



# Type 2 Diabetes: SGLT2 Inhibitors and Diabetic Ketoacidosis

B.C. Provincial Academic Detailing Service

Appendix: October 2019

Health Canada, the US Food and Drug Administration, and the European Medicines Agency have issued warnings that SGLT2 inhibitors increase the risk of diabetic ketoacidosis (DKA).<sup>1-3</sup>

The first SGLT2 inhibitor (SGLT2i) was approved by Health Canada in 2014. The class now includes: **canagliflozin, empagliflozin, dapagliflozin and ertugliflozin**. An August 2019 search of Health Canada's Drug and Health Product Register for these agents identifies approximately 600 adverse reaction reports in which the term 'acidosis' occurs.<sup>4</sup> Large randomized controlled trials (RCTs) of SGLT2 inhibitors demonstrate an increased risk of DKA.<sup>5</sup>

- In cardiovascular outcome trials, the risk is two times higher in people randomized to an SGLT2i compared to placebo (HR 2.20, 95%CI 1.25 to 3.87): DKA event rates < 1 per 1000 patient years.<sup>5</sup>
- In a 2019 RCT of patients with diabetic nephropathy, the risk was increased approximately 10 fold with canagliflozin compared to placebo (HR 10.8, 95%CI 1.39 to 83.65): DKA event rate 2.2 per 1000 patient years.<sup>6</sup>

Predisposing and/or precipitating factors for SGLT2 inhibitor DKA may include:<sup>1-3,7</sup>

- Pancreatic disorders causing insulin deficiency (e.g. type 1 diabetes, pancreatitis, pancreatic surgery)
- Long-standing type 2 diabetes / latent autoimmune diabetes in adults
- Sudden reduction or omission of insulin dose
- Acute serious illness / infection / acute febrile illness
- Major surgery / hospitalization
- Reduced caloric intake / low carbohydrate diet / intensive exercise
- High alcohol consumption

SGLT2 inhibitor DKA may occur with lower-than-anticipated blood glucose values.<sup>1-3,8</sup>

DKA is often accompanied by glucose levels greater than 14 mmol/L, however DKA with lower-than-anticipated glucose levels has been reported in young individuals with type 1 diabetes, pregnant women, and more recently, in individuals receiving SGLT2 inhibitor therapy.<sup>8</sup> **DKA should be suspected** in individuals prescribed an SGLT2i who present with DKA symptoms (Table 1), **despite normal or near-normal glucose values.**<sup>8</sup>

**Patients and clinicians should be aware of the signs and symptoms of DKA.**

Educate patients that they should seek medical attention based on their symptoms (Table 1), rather than their blood glucose levels.<sup>10</sup> Patients should also receive **clear instructions** on when to withhold their SGLT2 inhibitor in the case of illness or surgery, and when it can be restarted (Table 2).

DKA is a **medical emergency** requiring prompt treatment and immediate discontinuation of the SGLT2i with assessment of the appropriateness of re-initiation after recovery.<sup>3,11</sup> Note that the glycosuric effects of SGLT2i can persist for at least a few days after discontinuation.<sup>7,8</sup>

**Table 1: Possible Symptoms of DKA<sup>7,9</sup>**

- fast deep breathing / feeling short of breath
- nausea or vomiting / stomach pain
- loss of appetite / excessive thirst
- unusual sleepiness or tiredness
- confusion / slurred speech
- rapid heart rate

## Strategies aimed at addressing the risk of DKA have been proposed.

**Table 2: Proposed strategies to address the risk of DKA<sup>2,3,8,10,12</sup>**

Acute Serious Illness	<ul style="list-style-type: none"> <li>▪ hold SGLT2i at onset of illness</li> <li>▪ restart when feeling well and able to eat and drink</li> </ul>
Major Surgery	<ul style="list-style-type: none"> <li>▪ hold 3 days before surgery</li> <li>▪ restart after acute phase response and physiological stress has resolved, and is feeling well and able to eat and drink</li> </ul>
Bariatric Surgery	<ul style="list-style-type: none"> <li>▪ hold SGLT2i during preoperative low-carbohydrate diet</li> <li>▪ reassess postoperatively</li> </ul>
Low Intake of Carbohydrates	<ul style="list-style-type: none"> <li>▪ hold until normal diet resumes</li> </ul>
Excess Intake of Alcohol	<ul style="list-style-type: none"> <li>▪ stop immediately</li> <li>▪ reassess at later date</li> </ul>

## References

1. Summary Safety Review - SGLT2 Inhibitors (canagliflozin, dapagliflozin, empagliflozin) - Assessing the Risk of the Body Producing High Levels of Acids in the Blood (diabetic ketoacidosis) <https://hpr-rps.hres.ca/reg-content/summary-safety-review-detail.php?linkID=SSR00013>
2. FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about>
3. EMA confirms recommendations to minimise ketoacidosis risk with SGLT2 inhibitors for diabetes <https://www.ema.europa.eu/en/medicines/human/referrals/sglt2-inhibitors>
4. Government of Canada. Drug Product Database. [Internet]. <https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>. Accessed August 14, 2019.
5. Zelniker TA et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet*. 2019; 393(10166):31-39
6. Perkovic V et al. Canagliiflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *NEJM*. 2019; DOI: 10.1056/NEJMoa1811744
7. Handelsman Y et al. American association of clinical endocrinologists and American college of endocrinology position statement on the association of SGLT-2 inhibitors and diabetic ketoacidosis. *Endocrine Practice* 2016;22(6):753-762
8. Goldenberg RM et al. SGLT2 inhibitor-associated diabetic ketoacidosis: clinical review and recommendations for prevention and diagnosis. *J Clin Ther* 2016. <http://dx.doi.org/10.1016/j.clinthera.2016.11.002>
9. Goguen J, Gilbert J. Hyperglycemic Emergencies in Adults: 2018 Clinical Practice Guidelines. *Can J Diabetes* 2018. <https://doi.org/10.1016/j.jcjd.2017.10.013>
10. Zhang L, Tamilia M. Euglycemic diabetic ketoacidosis associated with the use of a sodium-glucose cotransporter-2 inhibitor. *CMAJ* 2018;190:E766-8. doi: 10.1503/cmaj.171319
11. Gosmanov AR, Wall Barry M. Diabetic Ketoacidosis. *Conn's Current Therapy* 2019. DOI:10.1016/B978-0-323-59648-0.00066-3
12. Kerridge R et al. The good, the bad, and the ugly: sodium-glucose cotransporter-2 inhibitors (gliflozins) and perioperative diabetes. *Anaesth Intensive Care* 2018; 46(2):155-158