlanta Diabetes Associates, Atlanta, GA

<sup>11</sup>Clinique d'endocrinologie, L'institut du thorax, CHU Nantes, CIC 1413 INSERM, Nantes, France

<sup>12</sup>The diaTribe Foundation, San Francisco, CA

<sup>13</sup>Division of Endocrinology, Diabetes and Metabolism, University at Buffalo, The State University of New York, Buffalo, NY

<sup>14</sup>JDRF International, New York, NY

<sup>15</sup>National Research Council (CNR) Institute of Clinical Physiology, Pisa, Italy

<sup>16</sup>Department of Diabetes and Endocrinology, Royal Melbourne Hospital, Melbourne, Australia

<sup>17</sup>Grunberger Diabetes Institute, Bloomfield Hills, MI

<sup>18</sup>Academic Unit of Diabetes, Endocrinology & Metabolism, University of Sheffield, Sheffield, U.K.

<sup>19</sup>Close Concerns, San Francisco, CA

<sup>20</sup>McNair Interests, Houston, TX

<sup>21</sup>Jesse Z and Sara Lea Shafer Institute of Endocrinology and Diabetes, National Center for

established atherosclerotic cardiovascular disease as well as chronic kidney disease, based on the results of the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) (6,7) and the Canagliflozin Cardiovascular Assessment Study (CANVAS) (8,9). Similar reductions in hospitalizations for heart failure were seen in patients at high risk for cardiovascular disease (10).

These agents are being increasingly used off-label in management of type 1 diabetes (11) and are currently under review by the U.S. Food and Drug Administration as well as by the European Medicines Agency as an adjunct to insulin therapy in adults with type 1 diabetes. Decisions from the U.S. and European agencies for sotagliflozin, an SGLT1+2 inhibitor, and dapagliflozin, an SGLT2 inhibitor, are expected in 2019. It should be noted that ipragliflozin, an SGLT2 inhibitor currently available in Japan, Korea, and Thailand, has recently been approved in Japan to be coadministered with insulin to adults with type 1 diabetes (12).

In adults with type 1 diabetes, SGLT inhibitor therapy with dapagliflozin added to intensified insulin therapy showed moderate efficacy, reducing A1C by  $\sim 0.4\%$  (4.4 mmol/mol) at 6 months and  $\sim 0.3\%$  (3.3 mmol/mol) at 12 months while demonstrating improvement in time in range (70–180 mg/dL [3.0–10.0 mmol/L]) by continuous glucose monitoring (CGM) without an increase in time with hypoglycemia ( $<70$  mg/dL [ $<3.9$  mmol/L]) (13–15). Importantly, this benefit was demonstrated in the setting of blinded studies where patients treated with both SGLT inhibitor and placebo had ongoing protocol-driven adjustments of basal and bolus therapy (16). This improvement in glycemia was achieved in the context of  $\sim 11.0\%$  reduction of total daily insulin

dose compared with  $\sim 8.0\%$  reduction in the placebo group ( $P < 0.0001$ ). Interestingly, although no substantial dose dependency was observed for the improvement in glycemic control, weight change did seem to be somewhat dose dependent (16). Moderate weight loss ( $\sim 3.2\%$  at 6 months and  $\sim 3.5\%$  at 12 months) was seen with the SGLT inhibitor as compared with placebo ( $\sim 0.1\%$ ) (16).

The EASE (Empagliflozin as Adjunctive to insulin therapy) phase 3 program included two double-blind, placebo-controlled trials investigating the efficacy and safety of empagliflozin as an adjunct to insulin therapy in adults with type 1 diabetes (17). Significant reductions in A1C were observed at the three empagliflozin doses studied: 2.5 mg ( $-0.28\%$  [3.1 mmol/mol]), 10 mg ( $-0.54\%$  [5.9 mmol/mol]), and 25 mg ( $-0.53\%$  [5.8 mmol/mol]), all  $P < 0.0001$ , with no increase in hypoglycemia. Significant reductions in weight, blood pressure, and total daily insulin dose were also observed in the empagliflozin treatment groups. Treatment with sotagliflozin (SGLT1+2 inhibitor) showed similar reductions in A1C, weight, systolic blood pressure, and total daily insulin dose (18).

In studies that included patient-reported outcomes or quality of life assessment, significant benefits were associated with SGLT inhibition in type 1 diabetes (19,20). Results regarding the incidence or rate of severe hypoglycemia were somewhat mixed, but, in general, the expected increase in severe hypoglycemia in the context of the greater reduction in A1C with the SGLT inhibitor was not observed. CGM further revealed improved time in range, generally  $\sim 3$  h/day, with all three SGLT inhibitors (sotagliflozin, dapagliflozin, empagliflozin) studied at the highest dose, without an increase in time in hypoglycemia.

Although SGLT inhibitor therapy has shown improvements in glycemic control, weight loss, and other risk reductions, current studies have reported a significant increase in the risk for DKA (13–15,17,21,22), which appears to be dose dependent (13–15,17). Supplementary Table 1 presents information about the differences in DKA adjudication definitions. Supplementary Tables 2–4 review the clinical data of the pivotal trials for SGLT inhibitors in type 1 diabetes. The definitions for probable/possible/potential events were very different between the programs, and the trigger event identification process to identify potential events differed. Therefore, a direct comparison between the programs is difficult. Supplementary Fig. 1 presents a common process for DKA monitoring and adjudication in clinical studies. Importantly, some study participants who experienced DKA presented with only slightly elevated glucose levels, a condition referred to as euglycemic DKA (euDKA). When euDKA occurs, the usual clinical alert provided by hyperglycemia is absent and many case reports have demonstrated substantial delays in recognition, diagnosis, and treatment.

The Advanced Technologies & Treatment for Diabetes (ATTD) Congress convened a consensus conference in June 2018, with an international panel of 26 physicians and researchers with expertise in using SGLT inhibitor therapy, to develop strategies to mitigate DKA and euDKA risk. Following the conference, 24 participants completed an online survey to better delineate areas of consensus and areas of disagreement, including appropriate cut points for DKA diagnosis, risk factors, patient selection, and patient management. This review summarizes our consensus recommendations and key considerations for the safe use of SGLT inhibitors in patients with type 1

Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

<sup>22</sup>Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

<sup>23</sup>CGParkin Communications, Inc., Boulder City, NV

<sup>24</sup>Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, Graz, Austria

<sup>25</sup>Endocrine and Metabolic Consultants, Rockville, MD

<sup>26</sup>Division of Endocrinology, Department of Pediatrics, University of Florida, Gainesville, FL

<sup>27</sup>Division of Endocrinology, Diabetes and Metabolism, Miller School of Medicine, University of Miami, Miami, FL

<sup>28</sup>Department of Pediatrics, Yale School of Medicine, New Haven, CT

<sup>29</sup>Department of Diabetes, Metabolism and Endocrinology, Chiba University Graduate School of Medicine, Chiba, Japan

Corresponding author: Christopher G. Parkin, [chris@cgparkin.org](mailto:chris@cgparkin.org)

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-2316/-/DC1>.

This article is featured in a podcast available at <http://www.diabetesjournals.org/content/diabetes-core-update-podcasts>.

© 2019 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

See accompanying article, p. 991.

diabetes. Scientific questions requiring further research are also identified.

**BACKGROUND**

**Ketoacidosis With SGLT Inhibitors in Type 1 Diabetes: Possible Mechanisms**

Several mechanisms likely operate to predispose individuals with type 1 diabetes to develop ketosis (increased levels of β-hydroxybutyrate and acetoacetate) and ketoacidosis in the setting of SGLT inhibitor therapy. The reduction of total daily insulin doses and particularly basal insulin in patients treated with an SGLT inhibitor may cause failure to suppress lipolysis and ketogenesis even if blood glucose levels do not rise (23,24). SGLT inhibitors are associated with an increase in glucagon, perhaps as a result of urinary glucose loss or through direct action upon pancreatic α-cells, which increases lipolysis and ketogenesis (25,26). The balance of glucagon and insulin are critical to regulating these metabolic pathways (23,27–29). It has also been proposed that SGLT inhibitors decrease renal clearance of ketone bodies (23).

Starvation ketosis, which is also mediated by reduced insulin levels and increased glucagon levels, can occur in individuals without diabetes with prolonged periods of fasting or very low-carbohydrate diets (often referred to as ketogenic diets) and is accelerated by physical activity, physiological stress (e.g., infection or pregnancy), and alcohol consumption. SGLT inhibition, by increasing urinary glucose losses, may be causing a pharmacologic push toward ketosis, particularly when the behavioral

and physiological factors mentioned are present (23,30). Readers are referred elsewhere for a comprehensive review of the physiology and pharmacology of this system (23,31).

**Diagnosing DKA**

The spectrum of ketosis (measured ketones in the blood or urine) to ketoacidosis (ketosis associated with anion gap metabolic acidosis) is quite broad, involving an approximately 10-fold range of ketone body concentration. The increase in ketonemia and ketonuria is not due to reduced renal ketone excretion (9) unless there is severe dehydration (hence, frequently with DKA).

DKA is usually associated with hyperglycemia in individuals with diabetes and serum ketones >3.0 mmol/L. Similar to DKA, the development of euDKA is characterized by anion gap metabolic acidosis, ketonemia, and ketonuria but with normal or modestly elevated blood glucose levels (<250 mg/dL [13.9 mmol/L]) (31,32). As such, patients can present with full-blown DKA but with glucose levels <250 mg/dL (<13.9 mmol/L). Table 1 lists the levels of serum/urine ketones that are associated with concern and what should be done in response to those values.

**APPROACHES TO PREVENTION OF DKA RELATED TO SGLT INHIBITOR THERAPY**

**Patient Selection**

Selection of appropriate patients for SGLT inhibitor therapy is critical for minimizing DKA risk. The paramount criterion

for patient selection is presentation with normal ketone levels (<0.6 mmol/L blood ketones; negative urine ketones). However, the risk factors associated with each patient’s lifestyle/behaviors (Table 2) and willingness/ability to follow prescribed regimens for monitoring ketones and responding appropriately to elevated ketone levels when present must also be considered (Table 3).

As a general guideline, SGLT inhibitor therapy should not be used in patients using low-carbohydrate or ketogenic diets as, anecdotally, they seem to be at increased risk of adverse ketosis effects and certainly create a diagnostic dilemma in evaluating the clinical significance of ketosis. Also, with regard to diet, patients who skip meals and/or consume excessive alcohol seem to be at increased risk. Patients who use an insulin pump are also at increased risk because of the possibility of pump or insulin infusion set malfunction. Patients with type 1 diabetes who miss insulin doses, have recurrent episodes of DKA, or experience prolonged significant hyperglycemia (particularly >350 mg/dL) and/or display low engagement with their diabetes regimen are certainly at high risk of DKA when on SGLT inhibitor therapy. However, these patients may be considered candidates if they can demonstrate the sustained necessary changes in lifestyle and self-management behaviors, as well as monitor their capillary/urine ketone levels.

Because adequate studies of SGLT inhibitors have not been performed in pregnant women, SGLT2 inhibitors should

**Table 1—Cut points for ketosis/DKA and corresponding remedial actions**

Blood ketone (BHB) level	Urine ketone*	Remedial actions
<0.6 mmol/L (normal)	Negative	No action needed
0.6–1.5 mmol/L (ketonemia)	Trace or small	Treat as follows or per clinician instructions: <ul style="list-style-type: none"> <li>• Ingest 15–30 g rapidly absorbed carbohydrate and maintain fluid consumption (300–500 mL) hourly</li> <li>• Administer rapid-acting insulin based on carbohydrate intake (hourly)</li> <li>• Check blood/urine ketones (every 3–4 h) until resolution</li> <li>• Check blood glucose frequently to avoid hyperglycemia and hypoglycemia</li> </ul> Seek medical attention if levels persist and symptoms present
1.6–3.0 mmol/L (impending DKA)	Moderate	Follow treatment recommendations listed above Consider seeking immediate medical attention
>3.0 mmol/L (probable DKA)	Large to very large	Seek immediate medical attention

BHB, β-hydroxybutyrate. \*Urine ketone concentrations are dependent on hydration and other factors; these values do not closely correlate with blood BHB levels.

**Table 2—Risk factors for DKA associated with SGLT inhibitor therapy**

Risk level for DKA	Factor
Moderate/high	<ul style="list-style-type: none"> <li>• Reduced basal insulin by more than 10–20%</li> <li>• Insulin pump or infusion site failure</li> <li>• Reduced or inconsistent carbohydrate intake</li> <li>• Excessive alcohol use</li> <li>• Use of illicit drugs</li> <li>• Volume depletion/dehydration</li> <li>• Acute illness of any sort (viral or bacterial)</li> <li>• Vomiting</li> </ul>
Low/moderate	<ul style="list-style-type: none"> <li>• Vigorous or prolonged exercise</li> <li>• Reduced prandial insulin dose by more than 10–20%</li> <li>• Travel with disruption in usual schedule/insulin regimen</li> <li>• Insulin pump use</li> </ul>
Minimal/low	<ul style="list-style-type: none"> <li>• Low BMI (&lt;25 kg/m<sup>2</sup>)</li> <li>• Inconsistent caloric intake</li> <li>• Moderate alcohol use*</li> <li>• Female sex</li> </ul>

\*If ketone levels increase from baseline.

not be used in pregnant women with type 1 diabetes as pregnancy is associated with an increased risk of ketoacidosis, which is associated with a high risk of fetal mortality (33). No data are currently available on use of SGLT inhibitor therapy in children and youth <18 years of age with type 1 diabetes.

### Insulin Dose Adjustments

When initiating SGLT inhibitor therapy in individuals with type 1 diabetes, insulin must be reduced cautiously in order to prevent ketosis and DKA. In clinical trials of SGLT2 inhibitors, the proportional dose reductions seen for basal and bolus insulin were similar (13,14) or reductions were primarily in basal insulin doses (34).

However, when using sotagliflozin, the dose reductions observed in the clinical trials were largely in the prandial or meal-associated insulin (18). Therefore, the clinician needs to individualize such reductions for each patient based primarily on degree of hyperglycemia as well as the specific SGLT inhibitor used.

In patients who are relatively well controlled (A1C <7.5% [ $<58$  mmol/mol]), 10–20% reductions in insulin doses, accompanied by frequent blood glucose monitoring or CGM, and rapid readjustment with health care provider input are recommended. Some patients may need to decrease their carbohydrate intake in order to accommodate the reduced insulin dose as long as ketone levels do not rise. Others may need to increase their carbohydrate intake in order to maintain adequate exogenous insulin levels to prevent ketosis. Adjustments in insulin doses should be made at least every 24–48 h initially.

For less well-controlled patients (A1C  $\geq 7.5\%$  [ $\geq 58$  mmol/mol]), only slight or no reductions in prandial and basal insulin may be needed. Determination of which insulin doses should be reduced should be based on detailed assessment of blood glucose profiles or, preferably, CGM data as well as hypoglycemia history and awareness.

### Initiation and Dosing of SGLT Inhibitors

As discussed, blood ketone ( $\beta$ -hydroxybutyrate) levels should be  $<0.6$  mmol/L prior to initiating SGLT inhibitor therapy. If blood ketones are  $\geq 0.6$  mmol/L, additional baseline blood

ketone values should be obtained to determine whether the elevated ketones are normal for the patient (due to lifestyle factors) or an indication of chronic inadequate insulin coverage in the fasting state.

We recommend that SGLT inhibitor therapy be initiated at the lowest dose available. Some suggest even splitting tablets for the currently marketed SGLT2 inhibitors to get to lower-than-marketed doses. Patients who have a good experience with low-dose SGLT inhibitor therapy could be considered for dose escalation based on clinical response.

As observed in clinical trials, lower doses of SGLT inhibitors are associated with reasonable efficacy and lower risks of DKA (13,14). Specifically, the EASE program included a lower dose (i.e., empagliflozin 2.5 mg), which is not currently available, in addition to the doses approved for use in patients with type 2 diabetes (i.e., empagliflozin 10 and 25 mg) (17). The ketoacidosis rate was comparable between empagliflozin 2.5 mg and placebo but increased with doses of 10 mg and 25 mg. These data suggest that SGLT2 inhibitor dose selection itself is an important factor in terms of DKA risk mitigation.

### Ketone Monitoring

Ketone testing is required because development of euDKA cannot be detected by glucose monitoring. Although laboratory testing is the most precise method for assessing  $\beta$ -hydroxybutyrate levels in the clinical settings (35), self-testing via a blood ketone meter or urine testing is sufficient for patient use in detecting ketosis and early development of DKA—blood ketone ( $\beta$ -hydroxybutyrate) concentrations  $>0.6$  mmol/L or trace (or greater) urine ketones (acetoacetate).

We recommend patient self-measurement of capillary blood ketones, specifically  $\beta$ -hydroxybutyrate (the most prevalent ketone body) as a matter of routine in assessing the metabolic state of patients with type 1 diabetes treated with SGLT inhibitors (36–40). In patients who cannot afford or do not have access to capillary blood ketone measurements, urine ketone measurements are acceptable. However, it must be recognized that the urine test only measures acetoacetate, not  $\beta$ -hydroxybutyrate, and estimation of urine ketones will be an average of the concentration within the urine held in the bladder since the last void (41).

**Table 3—Patient criteria for SGLT inhibitor therapy**

• >18 years of age
• Adherent to prescribed diabetes regimen
• Willing/able to perform all prescribed diabetes self-management tasks
• Performs blood glucose monitoring or uses CGM as prescribed
• Willing/able to perform ketone testing as prescribed
• Has received education/training in ketone testing and interpreting/acting upon test results
• Has access to ketone testing materials
• Has immediate access to a clinician if blood or urine ketone levels are elevated
• No or moderate use of alcohol; no use of illicit drugs
• Unimpaired cognition
• Not pregnant or wanting to become pregnant

Moreover, urine output is frequently low in patients with DKA due to dehydration, and it may take several hours until urine is produced again, which may delay appropriate treatment (41). Because  $\beta$ -hydroxybutyrate is oxidized to acetoacetate with treatment of DKA, urine ketone readings will rise with treatment even if blood  $\beta$ -hydroxybutyrate concentrations are dropping (41). The paradoxical rise in urine ketones could give the false impression that the DKA is not resolving.

Patients should not rely on a single ketone measurement for definitive determination of their metabolic state. In patients with elevated ketones, glucose and ketone measurements should be rechecked every 1–3 h to ensure resolution of ketonemia/ketonuria. Symptoms of ketosis do not correlate well with ketone levels, which can increase rapidly.

Currently, there is no evidence to support specific testing regimens. However, it is the consensus of the group that ketone testing frequency should be individualized according to the patient's lifestyle and/or risk factors after initiating therapy. However, for all patients, we recommend that ketones be measured with any symptoms consistent with DKA, including malaise, fatigue, nausea, and vomiting. Ketones should also be measured with changes in diet, activity, or insulin dose as well as for concomitant events such as infection, dehydration, surgery, injury, pump occlusion/malfunction, or stress. It should be noted that treatment with SGLT inhibitors in patients using insulin pumps with automated features, including low-glucose insulin suspend and hybrid closed-loop, has not been well studied. Ketones should be measured repetitively for as long as symptoms persist or stressors remain. Random or periodic measurement of ketones is also recommended to ensure that ketone testing supplies are readily available and not expired.

#### **Holding or Discontinuing SGLT Inhibitor Therapy**

Any nausea, vomiting, or abdominal discomfort should prompt discontinuation of SGLT inhibitor therapy and evaluation of ketosis. SGLT inhibitor therapy should be withheld immediately if the patient is hospitalized, acutely ill, or unable to eat and drink normally. SGLT inhibitors should be withheld or discontinued prior to any medical procedure (ideally for 3 days), particularly if the patient will be reducing food intake or will not be

allowed to eat or drink for some time before and after the procedure.

For patients who are switching their type of insulin therapy (e.g., injections to insulin pump therapy) or changing from manual mode to automode on an automated insulin delivery system, it is prudent that they hold their SGLT inhibitor until their insulin doses are adjusted, blood glucose is controlled, and ketone levels are normal.

#### **DKA Prevention**

When elevated ketones are present, patients should be instructed to first discontinue SGLT inhibitor therapy until ketones are back to baseline. Treatment must be initiated swiftly once elevated ketones are identified in order to avoid DKA and potential hospitalization. The key to treatment of ketosis is for patients to inject insulin and consume carbohydrates, as well as maintain adequate hydration. Even if the patient is on an insulin pump, it is often best to provide insulin by injection as the first step in treatment. If on insulin pump therapy, it is very important for patients to begin to troubleshoot the pump and give insulin by injection until they are sure that the insulin pump is delivering insulin and any pump or infusion set issues are resolved. Recommendations for DKA prevention are presented in Table 1.

#### **DKA Treatment**

If the symptoms and/or ketones are worsening, the patient should seek immediate medical assistance. Whether to send a patient for further medical evaluation needs to be decided individually for each patient based upon specific characteristics and may need to occur sooner in the presence of additional comorbidities, such as cardiovascular disease or pneumonia. If patients go to the emergency department or an urgent care center, they should inform the medical personnel that they have type 1 diabetes and are on an SGLT inhibitor, which means they may have DKA with a relatively normal glucose level. Patients should have an evaluation that includes measurements of capillary/venous pH, blood bicarbonate, anion gap, and blood ketones ( $\beta$ -hydroxybutyrate).

#### **Patient and Clinician Education**

##### **Patients**

All patients should receive thorough instruction in DKA risk factors, ketone

monitoring, and treatment protocols. This is especially important for patients for whom administration of both insulin and carbohydrates is counterintuitive when glucose levels are only slightly elevated.

Patients should also be instructed about anticipated situations in which they may wish to hold their SGLT inhibitor. This includes such events as increased physical activity and situations where they may become dehydrated or they choose to alter their dietary intake or consume more alcohol. Therefore, it is important that patients become familiar with how these factors impact their ketone levels. Importantly, patients should be empowered to make decisions regarding whether or not to stop their SGLT inhibitor. Stopping it for a day, if in doubt, is prudent and should not cause significant metabolic issues.

All patients treated with SGLT inhibitor therapy should be provided with educational materials (e.g., wallet cards, refrigerator magnets, etc.) that can serve as reminders regarding risk factors and provide "quick reference" resources for treatment.

##### **Clinicians**

Only practitioners knowledgeable in these principles should prescribe SGLT inhibitor therapy in people with type 1 diabetes. In the medical settings, DKA should be considered in all patients taking SGLT inhibitors who present with typical symptoms of DKA even when glucose levels are normal. Because current guidelines for treatment identify DKA as a hyperglycemic emergency, it is important that emergency departments are made aware that DKA can present without overtly elevated glucose levels in patients treated with SGLT inhibitors. This message must be part of all professional education initiatives. Educational components of a risk mitigation strategy when introducing SGLT inhibitors for type 1 diabetes are summarized in Table 4, which includes the STICH protocol for risk mitigation (42).

#### **RESEARCH QUESTIONS**

Because much of the evidence for DKA risk has been garnered from randomized clinical trials with highly selected patients, additional research is needed to evaluate the efficacy and DKA risk of SGLT

**Table 4—Educational components of a risk mitigation strategy when introducing SGLT inhibitors for type 1 diabetes**

Patient education	<ul style="list-style-type: none"> <li>● All patients initiating SGLT inhibitor therapy should receive through training/education in the following areas:               <ul style="list-style-type: none"> <li>○ DKA causes and symptoms</li> <li>○ Euglycemic ketoacidosis</li> <li>○ Importance of ketone monitoring</li> <li>○ Use of ketone monitoring—training in testing procedure, proactive monitoring, situations when monitoring is indicated</li> <li>○ Treatment protocol for addressing ketosis</li> <li>○ Guidance in when to seek medical attention</li> </ul> </li> </ul>
Clinician education	<ul style="list-style-type: none"> <li>● All prescribing clinicians should acquire full understanding of the safe use and risks associated with SGLT inhibitor therapy:               <ul style="list-style-type: none"> <li>○ Criteria for patient selection—baseline ketone level, demographic/behavioral considerations</li> <li>○ Training/educational needs of patients—detection (ketone levels, symptoms), prevention strategies, treatment</li> <li>○ Potential for missed DKA, euDKA</li> <li>○ Treatment strategies—STICH protocol recommended:                   <ul style="list-style-type: none"> <li>■ Stop SGLT inhibitor treatment for a few days</li> <li>■ Insulin administration</li> <li>■ Carbohydrate consumption</li> <li>■ Hydration with a suitable drink (e.g., water or noncaloric athletic drink with balanced electrolytes)</li> </ul> </li> </ul> </li> </ul>
Risk Communication	<ul style="list-style-type: none"> <li>● Product labeling, website</li> <li>● Health care professional education</li> <li>● Medication guide, patient alert card*</li> </ul>

\*See Supplementary Fig. 4.

inhibitors in larger cohorts of patients with type 1 diabetes, using real-world methodologies. It is also important to develop a better understanding of the apparent dose-dependent effect in both increased efficacy and increased DKA rates associated with higher doses of SGLT inhibitors. Currently available studies (13,22) suggest these relationships but were not definitive.

Another question that warrants further investigation is whether patients with extremely elevated A1C levels (>10% [86 mmol/mol]) should receive treatment with SGLT inhibitors. The 5-year follow-up data from the T1D Exchange reported significantly higher (>15%) incidence of DKA in patients with A1C above 10% (86 mmol/mol) but not treated with an SGLT inhibitor (43). Although some believe it is reasonable to recommend this therapy to all patients who are both willing and able to monitor ketones as prescribed and take the appropriate remedial steps as needed, some clinicians recommend adjusting insulin therapy to reduce A1C levels prior to initiation of SGLT inhibitor treatment, and others recommend not using these agents in anyone with an A1C >10% (86 mmol/mol). Additional data are needed to

determine whether elevated A1C is an independent risk factor for DKA in patients who are meticulous in their diabetes self-management.

Developing an evidence base and algorithms to support decisions on reducing insulin doses should also be a priority for future research. Although the recommendations for insulin adjustment presented in this Consensus Report are based on clinical trial experience, clinical judgment, and real-world experience with SGLT inhibitor therapy, more definitive approaches are needed to matching each formulation and dosage to reductions in the most appropriate insulin (prandial or basal) and to establishing the degree of reduction that will lessen DKA risk. There is a strong case for a clinical evaluation of the guidance presented here.

Determination of optimal frequency of ketone monitoring and how and when to respond to ketone levels that rise above the normal range also remain as questions for further investigation. Although daily ketone testing may reduce DKA risk, this approach could also lead to lower adherence if ketone levels are mostly low or zero and the patient does not feel that

this frequency of monitoring is needed (44). Moreover, there is no evidence that daily ketone monitoring actually prevents DKA; available clinical trials in patients with type 1 diabetes did not use protocols that included daily monitoring of ketones. Cost also represents a major barrier to increased frequency of ketone monitoring, which could further discourage patients from the practice. Although urine ketone strips are convenient and much less expensive than blood ketone meters/strips (\$0.20 vs. \$2.09 per strip, not including the cost of the blood ketone meter) (45), the sensitivity and specificity of the urine test for DKA are substantially less than those of blood ketone measurement (41).

Finally, we recommend evaluation of both patient and clinician education programs and materials. Although educational interventions for basic DKA prevention in type 1 diabetes appear to be effective, many patients are not familiar with ketone testing and DKA. It will be important to evaluate the efficacy and usability of materials specific to SGLT inhibitor therapy. At the very least, insulin pump-treated patients must be convinced that a “gluco-centric” approach to identifying infusion site problems is not appropriate when receiving adjunctive therapy with an SGLT inhibitor.

## CONCLUSIONS

SGLT inhibitor therapy is a promising option for adjunctive therapy in the treatment of type 1 diabetes. Studies in this population have already demonstrated that use of SGLT inhibitors confers significant benefits, including improved glycemic control, increased time in range, improved quality of life measures, and weight loss (13,18,22). Moreover, the cardiovascular and renal benefits demonstrated in the type 2 diabetes trials (7,8) may be a class effect that positively impacts all patients regardless of the type of diabetes.

As observed in clinical trials, the rate of DKA in the placebo arm is substantially less than incidence rates from the latest registries where the incidence of DKA with SGLT inhibitor therapy is relatively low. The increase in the absolute risk in SGLT inhibitor-treated patients versus placebo-treated patients was in the range of 4% per year, and in these clinical patients it was lower than reported in general practice but still higher than seen

with placebo. The potential benefits of SGLT inhibitors for people with type 1 diabetes appear clinically meaningful. Thus, strategies for mitigating DKA risk are vital to the adoption and safe use of SGLT inhibitors in all diabetes populations, particularly those requiring insulin. The consensus recommendations presented herein are based on current evidence from clinical trials and our expertise and experience using SGLT inhibitors with our patients with type 1 diabetes. Our goal is to provide a starting point for the safe use of SGLT inhibitor therapy in this population and to encourage additional investigations that will provide more comprehensive, evidence-based guidance for clinicians and patients.

**Acknowledgments.** The consensus group participants wish to thank ATTD for organizing and coordinating the meeting. We also wish to thank Rachel Naveh (ATTD) for assistance in organizing the meeting and Charles Alexander (Alexander Associates LLC), Martin Kurian (Close Concerns), and Richard Wood (dQ&A Market Research) for support in survey/questionnaire development and analysis. Editorial support was provided by James Hirsch.

**Funding and Duality of Interest.** Support for the DKA mitigation consensus conference and development of this article was provided by the ATTD Congress. Boehringer Ingelheim, AstraZeneca, and Sanofi provided an unrestricted grant to ATTD to support the consensus meeting. Editorial support was provided through a grant from The diaTribe Foundation. T.D. has received speaker honoraria and research support from and has consulted for Abbott, Bayer, Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, Dexcom, Eli Lilly, Medtronic, Novo Nordisk, Sanofi, and Roche. T.D. is a shareholder of DreaMed Ltd. S.G. reports receiving grant support and travel support from Sanofi, Lexicon, Novo Nordisk, MannKind, Roche Diagnostics, Zealand, Senseonics Inc., and Medtronic and grant support paid to his institution from Eli Lilly and Company, Dexcom, and Johnson & Johnson. A.L.P. has served on an advisory panel for Novo Nordisk, Eli Lilly and Company, Sanofi, Merck, Bigfoot, Abbott, MannKind, Lexicon, Becton Dickinson, Livongo, and Boehringer Ingelheim; has conducted clinical research for Dexcom, AstraZeneca, and MannKind; and participated in a speakers' bureau for Novo Nordisk. J.B.B. has received contracted consulting fees, paid to his institution, and travel support from Adocia, AstraZeneca, Dexcom, Elcelyx Therapeutics, Eli Lilly, Intarcia Therapeutics, Lexicon, Metavention, NovaTarg, Novo Nordisk, Sanofi, Senseonics, and vTv Therapeutics and grant support from AstraZeneca, Boehringer Ingelheim, Johnson & Johnson, Lexicon, Novo Nordisk, Sanofi, Theracos, and vTv Therapeutics. J.B.B. holds stock options in Mellitus Health and PhaseBio and served on the board of the AstraZeneca HealthCare Foundation. J.B.B. is supported by

a grant from the National Institutes of Health (UL1TR002489). C.M. serves or has served on the advisory panels for Novo Nordisk, Sanofi, Merck Sharp & Dohme, Eli Lilly and Company, Novartis, Bristol-Myers Squibb, AstraZeneca, Janssen Pharmaceuticals, Boehringer Ingelheim, Hanmi Pharmaceuticals, Roche, Medtronic, ActoBio Therapeutics, Pfizer, Dianax, and UCB; financial compensation for these activities has been received by her institution (KU Leuven). KU Leuven has received research support for C.M. from Medtronic, Novo Nordisk, Sanofi, Merck Sharp & Dohme, Eli Lilly and Company, Roche, Abbott, ActoBio Therapeutics, and Novartis. C.M. serves or has served on the speakers' bureaus for Novo Nordisk, Sanofi, Merck Sharp & Dohme, Eli Lilly and Company, Boehringer Ingelheim, AstraZeneca, and Novartis; financial compensation for these activities has been received by KU Leuven. J.H.P. has received consulting fees from Sanofi, Novo Nordisk, MannKind, Eli Lilly and Company, Insulet, and Senseonics. T.B. received honoraria for participating on the speakers' bureaus of Eli Lilly and Company, Bayer, Novo Nordisk, Medtronic, Sanofi, and Roche. T.B. served on advisory boards of Novo Nordisk, Sanofi, Eli Lilly and Company, Boehringer, Medtronic, and Bayer Health Care. T.B.'s institution received research grant support, with receipt of travel and accommodation expenses in some cases, from Abbott, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz, and Diamo. T.B. owns stock in DreaMed. F.J.A.-B. has served on advisory panels for Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, GlaxoSmithKline, LifeScan, Medtronic, Merck, Novartis, Novo Nordisk, Pfizer, Roche, and Sanofi and has received research support from Abbott, AstraZeneca, Boehringer Ingelheim, Bayer, Eli Lilly and Company, GlaxoSmithKline, LifeScan, Merck, Novo Nordisk, Pfizer, Sanofi, and Servier. B.W.B. reports stock ownership in Aseko; the receipt of consulting fees from Adocia, Intarcia, Janssen, Medtronic, MannKind, Novo Nordisk, and Sanofi; and the receipt of speakers' bureau fees from AstraZeneca, Eli Lilly/Boehringer Ingelheim, Janssen, Medtronic, MannKind, Novo Nordisk, and Sanofi. His employer (Atlanta Diabetes Associates) has received grant and research support from Abbott, Becton Dickinson, Dexcom, Diasome, GlaxoSmithKline, Janssen, Lexicon, Eli Lilly/Boehringer Ingelheim, Medtronic, the National Institutes of Health, Novo Nordisk, Sanofi, and Senseonics. B.C. has received research funding from Pfizer, Sanofi, and Regeneron Pharmaceuticals, Inc., and has served on scientific advisory boards and received honoraria or consulting fees from Abbott, Amgen, AstraZeneca, Genfit, Pierre Fabre, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, Regeneron, and Sanofi. K.L.C. and M.J.K. are employees of The diaTribe Foundation, which has received educational grants from SGLT2 manufacturers, including AstraZeneca, Lexicon, Sanofi, Boehringer Ingelheim, Eli Lilly and Company, and Merck. P.D. serves on the advisory boards of AstraZeneca, Novo Nordisk, Sanofi, Boehringer Ingelheim, Merck, Intarcia, and AbbVie and has received research grants from all of these companies, apart from Intarcia. E.F. received consulting and advisory board fees from Boehringer Ingelheim/Eli Lilly and Company, Sanofi, Janssen, AstraZeneca, and Tanabe-Mitsubishi; speaker honoraria from AstraZeneca,

Novo Nordisk, Sanofi, Tanabe-Mitsubishi, Eli Lilly and Company, Boehringer Ingelheim, and Merck Sharp & Dohme; and research grant support from Boehringer Ingelheim and AstraZeneca. S.F. has received speaker honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Medtronic, Novo Nordisk, and Sanofi-Aventis. G.G. has received research funding from Novo Nordisk, Eli Lilly and Company, and Medtronic (all revenues to his institution) and has served on speakers' bureaus of Novo Nordisk, Sanofi, Eli Lilly and Company, Boehringer Ingelheim, and AstraZeneca. S.R.H. has served as an advisory board panel member for Eli Lilly and Company, Novo Nordisk, Boehringer Ingelheim, Zealand Pharma, UNEEG medical, and Takeda Pharmaceuticals and is a member of speakers' bureaus for AstraZeneca, Novo Nordisk, Eli Lilly and Company, and Merck Sharp & Dohme. R.R.H. has served on advisory panels for AstraZeneca, Boehringer Ingelheim, Elcelyx Therapeutics, Intarcia Therapeutics, Ionis Pharmaceuticals, Janssen Pharmaceuticals, and Sanofi; has served as a consultant for Alere and Intarcia Therapeutics; and has received research support from AstaMed, Eli Lilly and Company, Hitachi, Lexicon, and ViaCyte. J.A.K. consults for Lexicon and Sanofi. He is employed by McNair Interests, a private equity group with several investments in life science-related for-profit and nonprofit entities. C.G.P. has received consulting fees from Dexcom, Insulet, Johnson & Johnson, MannKind, Roche Diabetes Care, and Senseonics. T.R.P. has served on advisory boards or received speaker honoraria from Novo Nordisk, Eli Lilly and Company, AstraZeneca, Roche Diagnostics, and Bristol-Myers Squibb. H.W.R. has conducted clinical research studies, lectured, and served as a consultant on advisory panels for AstraZeneca, Boehringer Ingelheim, Gann Lee, Janssen, Lexicon, Eli Lilly and Company, Merck, Novo Nordisk, Sanofi, and Regeneron. D.S. has served as a consultant to Sanofi, had a TrialNet grant in part from Sanofi, has been on the external advisory board for Sankyo, and had grants from JDRF and The Leona M. and Harry B. Helmsley Charitable Trust. J.S.S. has acted as an advisor to Adocia, Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, DalCor, Dance Biopharm, Diavacs, Duologics, Elcelyx, Eli Lilly and Company, Esperion, Geneuro, Ideal Life, Immunomolecular Therapeutics, Intarcia, Intrexon/ActoBio, Kamada, Merck, Orgenesis, Sanofi, Servier, Tolerion, vTv Therapeutics, Valeritas, ViaCyte, and Zafgen. J.S.S. has research funding from the National Institutes of Health, JDRF, and the Diabetes Research Institute Foundation; chairs the Strategic Advisory Board of the European Union INNODIA consortium; and has served as a member of the board of directors of Dexcom, Intarcia, and Moerae Matrix. W.V.T. declared receiving consulting fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk, Sanofi, and Medtronic. K.Y. has received speaker honoraria and research support and has consulted for Abbott, Astellas, AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Dainippon-Sumitomo, Eli Lilly and Company, Kowa, Kyowahakko-Kirin, Medtronic, Merck Sharp & Dohme, Novo Nordisk, Novartis, Ono, Sanofi, Taisho-Toyama, Takeda, and Tanabe-Mitsubishi. M.P.'s institute has received grants or research support from Medtronic, Novo Nordisk, Roche, Eli Lilly and Company, Merck, Sanofi, Bristol-Myers Squibb, Kamada, AstraZeneca,

and Lexicon. M.P. has received honoraria or consultation fees from Sanofi, Medtronic, Novo Nordisk, and Eli Lilly; has participated in advisory boards for Sanofi, Medtronic, AstraZeneca, and Eli Lilly; and is a stock shareholder in DreaMed Diabetes. No other potential conflicts of interest relevant to this article were reported.

The funding sources had no involvement in the content presented in this article.

## References

- Cryer PE. Hypoglycemia: still the limiting factor in the glycemic management of diabetes. *Endocr Pract* 2008;14:750–756
- Polonsky WH, Anderson BJ, Lohrer PA, Aponte JE, Jacobson AM, Cole CF. Insulin omission in women with IDDM. *Diabetes Care* 1994;17:1178–1185
- Polonsky WH, Anderson BJ, Lohrer PA, et al. Assessment of diabetes-related distress. *Diabetes Care* 1995;18:754–760
- Peyrot M, Skovlund SE, Landgraf R. Epidemiology and correlates of weight worry in the multinational Diabetes Attitudes, Wishes and Needs study. *Curr Med Res Opin* 2009;25:1985–1993
- U.S. Food and Drug Administration. FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood [Internet], 15 May 2015. Available from <https://www.fda.gov/downloads/drugs/drugSafety/ucm446954.pdf>. Accessed 25 May 2018
- Wanner C, Inzucchi SE, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;375:323–334
- Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–2128
- Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644–657
- Ferrannini E, Baldi S, Frascerra S, et al. Renal handling of ketones in response to sodium-glucose cotransporter 2 inhibition in patients with type 2 diabetes. *Diabetes Care* 2017;40:771–776
- Wiviott SD, Raz I, Bonaca MP, et al.; DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380:347–357
- Lyons SK, Hermann JM, Miller KM, et al. Use of adjuvant pharmacotherapy in type 1 diabetes: international comparison of 49,996 individuals in the prospective diabetes follow-up and T1D Exchange registries. *Diabetes Care* 2017;40:e139–e140
- Astellas Pharma. Approval of Suglat tablets, selective SGLT2 inhibitor, for additional indication of type 1 diabetes mellitus and additional dosage and administration in Japan. Press release [Internet], 2018. Available from [https://www.astellas.com/system/files/news/2018-12/181221\\_2\\_Eg\\_2.pdf](https://www.astellas.com/system/files/news/2018-12/181221_2_Eg_2.pdf). Accessed 24 December 2018
- Dandona P, Mathieu C, Phillip M, et al.; DEPICT-1 Investigators. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol* 2017;5:864–876
- Mathieu C, Dandona P, Gillard P, et al.; DEPICT-2 Investigators. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 study): 24-week results from a randomized controlled trial. *Diabetes Care* 2018;41:1938–1946
- Dandona P, Mathieu C, Phillip M, et al.; DEPICT-1 Investigators. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: the DEPICT-1 52-week study. *Diabetes Care* 2018;41:2552–2559
- McCrimmon RJ, Henry RR. SGLT inhibitor adjunct therapy in type 1 diabetes. *Diabetologia* 2018;61:2126–2133
- Rosenstock J, Marquard J, Laffel LM, et al. Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the EASE Trials. *Diabetes Care* 2018;41:2560–2569
- Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. *N Engl J Med* 2017;377:2337–2348
- Rodbard HW, Peters AL, Slee A, Cao A, Traina SB, Alba M. The effect of canagliflozin, a sodium glucose cotransporter 2 inhibitor, on glycemic end points assessed by continuous glucose monitoring and patient-reported outcomes among people with type 1 diabetes. *Diabetes Care* 2017;40:171–180
- Buse JB, Garg SK, Rosenstock J, et al. Fifty-two-week efficacy and safety of sotagliflozin, a dual SGLT and SGLT2 inhibitor, as adjunct therapy to insulin in adults with type 1 diabetes (inTandem1) (Abstract). *Diabetes* 2018;67(Suppl. 1):212-OR
- Sands AT, Zambrowicz BP, Rosenstock J, et al. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes. *Diabetes Care* 2015;38:1181–1188
- Henry RR, Thakkar P, Tong C, Polidori D, Alba M. Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. *Diabetes Care* 2015;38:2258–2265
- Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. *J Clin Endocrinol Metab* 2015;100:2849–2852
- Foster DW, McGarry JD. The regulation of ketogenesis. *Ciba Found Symp* 1982;87:120–131
- Liljenquist JE, Bomboy JD, Lewis SB, et al. Effects of glucagon on lipolysis and ketogenesis in normal and diabetic men. *J Clin Invest* 1974;53:190–197
- Kibbey RG. SGLT-2 inhibition and glucagon: cause for alarm? *Trends Endocrinol Metab* 2015;26:337–338
- Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. *Diabetes Care* 2015;38:1638–1642
- Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest* 2014;124:499–508
- Bonner C, Kerr-Conte J, Gmyr V, et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. *Nat Med* 2015;21:512–517
- Candelario N, Wykretowicz J. The DKA that wasn't: a case of euglycemic diabetic ketoacidosis due to empagliflozin. *Oxf Med Case Rep* 2016;2016:144–146
- Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. *J Diabetes Invest* 2016;7:135–138
- Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. *Diabetes Care* 2015;38:1687–1693
- Mosley JF II, Smith L, Everton E, Fellner C. Sodium-glucose linked transporter 2 (SGLT2) inhibitors in the management of type-2 diabetes: a drug class overview. *P T* 2015;40:451–462
- Perkins BA, Cherney DZ, Partridge H, et al. Sodium-glucose cotransporter 2 inhibition and glycemic control in type 1 diabetes: results of an 8-week open-label proof-of-concept trial. *Diabetes Care* 2014;37:1480–1483
- Laffel LM, Wentzell K, Loughlin C, Tovar A, Moltz K, Brink S. Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with T1DM: a randomized clinical trial. *Diabet Med* 2006;23:278–284
- Brooke J, Stiel M, Ojo O. Evaluation of the accuracy of capillary hydroxybutyrate measurement compared with other measurements in the diagnosis of diabetic ketoacidosis: a systematic review. *Int J Environ Res Public Health* 2016;13:E837
- Misra S, Oliver NS. Utility of ketone measurement in the prevention, diagnosis and management of diabetic ketoacidosis. *Diabet Med* 2015;32:14–23
- Klocker AA, Phelan H, Twigg SM, Craig ME. Blood  $\beta$ -hydroxybutyrate vs. urine acetoacetate testing for the prevention and management of ketoacidosis in type 1 diabetes: a systematic review. *Diabet Med* 2013;30:818–824
- Plüddemann A, Heneghan C, Price CP, Wolstenholme J, Thompson M. Point-of-care blood test for ketones in patients with diabetes: primary care diagnostic technology update. *Br J Gen Pract* 2011;61:530–531
- Sheikh-Ali M, Karon BS, Basu A, et al. Can serum  $\beta$ -hydroxybutyrate be used to diagnose diabetic ketoacidosis? *Diabetes Care* 2008;31:643–647
- Dhatariya K. Blood ketones: measurement, interpretation, limitations, and utility in the management of diabetic ketoacidosis. *Rev Diabet Stud* 2016;13:217–225
- Garg SK, Peters AL, Buse JB, Danne T. Strategy for mitigating DKA risk in patients with type 1 diabetes on adjunctive treatment with SGLT inhibitors: a STICH protocol. *Diabetes Technol Ther* 2018;20:571–575
- Weinstock RS, Xing D, Maahs DM, et al.; T1D Exchange Clinic Network. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. *J Clin Endocrinol Metab* 2013;98:3411–3419
- Albanese-O'Neill A, Wu M, Miller KM, Jacobsen L, Haller MJ, Schatz D; T1D Exchange Clinic Network. Poor adherence to ketone testing in patients with type 1 diabetes. *Diabetes Care* 2017;40:e38–e39
- Walmart. Health/Diabetes Care/Ketone Test Strips [Internet]. Available from [https://www.walmart.com/browse/health/ketone-test-strips/976760\\_1231757\\_3866822](https://www.walmart.com/browse/health/ketone-test-strips/976760_1231757_3866822). Accessed 21 December 2018