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AACE/ACE Position Statement

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON THE ASSOCIATION OF SGLT-2 INHIBITORS AND DIABETIC KETOACIDOSIS

Yehuda Handelsman, MD, FACP, FNLA, FACE, Co-Chair[1]; Robert R. Henry, MD, FACE, Co-Chair[2]; Zachary T. Bloomgarden, MD, MACE[3]; Sam Dagogo-Jack, MD, DM, FRCP, FACE[4]; Ralph A. DeFronzo, MD, BMS, MS, BS[5]; Daniel Einhorn, MD, FACP, FACE[6]; Ele Ferrannini, MD[7]; Vivian A. Fonseca, MD, FACE[8]; Alan J. Garber, MD, PhD, FACE[9]; George Grunberger, MD, FACP, FACE[10]; Derek LeRoith, MD, PhD, FACE[11]; Guillermo E. Umpierrez, MD, FACP, FACE[12]; Matthew R. Weir, MD[13]

This document represents the official position of the American Association of Clinical Endocrinologists and American College of Endocrinology. Where there were no randomized controlled trials or specific U.S. FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Position statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician.

From the [1]Medical Director & Principal Investigator, Metabolic Institute of America, Immediate Past President, American College of Endocrinology, Tarzana, California, [2]Professor of Medicine, University of California San Diego, Chief, Section of Diabetes, Endocrinology & Metabolism, VA San Diego Healthcare System, San Diego, California, [3]Clinical Professor, Icahn School of Medicine at Mount Sinai, Editor, the *Journal of Diabetes*, New York, New York, [4]A.C. Mullins Professor & Director, Division of Endocrinology, Diabetes and Metabolism, University of Tennessee Health Science Center, Memphis, Tennessee, [5]Professor of Medicine, Chief, Diabetes Division, University of Texas Health Science Center at San Antonio, San Antonio, Texas, [6]Immediate Past President, American College of Endocrinology, Past-President, American Association of Clinical Endocrinologists, Medical Director, Scripps Whittier Diabetes Institute, Clinical Professor of Medicine, UCSD, Associate Editor, *Journal of Diabetes*, Diabetes and Endocrine Associates, La Jolla, California, [7]Professor of Internal Medicine, CNR Institute of Clinical Physiology, Pisa, Italy, [8]Professor of Medicine and Pharmacology, Tullis Tulane Alumni Chair in Diabetes, Chief, Section of Endocrinology, Tulane University Health Sciences Center, New Orleans, Louisiana, [9]Professor, Departments of Medicine, Biochemistry, Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas, [10]President, American Association of Clinical Endocrinologists, Chairman, Grunberger Diabetes Institute, Bloomfield Hills, Michigan, Clinical Professor, Internal Medicine and Molecular Medicine & Genetics, Wayne State University School of Medicine, Detroit, Michigan, Professor, Internal Medicine, Oakland University William Beaumont School of Medicine, Rochester, Michigan, Visiting Professor, Internal Medicine, First Faculty of Medicine, Charles University, Prague, Czech Republic, [11]Director of Research, Division of Endocrinology, Diabetes and Bone Diseases, Mount Sinai School of Medicine, New York, New York, [12]Professor of Medicine, Emory University School of Medicine, Director, Endocrinology Section, Grady Health System, Atlanta, Georgia, and [13]Chief of Nephrology Division, Professor of Medicine, University of Maryland School of Medicine, Baltimore, Maryland.
Address correspondence to American Association of Clinical Endocrinologists, 245 Riverside Ave, Suite 200, Jacksonville, FL 32202.
E-mail: publications@aace.com. DOI:10.4158/EP161292.PS

EXECUTIVE SUMMARY

Recent reports of diabetic ketoacidosis (DKA) occurring in conjunction with sodium glucose-cotransporter 2 (SGLT-2) inhibitor therapy have raised concerns that these agents may increase the risk of DKA, especially among patients taking exogenous insulin. On May 15, 2015, the U.S. Food and Drug Administration (FDA) issued the following safety communication concerning 20 cases of acidosis in patients taking SGLT-2 inhibitors reported to the FDA Adverse Event Reporting System (1):

> *"We are continuing to investigate this safety issue and will determine whether changes are needed in the prescribing information for…SGLT-2 inhibitors…Health care professionals should evaluate for the presence of acidosis, including ketoacidosis, in patients experiencing [DKA] signs or symptoms; discontinue SGLT-2 inhibitors if acidosis is confirmed; and take appropriate measures to correct the acidosis and monitor sugar levels."*

To address these concerns, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) convened a public conference in which experts from Europe and the United States evaluated relevant cases and clinical data (see Appendix for agenda and participants). A detailed report on the scientific evidence for the association of SGLT-2 inhibitors with DKA follows this statement.

The **key points** described in this document are as follows:

1. For individuals with type 2 diabetes (T2D), it is unclear whether DKA occurs at a higher frequency than it did before the advent of SGLT-2 inhibitors. In 2010 in the United States, 142,000 hospitalizations were associated with DKA, 23% of which occurred in patients with T2D (2). In Denmark, the rate of DKA before the SGLT-2 inhibitor era was 1 to 2 cases per 1,000 patients with diabetes. The incidence of DKA in clinical trials of SGLT-2 inhibitors with T2D was 0.2 to 0.8 cases per 1,000 patient-years (3,4). However, the low observed incidence in clinical trials may not reflect real-world experience. Seemingly, most of the reported cases have come from clinical practice rather than trials. Patients with type 1 diabetes (T1D) have a higher risk of DKA than those with T2D, and their risk of developing DKA while taking SGLT-2 inhibitors should be further elevated. Up to 9.4% of patients with T1D participating in SGLT-2 inhibitor clinical trials developed ketosis, and up to 6% experienced DKA (5,6).
2. However, more data are needed to elucidate this relationship, as many recently reported cases have been poorly documented. Not all cases may have been actual DKA but rather ketosis (build-up of ketones)—which is not necessarily harmful—perhaps resulting from an earlier shift to fat metabolism potentially impacted by a mechanism related to SGLT-2 inhibition.
3. The majority of cases of SGLT-2 inhibitor–associated DKA have occurred in individuals with diabetes who are insulin deficient, such as those with latent autoimmune diabetes in adults (LADA) and T1D, but cases have also occurred in some patients with long-standing T1D. Generally, these patients presented with classical DKA signs and symptoms. However, some cases had an atypical presentation with a lower-than-expected degree of hyperglycemia. Lower-than-expected hyperglycemia, however, was observed with other agents years before the introduction of SGLT-2 inhibitors (7,8).
4. Precipitants of DKA in T1D and T2D include surgery, extensive exercise, myocardial infarction, stroke, severe infections, prolonged fasting, and other stressful physical and medical conditions; almost all cases of SGLT-2 inhibitor–associated DKA occurred in patients challenged with metabolically stressful events. In both T1D and T2D, diabetes-associated metabolic changes commonly shift substrate metabolism from carbohydrate to fat oxidation, thereby predisposing patients to more readily develop ketonemia and DKA during SGLT-2 inhibitor use.
5. For patients taking an SGLT-2 inhibitor who present with symptoms suggestive of DKA, such as abdominal pain, nausea, vomiting, fatigue, and dyspnea, a diagnosis of DKA should be considered and appropriate work-up carried out. Although a low bicarbonate and/or the presence of positive urinary ketones may be suggestive of DKA, these measures may be inaccurate. Therefore, AACE/ACE recommends direct measurement of blood ketones (β-hydroxybutyrate) and arterial pH as necessary to confirm the diagnosis. Normal or modestly elevated blood glucose does not exclude the diagnosis of DKA during SGLT-2 inhibitor use.
6. For management of DKA in patients taking SGLT-2 inhibitors, stop the drug immediately and proceed with traditional DKA treatment protocols. Note that although the drug is discontinued, SGLT-2 inhibitor–mediated increases in urinary glucose loss may persist for several days.
7. To minimize the risk of DKA associated with SGLT-2 inhibitors, AACE recommends the following:

- Consider stopping the SGLT-2 inhibitor at least 24 hours prior to elective surgery, planned invasive procedures, or anticipated severe stressful physical activity such as running a marathon. As noted above, urinary glucose loss due to SGLT-2 inhibition may persist after the drug is stopped.
- Avoid stopping insulin or decreasing the dose excessively.
- For emergency surgery or any extreme stress event, the drug should be stopped immediately, and appropriate clinical care should be provided.
- Routine measurement of urine ketones is not recommended during use of SGLT-2 inhibitors because this measurement can be misleading. Instead, measurement of blood ketones is preferred for diagnosis of DKA in symptomatic patients.
- Patients taking SGLT-2 inhibitors should avoid excess alcohol intake and very-low-carbohydrate/ketogenic diets.

8. SGLT-2 inhibitors are not approved for use in T1D. However, AACE/ACE encourages continuation of ongoing studies because initial study results have shown that SGLT-2 inhibition has a promising impact on glycemic regulation in this population. AACE/ACE suggests that in future T1D trials, lower SGLT-2 inhibitor doses should be considered and insulin dose should not routinely be reduced when SGLT-2 inhibitors are begun. Instead, insulin should be adjusted based on the individual response to the SGLT-2 inhibitor, and carbohydrate intake should be maintained. These recommendations should also be applied if SGLT-2 inhibitors are prescribed off-label to patients with T1D and may be considered for patients with T2D who receive exogenous insulin therapy.

Conclusion: Review of available data on the prevalence of SGLT-2–associated DKA as well as the impact of SGLT-2 inhibitors on human metabolism suggests that DKA occurs infrequently and that the risk-benefit ratio overwhelmingly favors continued use of SGLT-2 inhibitors with no changes in current recommendations. However, DKA diagnosis may be missed or delayed due to atypical presentation involving lower-than-anticipated glucose levels or other misleading laboratory values. This presentation has been seen with SGLT-2 inhibitors but has also been observed for decades before the introduction of these agents (9). Gaps in understanding call for more studies of the mechanisms behind the metabolic effect of SGLT-2 inhibitors as well as more healthcare professional education focused on the proper diagnosis and treatment of DKA. **(Endocr Pract. 2016;22:xxx-xxx)**

Abbreviations:
AACE = American Association of Clinical Endocrinologists; **ACE** = American College of Endocrinology; **DKA** = diabetic ketoacidosis; **EMA** = European Medicines Agency; **FDA** = U.S. Food and Drug Administration; **SGLT-2** = sodium glucose-cotransporter 2; **T1D** = type 1 diabetes; **T2D** = type 2 diabetes

INTRODUCTION

Diabetic ketoacidosis (DKA) is an acute, potentially fatal complication of diabetes that typically occurs when insulin deficiency results in excessive lipolysis and protein breakdown at the tissue level, with increased hepatic beta-oxidation of fatty acids to ketone bodies, leading to ketonemia and metabolic acidosis (8). Sodium glucose-cotransporter 2 (SGLT-2) inhibitors are a class of antihyperglycemic agents that reduce blood glucose levels by blocking glucose re-absorption in the proximal tubule of the kidney, causing glycosuria (10). Reports of DKA occurring with SGLT-2 inhibitor therapy in patients with diabetes prompted a U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) safety communication (1,11). In October 2015, the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) convened a conference of experts from Europe and the United States to evaluate reported cases, critically assess the scientific evidence for the association of SGLT-2 inhibitor therapy with DKA, and provide recommendations for the care of affected patients (see Appendix for agenda and participants). This position statement describes the findings of the conference and also represents the official position of AACE and ACE on DKA associated with SGLT-2 inhibitor use.

DOES DKA OCCUR AT A HIGHER RATE WITH SGLT-2 INHIBITORS THAN WITH OTHER ANTIHYPERGLYCEMIC MEDICATIONS?

Whether DKA currently occurs at a higher frequency than before the introduction of SGLT-2 inhibitors remains unclear. The Centers for Disease Control and Prevention estimated that the rate of DKA was 7.1 per 1,000 patient-years with diabetes in 2009, and in 2010, DKA accounted for 142,000 hospitalizations in the U.S., 33,000 of which involved patients with type 2 diabetes (T2D) (2,12). In an analysis of 4 large U.S.-based commercial claims databases, the incidence of DKA ranged between 0.32 and 2.0 per 1,000 patient-years (3). In Denmark, the rate of DKA between 2005 and 2012 ranged between 1.4 and 2.2 DKA events per 1,000 patient-years, and the overall rate

during that period was 1.8 events per 1,000 patient-years (J. Nolan, FRCPI, FRCP[ED], data presented at consensus meeting). Between 1997 and 2000 in Sweden, the overall incidence of DKA was 1.5 per 1,000 patient-years; 32% of cases occurred in T2D patients, with an incidence of 0.5 per 1,000 patient-years (13).

Postmarketing reports of SGLT-2 inhibitor–associated acidosis (including DKA, ketoacidosis, and ketosis) include 20 cases reported to the FDA Adverse Event Reporting System through June 2015 and 147 cases in the Eudravigilance database (96 with canagliflozin, 46 with dapagliflozin, and 5 with empagliflozin) (1,14). In clinical trials with SGLT-2 inhibitors, DKA rates ranged between 0.2 to 0.8 cases per 1,000 patient-years among T2D patients (3,4). Canagliflozin received approval from U.S. and European agencies in 2013. In clinical trials with this agent, DKA and related events were reported in 12 of 17,596 study participants with T2D (0.07%). Canagliflozin 100 and 300 mg were associated with 4 and 6 DKA cases, respectively, whereas 2 events occurred in patients receiving a comparator. The corresponding incidence rates were 0.52, 0.76, and 0.24 per 1,000 patient-years, respectively (3). Empagliflozin received marketing approval in 2014, and data from both clinical and outcomes trials are available. Among 7,020 patients participating in the EMPA-REG OUTCOME trial, 5 DKA cases occurred over a median of 3 years, at a rate of 0.5 per 1,000 patient-years with empagliflozin 10 mg (3 cases) and 0.2 per 1,000 patient-years with empagliflozin 25 mg and placebo (1 case each) (4). In a retrospective analysis of randomized phase 2 and 3 empagliflozin trials (>13,000 T2D participants, including >8,000 patients treated with empagliflozin), there were 8 events consistent with DKA: 2 events with empagliflozin 10 mg, 1 event with empagliflozin 25 mg, and 5 events with placebo. The corresponding DKA event rates were 0.5 and 0.2 per 1,000 patient-years with empagliflozin 10 and 25 mg, respectively, whereas 1.2 events per 1,000 patient-years occurred among placebo-treated patients (T. Seck, MD, data presented at consensus meeting). Dapagliflozin gained European approval in 2012 and U.S. approval in 2014. In the phase 2b/3 dapagliflozin clinical development program (21 studies), 1 case of DKA was reported among the 5,936 dapagliflozin-treated patients (6,247.2 patient-years), or 0.015 per 1,000 patient years (N. Iqbal, MD, MSCE, FACE, data presented at consensus meeting).

Patients with type 1 diabetes (T1D) have a higher risk of DKA than those with T2D (15,16). The total incidence of DKA in patients with T1D treated with SGLT-2 inhibitors is impossible to determine at this stage, although in clinical trials, up to 6% of patients experienced DKA (5,6).

IN WHOM HAS SGLT-2 INHIBITOR–ASSOCIATED DKA OCCURRED?

The consensus group reviewed over 80 DKA cases from the literature (3,9,11,17-20), including those involving SGLT-2 inhibition and cases occurring before these agents were available. Conference participants from clinical practice and industry also presented detailed case reports of SGLT-2 inhibitor–associated DKA. In patients taking SGLT-2 inhibitors, DKA occurred most often in insulin-deficient individuals, including those with long-standing T2D, T1D, or LADA. In the case series from the canagliflozin clinical trials, 6 of 12 patients had low C-peptide levels (≤0.51 ng/mL) and/or were positive for GAD65 antibodies, and in the American case series that prompted the FDA safety warning, 7 of 9 patients had T1D (3).

Blood glucose levels were not documented for many cases. The lowest recorded value was 90 mg/dL, and 13 cases were associated with blood glucose <180 mg/dL. However, the majority of recorded values were ≥250 mg/dL (3,11,17-20). Patients otherwise had classic signs and symptoms of DKA (Table 1), including pH, bicarbonate, and urine ketones within expected ranges. Metabolic stress was the unifying theme among the cases; nearly all involved surgery, injury, acute illness, exercise, or severely reduced carbohydrate intake.

WHICH PATHOPHYSIOLOGIC FACTORS CONTRIBUTE TO SGLT-2 INHIBITOR–ASSOCIATED DKA?

Ketones such as acetoacetate and β-hydroxybutyrate are acidic alternate fuel molecules produced in the liver through the oxidation of fatty acids when dietary carbohydrates are in short supply. Ketones can be metabolized for energy by cardiac and skeletal muscle, the intestine, kidney, and the brain when sufficient glucose is not readily available, and they are excreted in the urine and through the lungs as acetone. When ketone production exceeds clearance, ketoacidosis may occur (21). DKA results from a combination of glucagon elevations, which promote a shift to fat metabolism, and insulin deficiency that may manifest as either an absolute insulin deficiency or a relative deficiency coupled with severe insulin resistance. Hyperglycemia occurs when the lack of insulin and increased glucagon stimulate glycogenolysis and gluconeogenesis in the liver, whereas insu-

Table 1
Classic signs and symptoms of DKA

Polyuria
Polydipsia
Nausea, vomiting, abdominal pain
Visual disturbance
Lethargy, altered sensorium
Tachycardia, tachypnea
Kussmaul respirations (dyspnea)
Acetone smell to breath

Abbreviation: DKA = diabetic ketoacidosis.

lin deficiency, insulin resistance exacerbated by lipolysis, and elevated counterregulatory hormones act in concert to reduce glucose utilization in peripheral tissues. Reduced insulin action coupled with increased glucagon and free fatty acid (FFA) levels promote β-oxidation and hepatic ketogenesis and possibly decreasing ketone utilization in other tissues (8,22). External factors that can precipitate DKA include surgery, infections, sepsis, alcohol, severe injury, hypovolemia, pancreatitis, and severe metabolic stress–related conditions such as myocardial infarction or marathon running (8,22,23).

Changes in diet, notably decreased carbohydrate intake, shifts metabolism to utilization of fat for energy, which promotes ketone production and may contribute to eventual development of DKA under stressful conditions. Very-low-carbohydrate and ketogenic diets (e.g., the Atkins diet) deprive the body of glucose, and the resulting ketosis may develop into ketoacidosis when conditions favor an excessive increase in counterregulatory hormones and the glucagon to insulin ratio (7,19,24-26), such as during severe metabolic stress and (relative) insulin deficiency. Reduced carbohydrate intake was the common factor in a 1973 case series describing 37 T1D patients with "euglycemic" DKA (9). Counterregulatory hormones, including catecholamines, cortisol, and growth hormone—which may be increased by severe stress such as hypovolemia or hypotension—also promote lipolysis and may increase ketone metabolism (27-31). In the setting of insulin deficiency, elevated glucagon also stimulates ketogenesis through promotion of lipolysis in adipocytes and stimulation of β-oxidation of FFAs in the liver (31). People with diabetes are typically already more prone to ketosis compared to healthy individuals, perhaps because they may have dopamine deficiency in the brain and central nervous system, which may unleash sympathetic control of glycolysis, lipolysis, neoglucogenesis, and ketogenesis (32).

The kidney plays a central role in conservation of both glucose and ketones, particularly in the fasting state (33,34). During starvation, renal re-absorption of ketones increases with blood concentrations, with no apparent excretion threshold, but renal utilization of ketone bodies is reduced (34,35). By lowering the renal glucose excretion threshold, SGLT-2 inhibition may mimic starvation conditions and cause an increase in ketone production and renal re-absorption (36-40). These findings suggest that ketonuria may be an insensitive biomarker for hyperketonemia and should not be used to diagnose DKA. Similarly, analyses have shown no correlation between plasma glucose and serum bicarbonate values in DKA, in general and specifically during SGLT-2 inhibitor use (41,42).

Proposed causative factors for DKA with lower-than-anticipated glucose levels include partial treatment of DKA, fasting, carbohydrate avoidance, dehydration, alcohol intake, and persistent glycosuria (7,11). "Euglycemic" DKA was first described as being associated with blood glucose values <300 mg/dL (9), and later, a 2009 American Diabetes Association consensus on DKA defined it as glucose level <250 mg/dL (8). However, although blood glucose <140 mg/dL (the postmeal upper limit of normal) has been occasionally reported, the vast majority of so-called euglycemic DKA involves glucose levels above the defined threshold. Therefore, AACE/ACE considers *euglycemic* DKA a misleading term and instead recommends use of "DKA with lower-than-anticipated glucose levels."

WHICH SIGNS AND SYMPTOMS ARE DIAGNOSTIC OF DKA IN PATIENTS TAKING AN SGLT-2 INHIBITOR?

Table 1 lists classic signs and symptoms of DKA, and Table 2 shows recommended diagnostic criteria. Patients with any form of diabetes who have abdominal pain, nausea, vomiting, fatigue, and/or dyspnea should be evaluated for DKA. Because SGLT-2 inhibitors lower the threshold for glucose excretion, normal or modestly elevated blood glucose does not exclude the diagnosis of DKA during SGLT-2 inhibitor use.

Ketonuria and elevated bicarbonate may be suggestive of DKA, but evidence suggests these measures may be inaccurate (36-42). Instead, the diagnosis should be confirmed with direct measurement of β-hydroxybutyrate in blood and arterial pH (Table 2).

HOW SHOULD DKA ASSOCIATED WITH SGLT-2 INHIBITORS BE MANAGED?

Once the diagnosis is suspected, the SGLT-2 inhibitor should be stopped immediately and the DKA protocol initiated, including fluids, insulin, and other standard interventions as described elsewhere (8).

Table 2
Diagnostic Criteria for DKA

Parameter	Laboratory value
Arterial pH	<7.3
β-Hydroxybutyrate	≥31 mg/dL (3.0 mmol/L) in children ≥40 mg/dL (3.8 mmol/L) in adults
Serum ketone[a]	Positive
Anion gap[b]	>10
Mental status	Drowsy, stupor, or coma in moderate to severe DKA

Abbreviation: DKA = diabetic ketoacidosis.
[a]Nitroprusside reaction method.
[b]Anion gap: $(Na^+) - [Cl^- + HCO_3^-$ (mEq/L)].

HOW SHOULD DKA BE PREVENTED?

Canagliflozin, dapagliflozin, and empagliflozin have similar half-lives, of approximately 13 hours (10). Because of prolonged action on SGLT-2 transporters, these agents should be stopped at least 24 hours before scheduled surgery or other planned activities that might precipitate DKA, such as invasive procedures or extreme physical activity (e.g., running a marathon). For patients with diabetes undergoing emergency surgery or a under sudden external severe stress event, the drug should be stopped immediately and, if DKA develops, management with intravenous insulin and glucose considered along with monitoring of anion gap, serum β-hydroxybutyrate, and arterial pH.

Routine measurement of urine ketones is not recommended during use of SGLT-2 inhibitors in T2D because urine ketone measurement can be misleading. Measurement of blood ketones is preferred for diagnosis and monitoring of DKA (Table 2).

Patients taking SGLT-2 inhibitors should avoid excess alcohol intake and very-low-carbohydrate/ketogenic diets.

SHOULD SGLT-2 INHIBITORS BE USED IN PATIENTS WITH T1D?

SGLT-2 inhibitors are not approved for use in T1D, but clinical trials investigating their efficacy and safety in this population are underway. As yet, few data are available to assess the risk of DKA. In an 18-week, phase 2 canagliflozin study involving 351 patients, ketone-related adverse events (including DKA) occurred among 5.1 and 9.4% of T1D patients receiving canagliflozin 100 and 300 mg, respectively, whereas DKA itself occurred among 4.3 and 6.0% of patients, respectively. No ketone-related events occurred in placebo-treated patients (5). No cases of DKA were reported during a 2-week proof of concept study or in a 24-week, open-label study of dapagliflozin in T1D (6,43). In an 8-week, single-arm, open-label study of empagliflozin, 2 patients experienced DKA after insulin pump failure (44), but no cases of DKA occurred during a 4-week, placebo-controlled empagliflozin study (45). Finally, in a 29-day, placebo-controlled study of sotagliflozin, an investigational dual SGLT-1/2 inhibitor, DKA occurred in 2 sotagliflozin-treated patients after insulin pump malfunctions (46).

AACE/ACE recommends continued study of SGLT-2 inhibitors in patients with T1D based on results to date, which suggest addition of an SGLT-2 inhibitor to insulin may enhance glycemic control without increasing the risk of hypoglycemia or weight gain (5,6,43-45). However, in light of the possibility that SGLT-2 inhibition may increase the risk of DKA in T1D, investigators should consider the following when designing future T1D trials:

- Use of lower SGLT-2 inhibitor doses
- Adjustment of insulin doses based on individual response rather than standardized reductions in insulin dose when starting SGLT-2 inhibitor therapy
- Maintenance of current carbohydrate intake

Clinicians should consider applying these recommendations if prescribing SGLT-2 inhibitors off-label to patients with T1D and also when using SGLT-2 inhibitors in combination with insulin to treat T2D.

CONCLUSION

The incidence of DKA in T2D treated with SGLT-2 inhibitors does not appear to exceed the low levels occurring in the general diabetes population. Further study of the mechanisms behind the metabolic effects of SGLT-2 inhibitors is needed to better define the risk of DKA with these agents. Nevertheless, the risk to benefit ratio overwhelmingly favors continued use of SGLT-2 inhibitors in T2D, with no changes in current recommendations. This class has proven benefits in terms of hemoglobin A1C reduction, weight control, and low risk of hypoglycemia (10,47). Because DKA diagnosis is often missed or delayed when patients present with atypical or misleading laboratory values, greater healthcare professional education efforts that focus on the proper diagnosis and treatment of DKA with SGLT-2 inhibitor use, and perhaps other antihyperglycemic agents, are needed.

Comment: After the AACE/ACE consensus meeting concluded, the FDA added a precaution regarding the potential risk of DKA regardless of glucose level with SGLT-2 inhibitors (48-50). They suggested to evaluate affected patients and consider risk factors for ketoacidosis. Patients taking an SGLT-2 inhibitor may require monitoring and temporary discontinuation of the drug in clinical situations known to predispose to ketoacidosis. The EMA issued similar precautionary language, recommending that clinicians consider the possibility of ketoacidosis in patients taking SGLT-2 inhibitors who have symptoms consistent with the condition, even if blood sugar levels are not high. The EMA also asserted that the benefits of SGLT-2 inhibitor therapy outweigh the risks (51).

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DISCLOSURE

Dr. Yehuda Handelsman has served as a consultant and/or speaker for Amarin, Amgen, Amylin, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Halozyme, Janssen, Merck, NovoNordisk, Sanofi, and Vivus. He has received

research grants from Amgen, Boehringer Ingelheim, GlaxoSmithKline, Gilead, Intarcia, Lexicon, Merck, NovoNordisk, Sanofi, and Takeda.

Dr. Robert R. Henry has served as a consultant for Alere, AstraZeneca, Boehringer Ingelheim, Ionis, Johnson & Johnson/Janssen, and NovoNordisk. He has received research grants from Hitachi, Johnson & Johnson/Janssen, Sanofi Aventis, and Viacyte.

Dr. Zachary T. Bloomgarden has served as a speaker or consultant for BMS/Astra Zeneca, Boehringer Ingelheim, Johnson & Johnson, Merck, Novartis, Novo Nordisk, and Santarus. He owns stock in Abbott, Amgen, Covidien, Hospira, Novartis, Pfizer, Roche, St Jude, and Zoetis.

Dr. Sam Dagogo-Jack has served as a consultant for AstraZeneca, Boehringer Ingelheim, Janssen, Merck, and Novo Nordisk. He has received research grants from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk.

Dr. Ralph A. DeFronzo has served on advisory boards for Astra Zeneca and Boehringer Ingelheim and as a speaker for Astra Zeneca. He has received research grants from Astra Zeneca, Boehringer Ingelheim, Bristol Myers Squibb, and Takeda.

Dr. Daniel Einhorn has served as a consultant and/or speaker for BMS-AZ-Amylin, Eli Lilly, Freedom-Meditech, Glysens, Halozyme, Janssen, and NovoNordisk. He has received research grants from AstraZeneca, Eli Lilly, Janssen, Mannkind, Sanofi, and Takeda.

Dr. Ele Ferrannini has served on advisory boards for Boehringer Ingelheim, Eli Lilly & Co, GlaxoSmithKlein, Janssen, MSD, Sanofi, and Takeda. He has research grants from Boehringer Ingelheim and Eli Lilly & Co.

Dr. Vivian A. Fonseca has served as a consultant and/or speaker for Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Novo-Nordisk, Sanofi-Aventis, Pamlabs, and Takeda. His institution has received research grant support from Asahi Kasei, Eli Lilly, Halozyme, Novo-Nordisk, Pamlabs, Reata, and Sanofi-Aventis.

Dr. Alan J. Garber has served as a consultant for Novo Nordisk.

Dr. George Grunberger has served as a consultant and/or speaker for AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Novo Nordisk, and Sanofi. He has received research support from AstraZeneca, Eli Lilly, Lexicon, Medtronic, Merck, and Novo Nordisk.

Dr. Derek LeRoith has served as a consultant for AstraZeneca, BMS/AstraZeneca, Janssen, and Sanofi.

Dr. Guillermo E. Umpierrez has served as a consultant for Boehringer Ingelheim, Glytec, Merck Novo Nordisk, Regeneron, and Sanofi. He has received research grants from AstraZeneca, Boehringer Ingelheim, Merck, Novo Nordisk, and Regeneron.

Dr. Matthew R. Weir has served as a scientific advisor for AstraZeneca, Janssen, Lily/BI, and Lexicon.

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APPENDIX

The Consensus statement was based on a 2-day international experts' workshop: AACE/ACE Scientific and Clinical Review: Association of SGLT-2 Inhibitors and DKA

Chairs: Yehuda Handelsman, MD, FACP, FNLA, FACE & Robert R. Henry, MD, FACE
Writing Committee: Zachary T. Bloomgarden, MD, MACE; Sam Dagogo-Jack, MD, DM, FRCP, FACE; Ralph A. DeFronzo, MD, BMS, MS, BS; Daniel Einhorn, MD, FACP, FACE; Ele Ferrannini, MD; Vivian A. Fonseca, MD, FACE; Alan J. Garber, MD, PhD, FACE; George Grunberger, MD, FACP, FACE; Derek LeRoith, MD, PhD, FACE; Matthew R. Weir, MD
The writing committee, AACE, and ACE are grateful to the presenters for their expert contribution to the consensus.

Agenda

Topics	Speakers
Normal Physiology	
Whole Body Energy Balance – Focus on the Brain	Aaron Vinik, MD, PhD, FCP, MACP, FACE
Carbohydrate Metabolism: The Importance of Nutrient Sensing	W. Timothy Garvey, MD
Regulation of Adipose Tissue Lipolysis and Its Relationship with Ketogenesis	John Miles, MD, FACE
Glucagon Therapeutics, New Biology of Diabetes	Roger Unger, MD
Pathophysiology	
SGLT-2 Inhibitors and Ketoacidosis: Learnings from the Scientific Literature	Simeon I. Taylor, MD, PhD
Ketogenesis, Ketosis, and Ketoacidosis	Richard E. Pratley, MD
DKA: What Is It? Who Gets It? How Does It Happen?	Mary Korytkowski, MD
The Role of the Kidneys in the Clearance or Re-absorption of Ketone Bodies	Matthew Weir, MD

Epidemiology	
SGLT-2 Inhibitors and DKA: The Clinical Stories	George Grunberger, MD, FACP, FACE
Personal Cases	Sam Dagogo-Jack, MD, DM, FRCP, FACE
Background Prevalence of DKA in T2D in Denmark Prior to the SGLT-2 Inhibitors	John Nolan, FRCPI, FRCP(ED),
SGLT-2 Inhibitors Treatment in Type 1 Diabetes	Paresh Dandona, MBBS, DPhil, FRCP, FACP, FACC
Regulatory	
The European Experience of SGLT-2 Inhibitors and Diabetic Ketoacidosis	Henning Beck-Nielsen, MD, DMSc
Town Hall Meeting	
Sustained Response of SGLT-2 Inhibitors on the Kidney	David Polidori, PhD
AstraZeneca Dapagliflozin and DKA Cases: Throughout the Clinical Development & Post Marketing Reports	Nayyar Iqbal, MD, MSCE, FACE
Case Study: Patient with SGLT-2 Inhibitor–Related DKA	Sandra Williams, MD
The Boehringer Ingelheim Available Experience	Thomas Seck, MD
The Public Perspective	Emily Regier, BS
The Lexicon Experience: Type 1 Diabetes	Paul Strumph, MD, FACE
Type 2 Diabetes Patient Profile: DKA After SGLT-2 Inhibitors and Ways to Prevent DKA	Lance Sloan, MD, FACE
Cases, DKA, and Concepts I	**Yehuda Handelsman, MD, FACP, FACE, FNLA, Chair**
DKA in Type 2 Diabetes: Canagliflozin Clinical Program	Daniel Einhorn, MD, FACP, FACE
Ketoacidosis in Canaglifozin: Phase 2 Trial of Type 1 Diabetes	Robert Henry, MD, FACE
Update on DKA in Type 1 Diabetes with SGLT-2 Inhibitors	Anne Peters, MD
Cases, DKA, and Concepts II	
SGLT-2 Inhibitors and Ketosis	Ele Ferrannini, MD
The Pathophysiology of DKA in Patients with Diabetes on SGLT-2 Inhibitors	Ralph A. DeFronzo, MD, BMS, MS, BS
Common Features and Contributing Characteristics of DKA in Patients on SGLT-2 Inhibitors	Jaime Davidson, MD, FACP, MACE
Panel & Open Discussion: Clinical Implications and Recommendations for Practice	Moderators: Robert Henry, MD, FACE, and Yehuda Handelsman, MD, FACP, FACE, FNLA

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