Clarity around ketoacidosis with SGLT2 inhibitors in routine practice

30-second summary:

This Scandinavian cohort and nested case–control study, published in *The Lancet Diabetes & Endocrinology*, identified a diabetic ketoacidosis (DKA) incidence of 2.43 per 1000 person-years among users of SGLT2 inhibitors in routine practice. The study identified risk factors, potential triggers and co-occurring conditions associated with DKA, including high HbA_{1c}, malnutrition, previous ketoacidosis, low BMI and recent hypoglycaemia, with infection being the most common precipitating or co-occurring event. The authors suggest that SGLT2 inhibitors might increase overall susceptibility to DKA, such that these risk factors and events confer a greater absolute risk increase in people taking these agents. The cardiorenal and metabolic benefits of SGLT2 inhibitors greatly outweigh the adverse event risks, including ketoacidosis. NICE recommends SGLT2 inhibitors as part of dual first-line therapy for most people with type 2 diabetes, so it is important to understand when these drugs may be contraindicated and what guidance we should provide to people initiating them.



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There is a known small increased incidence of diabetic ketoacidosis (DKA) in people with type 2 diabetes who are taking SGLT2 inhibitors, with the level of increased risk varying across studies:

- Cardiovascular outcome trials: incidence of 0.3–2.2 events per 1000 person-years (selected populations).
- Observational studies: <1 to 8 events per 1000 person-years.

Risk factors and triggering events remain unclear. The updated NICE NG28 guideline is likely to increase use of SGLT2 inhibitors across UK, so it is important to clarify DKA risks in routine practice populations.

The present study

In this Scandinavian cohort study published in *The Lancet Diabetes & Endocrinology*, Kadesjö and colleagues reviewed 322 597 initiations of SGLT2 inhibitors in 282 282 people with type 2 diabetes, in order to identify ketoacidosis incidence. Mean age was 63 years and 36% of the cohort were women.

In the nested case–control design, 1428 DKA events were compared with 14 233 matched control treatment episodes to assess risk factors for DKA and potential precipitating or co-existing factors.

Results

Over a median follow-up of 1.3 years (range 0.7–2.8 years):

- DKA incidence was 2.43 per 1000 person-years of treatment with an SGLT2 inhibitor.
- DKA was most common in the first 180 days after initiation; however, there was an increased risk throughout the follow-up.
- The absolute risk of DKA was increased by 0.12–0.16% in SGLT2 inhibitor users.
  - ➤ Number needed to harm: 625–833 per year.

Significant risk factors for DKA (updated at the time of event) were:

- High HbA_{1c} (≥83 vs ≤52 mmol/mol): odds ratio (OR) 15.37
- Low BMI (<20 vs 20–25 kg/m^2): OR 9.98
- eGFR (<30 vs ≥90 mL/min/1.73 m^2): OR 2.67
- Malnutrition: OR 10.54
- Previous DKA: OR 10.40
- Hypoglycaemia within last year: OR 5.22
- End-stage kidney disease: OR 4.91

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- Alcohol misuse: OR 4.11
- Pancreatitis/major pancreatic disease: OR 3.93
- Longer use of diabetes medications (≥7 years vs <1 year): OR 1.68

Medications associated with increased risk were:

- Antipsychotics: OR 2.31
- SGLT2 inhibitor monotherapy: OR 2.21
- Insulin: OR 1.71
- Sulfonylureas: OR 1.47
- Antidepressants: OR 1.41
- Systemic steroids: OR 1.37
- GLP-1 receptor agonists: OR 1.25

The most common precipitating or co-occurring event was infection, which occurred in 31.8% of those with DKA versus 6.1% of controls (OR 7.6). Other associations included alcohol intoxication, acute renal events, acute stroke, acute abdomen events and major surgery. Some transient exposures may not have been fully documented.

A significant mortality rate was noted in those who experienced DKA – 274 deaths over a follow-up time of 1.4 years. The mortality rate was up to 10% in the first few weeks after DKA; however, not all deaths were directly attributable to the DKA, as there were significant triggering conditions and comorbidities.

Surprisingly, 25% of those with DKA remained on an SGLT2 inhibitor 1 year later, suggesting that there was a non-recurring reason identified for the DKA episode. At the same time point, insulin use had also increased, from 25.1% to 73%, and there was a small increase in GLP-1 RA use, from 26% to 31%.

Further exploration of risk factors and triggering or co-occurring events in people taking DPP-4 inhibitors showed a similar magnitude and direction of association as with SGLT2 inhibitor use, and thus the authors suggest that SGLT2 inhibitors might increase overall susceptibility to DKA, such that the risk factors and events identified here confer a greater absolute risk increase in people taking these agents.

Implications for practice

The cardio–kidney–metabolic benefits of SGLT2 inhibitors greatly outweigh the associated risk of adverse events, including the small risk of DKA. The updated NICE NG28 guideline recommends SGLT2 inhibitor use as the first line, alongside modified-release metformin, for most people with type 2 diabetes; therefore, it is important for clinicians to prescribe safely and effectively. If new to prescribing SGLT2 inhibitors, we should take time to learn where extra caution is required and where these drugs are contraindicated.

- A useful interactive tool to aid prescribing can be found here (Newland-Jones et al, 2026).

It is important to consider DKA at all stages of SGLT2 inhibitor treatment, not just early after initiation, and not just if glucose is high, since the DKA may be euglycaemic, especially if there is an associated condition or a possible triggering event occurs. We should reinforce sick day rules at every consultation, and this should include the importance of restarting the SGLT2 inhibitor as soon as the person is eating and drinking normally again.

Encourage people to follow local recommendations for elective surgery – usually stopping the drug for 3 days prior to surgery – to reduce risk of DKA, and remembering to restart afterwards.

Finally, ensure all clinicians in your practice are aware of the risk of DKA with SGLT2 inhibitors, the potential triggers, and the importance of checking not just point-of-care glucose but also ketone levels if someone taking an SGLT2 inhibitor is unwell and at risk of DKA. ■

Ketoacidosis with SGLT2 inhibitors in routine clinical practice of type 2 diabetes: Scandinavian cohort and nested case–control study

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References

Kadesjö E, Söderling J, Hviid A et al (2026) Ketoacidosis with SGLT2 inhibitors in routine clinical practice of type 2 diabetes: Scandinavian cohort and nested case–control study. *Lancet Diabetes Endocrinol* **14**: 903–13

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