Rare but significant risk of Diabetic Ketoacidosis associated with SGLT2 inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a newer class of medications for Type 2 diabetes (T2D) for which the US Food and Drug Administration (FDA) warned about possible "atypical" presentation of diabetic ketoacidosis (DKA) as early as May 2015. Case studies showed SGLT2 treated diabetics were at greater risk of DKA. Two things complicate this scenario, the possible atypical presentation of DKA, delaying its diagnosis and treatment, and identifying the SGLT2 therapy as a possible contributing factor.

Atypical DKA presentation may include:

- Euglycemia or only slightly elevated blood glucose levels
- Protracted hyperglycosuria, even after the discontinuation of the SGLT2 inhibitor

Who is most at risk?

Those undergoing surgery or are dehydrated, fasting, or reducing insulin doses

How can I reduce the risk of this complication?

Encourage proper hydration

Stop SGLT2 therapy 3 days before surgery (4 if using ertugliflozin) and do not restart until oral intake has returned to normal.

How should I educate members about this potential side effect?

- Tell patients that ketoacidosis can occur with normal to slightly elevated blood glucose. As such blood glucose or urine ketone testing may not rule it out.
- Report any signs of vomiting, fatigue or trouble breathing
- Dehydration increases risk, so staying hydrated is important.

DKA has been observed in T2D patients taking Glucagon-Like Peptide 1 Receptor (GLP-1) agonists and DPP-4 inhibitors. However, the risk of DKA with SGLT2i is two to three times more than other oral T2D medications. The increased risk of DKA with SGLT2 inhibitors is among the factors to be considered at the time of prescribing and throughout therapy if patients present with symptoms suggestive of DKA regardless of blood glucose levels.

References:

1. Diabetes Care 2020 Jan; 43(Supplement 1): S98-S110. https://doi.org/10.2337/dc20-S009
2. Douros A, Lix LM, Fralick M, et al. Sodium-glucose cotransporter-2 inhibitors and the risk for diabetic ketoacidosis. *Ann Intern Med.* Published online July 27, 2020. doi:10.7326/M20-0289
3. New England Journal of Medicine 2017; 376:2300-2302. DOI: 10.1056/NEJMc1701990
4. *9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2020.* DOI: 10.2337/dc20-ad08a
5. Article, Educate About Serious SGLT2 Inhibitor Risks, Pharmacist's Letter, May 2020