Conclusion Summary

Following recent reports of cases of diabetic ketoacidosis (DKA) in patients treated with sodium glucose cotransporter 2 (SGLT2) inhibitors, 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 each case and case series. Upon review of the available material, together with a thorough discussion of the impact of SGLT2 inhibitors on human metabolism, the experts concluded that the prevalence of DKA is infrequent and the risk-benefit ratio overwhelmingly favors continued use of SGLT2 inhibitors with no changes in current recommendations.

The following conclusions were reached:

- For individuals with type 2 diabetes (T2D), it is unclear whether DKA occurs at a higher frequency than it did before the advent of SGLT2 inhibitors. In 2012, there were more than 500,000 cases of DKA in the USA, with 20 to 50% of hospital admissions involving patients with T2D. In Denmark, the rate of DKA before the SGLT2 inhibitor era was 1-2 cases per 1000 patients. The incidence of DKA in clinical trials of SGLT2 inhibitors with T2D was 0.5-0.8 cases per 1000 patient-years. Although the incidence rates in clinical trials are low, clinical trial data may not reflect real world experience. Patients with type 1 diabetes (T1D) have a higher risk of DKA than those with T2D. As such, their risk of developing DKA while taking SGLT2 inhibitors may be further elevated. However, more data are needed to elucidate this relationship. Many recently reported cases have been poorly documented, so not all cases may have been actual DKA, but rather a build-up of ketones resulting from the mechanism of SGLT2 inhibition. These ketones are not necessarily harmful.

- It appears that the majority of DKA occurs in people with diabetes who are insulin deficient, such as long-standing T2D, latent autoimmune diabetes in adults (LADA), and T1D. Generally, patients presented with classical DKA signs and symptoms. However, some cases had an atypical presentation due to lower-than-anticipated glucose levels.

- Precipitants of DKA in T1D and T2D include surgery, extensive exercise, myocardial infarction, severe infections, stroke, and other stressful medical conditions; almost all cases of SGLT2 inhibitor–associated DKA occurred in patients challenged with such 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 DKA during SGLT2 inhibitor use.

- For patients taking an SGLT2 inhibitor who present with symptoms suggestive of DKA such as abdominal pain, nausea, vomiting, fatigue, and dyspnea, a diagnosis of DKA should be considered. 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 measurements of beta hydroxybutyrate and arterial pH, which are necessary to confirm the diagnosis. It should be emphasized that normal or moderately elevated blood glucose does not exclude the diagnosis of DKA during SGLT2 inhibitor use.

- For management of DKA in patients taking SGLT2 inhibitors, stop the drug immediately and proceed with traditional DKA treatment protocols.

- To minimize the risk of DKA associated with SGLT2 inhibitors:
  - Consider stopping the SGLT2 inhibitor at least 24 hours prior to elective surgery, planned invasive procedures, or anticipated severe stressful physical activity such as running a marathon.
  - For emergency surgery or any extreme stress event, the drug should be stopped immediately and appropriate clinical care should be provided.
  - Routine measurement of blood ketones is not recommended during use of SGLT2 inhibitors in T2D. Because urine ketone measurement can be misleading, measurement of blood ketones is preferred for diagnosis of DKA in symptomatic patients.
  - Patients taking SGLT2 inhibitors should avoid excess alcohol intake and very-low-carbohydrate/ketogenic diets.

- SGLT2 inhibitors are not approved for use in T1D. However, AACE/ACE encourages continuation of ongoing studies because initial results have shown a promising impact on glycemic regulation. AACE/ACE suggests that in future T1D trials, lower SGLT2 inhibitor doses be considered and insulin dose should not automatically be reduced when SGLT2 inhibitors are begun. Instead, insulin should be adjusted based on the individual response to the SGLT2 inhibitor and carbohydrate intake should be maintained. These recommendations should also be applied if SGLT2 inhibitors are prescribed off-label to patients with T1D and may be considered for patients with T2D who receive exogenous insulin therapy.

We call upon pharmaceutical companies to continue to investigate the mechanisms behind the metabolic effect of SGLT2 inhibitors. The diagnosis of DKA is often missed or delayed due to atypical presentation involving lower-than-anticipated glucose levels or other misleading laboratory values. This presentation has been seen with SGLT2 inhibitors but was also observed before the introduction of these agents. We therefore encourage all associated stakeholders including medical societies, insurance companies, the pharmaceutical industry, hospitals, patient associations, and other interested parties to initiate wide education activities teaching physicians and other related healthcare professional who manage diabetes the proper ways to identify and treat DKA.