Real life evaluation of sodium-glucose cotransporter 2 inhibition in type 1 diabetes and the risk of diabetic ketoacidosis

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Abstract

Background: The indication for treatment of type 1 diabetes(T1D) with the sodium–glucose cotransporter 2 inhibitor (SGLT2i) dapagliflozin has been withdrawn in Europe likely because of concern for diabetic ketoacidosis (DKA). We calculated the incidence of DKA in people with T1D treated with SGLT2i in Denmark.
Methods: Clinical data from adults with T1D in Denmark were collected from nine outpatient clinics. Electronic health records made the search for DKA accurate.
Results: From a population of 10.500 we observed 134 people treated with SGLT2i over a total period of 222 patient-years. Of those 72% were female, mean age (SD) was 51.4 (13.6) years and median duration of treatment (median, IQR) with an SGLT2i were 12.0 (6.0–29.0) months. The incidence of DKA was zero%.
Conclusion: In 134 people with T1D treated with SGLT2i we found that none of the participants developed DKA during the treatment.

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Type 1 diabetes, sglt2 inhibitors, diabetic ketoacidosis

Key messages

Estimating the incidence of DKA in type 1 diabetes during SGLT2i treatment.

No events of DKA over an observation time of 222 patient years.

SGLT2i may be safe in people with type 1 diabetes.

The sodium–glucose cotransporter 2 inhibitor (SGLT2i) dapagliflozin, was approved in Europe as adjunctive therapy for type 1 diabetes (T1D) in 2019. Recently AstraZeneca withdrew dapagliflozin for this indication due to concern for diabetic ketoacidosis (DKA). We have collected data from 134 people with T1D treated with SGLT2i and calculated the incidence of DKA.

This is a retrospective observational study, based on reports from nine participating centers in Denmark. Data were collected in the form of anonymized mean values of age, sex, treatment duration and incidence of DKA. We searched electronic health records for the diagnosis of DKA in an outpatient setting and during hospitalization. The system can discriminate between different types of diabetes allowing us to focus on T1D. As this is a quality assurance project with gathering of minimal data, consent from subjects or approval from institutional review boards were not required.

The observed population consisted of 134 adults with T1D of which 72% were female. Mean age (SD) was 51.4 (13.6) years and the median duration of SGLT2i treatment (median, IQR) was 12.0 (6.0–29.0) months corresponding to a total observation time of 222 patient-years. There were no cases of DKA (Table 1).

In the randomized controlled trials with dapagliflozin 5 mg once daily 4.0% of the participants with T1D developed DKA, compared to 1.1% in the placebo group over a period of 24–52 weeks.[1] This increased risk has been a limiting factor for more widespread use of SGLT2i in T1D.

Table 1. Characteristics of the study population.

N	134
Age (years)	51.4 (13.6)
Female (%)	72 (53.7)
Duration of treatment (months)	12.0 (6.0–29.0)
Diabetic ketoacidosis (%)	0

Data are means (SD), median (IQR) and percentages.

Palanca et al. evaluated real-world safety of SGLT2i use in people with T1D in 199 adults and found DKA incidence to be 3.5%.[2] However, in the subgroup analysis of participants in whom the EU label was followed (dapagliflozin 5 mg once daily and BMI $\geq$ 27 kg/m^2) there were no DKA events.

Several studies have shown that the SGLT2i have beneficial cardiovascular and kidney protective effects in people with and without type 2 diabetes (T2D).[3] There are no studies of heart and kidney outcomes in participants with T1D and there is currently no prospect that such studies will be made, although both sotagliflozin and empagliflozin have been demonstrated to reduce albuminuria in persons with T1D.[4,5] If the cardiorenal effects seen in T2D and in populations without diabetes could be proven in T1D, these effects may outweigh the risk of DKA. As people with T1D have higher mortality compared with the general population, with cardiovascular disease (CVD) being the main cause of death, improved treatment of diabetic kidney disease and CVD is needed. It is therefore important to consider whether the risk of DKA with SGLT2i treatment observed in clinical trials of T1D can be offset by the large risk reductions seen in cardiovascular and kidney outcome studies in T2D populations.

This study is limited by its observational and retrospective character. We have no data about how individuals were selected, which was likely based on the judgement of the treating physician. Due to limited access to detailed clinical data, we cannot provide a thorough analysis of the characteristics of the population, such as BMI, insulin pump use, diabetes duration, glucose control and frequency of side effects. Being a real-world study with a population of 134 individuals interpretation needs to be done with care especially in respect to a relatively uncommon event such as DKA.

Persons with T1D in Denmark offered treatment with SGLT2i are carefully selected by the attending physician, receive training regarding the risks of this treatment and must demonstrate an understanding of how this is handled before treatment is initiated. This indicates that SGLT2i treatment may be safe in people with T1D if patients are carefully selected and instructed.

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FP and ES initiated this study. EBS analyzed the data and drafted the first version of the manuscript, with subsequent discussion and input from all authors, who had access to all data. FP is the guarantor of this work and all authors approved the final version of the manuscript.

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