SGLT Inhibitors for Type 1 Diabetes: Proceed With Extreme Caution

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Intensive insulin management is currently the only option for effective treatment of type 1 diabetes. Recent data from the T1D Exchange (T1DX) registry (1), which comprises leading U.S. diabetes treatment centers, show that despite the widespread availability of insulin analogs and increasing use of insulin pumps and continuous glucose monitoring systems, only about 20% of adult patients achieve the A1C target of <7% (53 mmol/mol) recommended by the American Diabetes Association (2). It is reasonable to assume that glycemic control of patients receiving care outside of major centers might be even worse. The T1DX registry has also shown that nearly 5% of adult participants experienced one or more episodes of diabetic ketoacidosis (DKA) within the past 12 months (3), and the Centers for Disease Control and Prevention recently reported a 6.3% annual increase in hospitalization rates for DKA from 2009 to 2014, with highest rates in persons aged <45 years (4). Moreover, the majority of patients are either overweight or obese, potentially increasing their risk of cardiovascular disease (1). There is clearly an unmet need for non-insulin adjunctive therapies that improve glycemic control without increasing the risk of hypoglycemia or contributing to weight gain, and it is noteworthy that among nearly 50,000 pediatric and adult participants in the T1DX registry in the U.S. and the Prospective Diabetes Follow-up (DPV) registry in Germany and Austria, two large consortia of diabetes centers, adjuvant medications are being used off-label by 5.4% of participants in T1DX and 1.6% in DPV (5).

Sodium–glucose cotransporter 2 (SGLT2) inhibitors block the SGLT2 transporter in the proximal renal tubule resulting in glucosuria and natriuresis and are approved and indicated for type 2 diabetes. Dual SGLT1+2 inhibitors have the additional effect of inhibiting SGLT1 in the gastrointestinal tract, thereby delaying intestinal absorption of glucose and galactose. Owing to their oral route of administration, low risk of hypoglycemia, and proven cardiovascular and renal protection in type 2 diabetes, there is increasing interest in using these drugs for type 1 diabetes. Clinical trials of SGLT2 inhibitors added to intensified insulin therapy in adults with type 1 diabetes have shown moderate reductions in A1C, glycemic variability, total daily insulin dose, blood pressure, and body weight and increased time in range without an increase in hypoglycemia (6–9), accompanied by significant patient-reported benefits (10). SGLT2 inhibitors, therefore, are a potentially valuable adjunct to insulin therapy for people with type 1 diabetes. In fact, ipragliflozin, an SGLT2 inhibitor currently available in Japan, Korea, and Thailand, is now approved in Japan for use together with insulin in adults with type 1 diabetes (11). The dual SGLT1+2 inhibitor sotagliflozin, added to insulin therapy, has similarly shown improvements in A1C, weight loss, and systolic blood pressure and has enabled reductions in total daily insulin dose (12,13).

In contrast to these salutary effects, an increase in genital mycotic infections and a dose-dependent increase in the absolute risk of DKA have been reported. Importantly, some patients using these medications off-label (14) and study participants (12,13) have presented with euglycemic DKA (near-normal or only mildly elevated blood glucose levels), which delayed recognition, diagnosis, and treatment. Under experimental conditions, the rate of ketogenesis is not accelerated after interrupting insulin delivery (15). The increased risk of DKA appears to be attributable to the failure of patients on SGLT inhibitors to promptly recognize early metabolic decompensation, which occurs at substantially lower than usual glucose levels. Marked hyperglycemia is a typical feature of DKA; its absence, therefore, eliminates a vital alert to patients and clinicians that metabolic decompensation is occurring.

The U.S. Food and Drug Administration's (FDA) Endocrinologic and Metabolic Drugs Advisory Committee recently

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Table 1—Statistical comparison of DKA risk for sotagliflozin versus placebo

Trial no.	Sotagliflozin Events/*N* (incidence rate per 100 patient-years)	Placebo Events/*N* (incidence rate per 100 patient-years)	Hazard ratio* (95% CI)	Exposure-adjusted Mantel-Haenszel risk difference^ per 100 patient-years (95% CI)	Number needed to harm per year† (95% CI)
309/310	35/1,049 (3.40)	1/526 (0.19)	17.57 (2.41, 128.20)	3.21 (2.04, 4.38)	31 (22.8, 49.0)
312	21/699 (6.00)	4/703 (1.11)	5.37 (1.84, 15.64)	4.89 (2.17, 7.60)	21 (13.2, 46.1)

Source: FDA reviewer (16). *A Cox proportional hazards model stratified by trial was used for the 309/310 analysis, and a nonstratified Cox model was used for the 312 analysis, with actual treatment as the only covariate, with the two doses of sotagliflozin combined. Data were truncated 30 days after treatment end date. ^Exposure-adjusted Mantel-Haenszel risk difference, stratified by trial; the 95% CI was calculated using the Sato method. †Number needed to harm is the number of patient-years of exposure to sotagliflozin to observe one additional DKA event.

reviewed a new drug application for the use of sotagliflozin in type 1 diabetes. In the studies supporting the application, DKA was considered an event of special interest. Study participants received extensive protocol-driven education, strips and meters for ketone screening, and instructions on detecting and treating ketosis. Despite the exclusion of subjects with recent DKA or ketosis and the inclusion of specific steps to detect and manage ketosis, therapy with sotagliflozin increased the relative risk of DKA between 5- and 17-fold, with a number needed to harm per year between 21 and 31 (Table 1). The low incidence of DKA in the placebo control group clearly suggests that the precautions and intervention in the protocol were highly effective in reducing DKA risk in the absence of SGLT inhibitor therapy (16).

To address this important safety concern, an international group of experts has written a Consensus Report that comprehensively reviews the use of SGLT inhibitors in type 1 diabetes and provides detailed recommendations to enhance safety and mitigate the risk of DKA (17). The recommendations are based on evidence from clinical trials such as those described above and the expertise and experience of the authors using SGLT inhibitors with their patients with type 1 diabetes. Several specific criteria are listed for selecting appropriate patients for SGLT inhibitor therapy. Of these, perhaps the most important is the willingness and ability to follow prescribed regimens for monitoring ketones and responding appropriately to elevated ketone levels, as well as access to a clinician if blood or urine ketone levels are elevated. The authors also list numerous risk factors for DKA associated with SGLT inhibitor therapy, predominantly related to lifestyle and behavioral considerations. Because euglycemic DKA cannot be detected by glucose monitoring, ketone measurement (ideally with a blood ketone meter or urine testing) is absolutely essential. Blood β-hydroxybutyrate >0.6 mmol/L or a trace or greater of ketonuria indicates early ketosis. The Consensus Report recommends ketone measurement whenever there are symptoms consistent with DKA, including malaise, fatigue, nausea, or vomiting. In addition, ketones should be measured with changes in diet, physical activity, or insulin dose and in the event of infection, dehydration, surgery, injury, occlusion of the infusion cannula, pump malfunction, or stress. A major paradigm shift will be necessary to ensure patient safety and mitigate the occurrence of DKA. Both patients and their care providers must learn to replace a "glucose-centric" with a "ketone-centric" approach to metabolic monitoring.

It is instructive to consider the consensus recommendations in light of a recent report describing current ketone monitoring behaviors of adults with type 1 diabetes participating in the T1DX registry. The American Diabetes Association's *Standards of Medical Care in Diabetes* guidelines advise patients to monitor ketones with any condition leading to a deterioration in glycemic control (2), and yet ketone monitoring was infrequent when blood glucose was >300 mg/dL for 1 h or more, when participants experienced nausea or vomiting, and when fever was detected (18). It is evident, therefore, that adherence to the proposed ketone monitoring recommendations for patients using SGLT inhibitors will require robust and continuous patient education and support. The additional cost of a ketone meter and blood or urine ketone test strips must also be considered. Whereas urine ketone strips are relatively inexpensive ($14.99 for 50 Ketostix Reagent Strips, or about $0.30 per strip at a major U.S. pharmacy chain), blood ketone strips each cost 5–10 times as much. The authors of the consensus recommendations acknowledge that much of the evidence for DKA risk has been obtained from randomized clinical trials with highly selected patients and that additional research is needed to evaluate the efficacy and DKA risk of SGLT inhibitors in patients with type 1 diabetes in "real-world" practice (17).

In several countries with well-developed health care systems, hospitalization rates for DKA are increasing, and while mortality rates for DKA are generally low ($<1\%$ in the U.K. and U.S.), a report from India indicated that up to 30% of hospitalized DKA cases resulted in death (19). The risk of DKA is increased in young adults and is strongly associated with A1C levels, with a substantial increase in risk at A1C $\geq 9\%$ (75 mmol/mol), presumably representing more frequent missed insulin doses and less meticulous self-care and adherence to prescribed treatment (1,20). Thus, patients who might benefit most from therapy with SGLT inhibitors are least likely to adhere to the complex safety recommendations required to mitigate DKA risk and would be at highest risk of DKA (17).

In conclusion, the increase in absolute risk of DKA, even in closely supervised patients participating in clinical trials, raises a serious concern that DKA will be even more common if SGLT inhibitors are used in routine clinical practice by practitioners who do not have the expertise and resources of the clinical trialists to implement the complex recommendations necessary to mitigate risk for DKA. It would be prudent to limit

adjunctive use of SGLT inhibitors in type 1 diabetes to specialists well versed in the risks associated with such therapy and who have the requisite resources to educate, train, and support carefully selected patients.

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