



## Editorial: Euglycemic Ketoacidosis Concerns in Perioperative Use of SGLT2 Inhibitors: Re-Examining Current Recommendations

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Over the past decade, sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been well established as excellent therapeutic agents for the management of type 2 diabetes mellitus (T2DM).<sup>1</sup> Several randomized controlled trials (EMPEROR and CANVAS) have further established that SGLT2i demonstrate additional benefits in heart failure and chronic kidney disease, leading to their increased prevalence in the perioperative setting.<sup>2-4</sup> However, there has been growing concern regarding euglycemic ketoacidosis, an uncommon but life-threatening side effect associated with SGLT2i use.<sup>1</sup> SGLT2i inhibit glucose reabsorption in the proximal convoluted tubule resulting in glycosuria and reductions in serum glucose levels without an increase in insulin levels. Additionally, glucagon production can be stimulated resulting in lipolysis, ketoacid production, and, rarely, anion gap metabolic acidosis.<sup>5</sup> Since several perioperative factors (e.g., fasting state, increase in stress hormones) can exacerbate this risk, anesthesia professionals must carefully consider the risk of perioperative SGLT2i-associated ketoacidosis.

### REVIEW OF CURRENT RECOMMENDATIONS AND CHALLENGES

Currently, there is no consensus on perioperative management of SGLT2i and many published recommendations are outdated or based on limited data (Table 1). In 2020, an article in *Anesthesiology* recommended continuing SGLT2i for ambulatory surgery but stopping on the morning of surgery.<sup>6</sup> However, these recommendations were extrapolated from expert opinions. In addition, they were published before United States Food and Drug Administration (FDA) updated its recommendation to stop SGLT2i at least 3–4 days before all scheduled surgery. The FDA's current recommendations also appear to be based on limited case reports and the elimination half-life of SGLT2i.<sup>1</sup> In 2023, the validity of the FDA recommendations were evaluated by reviewing 99 reported cases of SGLT2i associated diabetic ketoacidosis; no cases were found in patients who held SGLT2i for longer than 3 days.<sup>7</sup> Despite this being the largest systematic review to date on the subject, only 58.6% of the reviewed cases discontinued SGLT2i preoperatively, making the study further underpowered, and none of the reviewed cases discontinued SGLT2i for more than 2 days preoperatively. Despite a lack of validity, the FDA's recommendation has been

**Table 1: Summary of Current Notable Recommendations on Perioperative SGLT2i Use.**

Organization	Perioperative Guideline	Consideration
<ul style="list-style-type: none"> <li>United States Food and Drug Administration (FDA)<sup>1</sup></li> </ul>	<ul style="list-style-type: none"> <li>Canagliflozin, dapagliflozin, empagliflozin—hold for 3 days prior to surgery.</li> <li>Ertugliflozin—hold for 4 days prior to surgery.</li> </ul>	<ul style="list-style-type: none"> <li>Updated in 2020 based on series of case studies and each agent's elimination half-life, which is not the same as pharmacologic half-life (SGLT2i have shown prolonged clinical effect over a week after cessation.)</li> <li>No studies to date that validate its 3-4 day hold time.</li> <li>No recommendation for emergency surgery or other surgical considerations.</li> </ul>
<ul style="list-style-type: none"> <li>American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE)<sup>8,9</sup></li> </ul>	<ul style="list-style-type: none"> <li>Stop 24–48 hours prior to scheduled surgery.</li> <li>Immediate cessation for emergent surgery.</li> </ul>	<ul style="list-style-type: none"> <li>Based on a small number of case reports and expert opinion.</li> <li>Initially published as position statement in 2016 and was re-iterated in consensus statement published in 2020, but without further updates.</li> </ul>
<ul style="list-style-type: none"> <li>American Diabetes Association</li> </ul>	<ul style="list-style-type: none"> <li>Endorses FDA recommendations.</li> </ul>	
<ul style="list-style-type: none"> <li>American College of Cardiology</li> </ul>	<ul style="list-style-type: none"> <li>Endorses FDA recommendations.</li> </ul>	

adopted by several organizations. Other individual institutions have published their own recommendations, but these are still based on limited case reports and do not demonstrate consensus on hold times for SGLT2i.<sup>8-10</sup>

Several factors contribute to the current lack of evidence for perioperative management of SGLT2i. The most concerning factor is that, due to its atypical presentation, SGLT2i-associated euglycemic ketoacidosis is underreported, which makes it challenging to understand its prevalence and impact on a patient's perioperative outcome.<sup>11</sup> In fact, outside the perioperative setting, two large meta-analyses assessing 82 randomized controlled trials demonstrated that SGLT2i are not significantly associated with a higher risk of diabetic ketoacidosis compared to other hypoglycemic agents.<sup>12,13</sup> Position statements from the American Association of Clinical Endocrinologists and American College of Endocrinology also suggest that the risk of diabetic ketoacidosis associated with SGLT2i is no greater than the low levels occurring in the general diabetes population.<sup>8</sup> However, neither the meta-analyses nor position statements specifically comment on the risk of euglycemic ketoacidosis, which is marked by a different

clinical presentation, diagnostic criteria, and occurrence rate. The question remains: what makes SGLT2i administration an exceptional risk factor for euglycemic ketoacidosis compared to other hypoglycemic agents during the perioperative period? Are there other perioperative factors that affect the risk of SGLT2i-associated euglycemic ketoacidosis? Several sources repeatedly comment that these critical questions are yet to be answered, which impedes the development of evidence-based perioperative guidelines for SGLT2i.

### RECENT UPDATES ON PERIOPERATIVE SGLT2I USE

Based on an updated review of current literature, there are new findings that elucidate the prevalence and impact of perioperative SGLT2i-associated diabetic ketoacidosis. In 2022, the first and largest population-based study examining the incidence rate of SGLT2i-associated postoperative diabetic ketoacidosis was published.<sup>14</sup> The incidence of postoperative diabetic ketoacidosis within 30 days postoperatively was six times higher in SGLT2i users compared to nonusers, which is much higher

## Recognition of Perioperative Euglycemic Ketoacidosis Can Be Challenging

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than previously suspected. SGLT2i users who developed diabetic ketoacidosis postoperatively had higher rates of complications (e.g., need for mechanical ventilation, infection, longer hospital stay) and overall increased mortality. This is the first study to establish SGLT2i as an independent risk factor for developing postoperative diabetic ketoacidosis.

However, this population study did not have uniform diagnostic criteria for diabetic ketoacidosis and did not clarify which of them, if any, were euglycemic at presentation. This is concerning since SGLT2i can cause prolonged glycosuria and ketonemia up to 9–10 days after cessation, which can confound the diagnosis.<sup>15</sup> In fact, a 2023 single-institution retrospective analysis showed that all patients on SGLT2i, after average preoperative hold time of 1.5 days, developed some degree of ketoacidosis with mean increase in anion gap from 12.6 mmol/L preoperatively to 13.4 mmol/L postoperatively.<sup>16</sup> These findings suggest that diagnosis of clinically significant ketoacidosis is a complex clinical consideration of not just pertinent laboratory values, but also clinical symptoms and presenting circumstances. Without clear diagnostic criteria differentiating the types of ketoacidosis, we may not understand the true incidence and impact of SGLT2i-associated euglycemic ketoacidosis, which continues to hinder the development of evidence-based perioperative SGLT2i guidelines.

### PRACTICE CONSIDERATIONS AND RECOMMENDATIONS

There are several perioperative factors that should be considered when assessing the risk of SGLT2i-associated diabetic ketoacidosis (Table 2). Advanced T2DM (HgbA1c >8%) was recently reported to increase the risk by 3.1-fold.<sup>14</sup> Emergent surgery, which was previously suggested as a risk factor given its inherent stress and urgency, was also recently reported to increase the risk by 24.5-fold.<sup>14</sup> Bariatric surgery has long been considered a risk factor as perioperative SGLT2i-associated euglycemic ketoacidosis was first reported in bariatric patients, thought due to postoperative dietary changes as well as complications.<sup>7,11</sup> This concern can be expanded to consider adequate postoperative nutritional intake (to overcome postoperative catabolic state) as an indicator for when to resume SGLT2i. Such a complex variety of factors should be incorporated when developing a guideline to manage patients on SGLT2i. For example, the University of Pennsylvania recently published a comprehensive single-center guideline incorporating factors such as anticipated procedure duration, anesthesia type, preoperative HgbA1c and glucose and basic metabolic panel, and underlying patient comorbidities to better identify which patients may be at high risk of perioperative SGLT2i-associated euglycemic ketoacidosis.<sup>17</sup> While this guideline still endorses the FDA recommendation for preoperative SGLT2i cessation and needs further evidence for optimization, this is the first published

**Table 2: Factors That Can Increase the Risk of Perioperative SGLT2i-Associated Euglycemic Ketoacidosis.**

Underlying comorbidities	
Female sex	Suggested based on case review. <sup>7</sup>
Advanced or poorly controlled T2DM	Previously suggested as an independent factor. <sup>7,19</sup> Recently, HgbA1c >8% reported to cause 3.1-fold increased risk. <sup>14</sup>
Liver disease	Suggested as liver function is critical in glucose metabolism. <sup>19</sup>
Concomitant insulin use	Recently reported to cause 2.8-fold increased risk. <sup>14</sup>
Obesity	Suggested due to ketosis. <sup>7</sup>
Surgical type	
Emergency	Previously suggested as an independent factor associated with as much as 25% of SGLT2-associated DKA. <sup>7,16</sup> Recently reported to cause 24.5-fold increased risk. <sup>14</sup>
Bariatric	Supported by several systematic reviews as a prominent factor due to its postoperative nutrition management. <sup>7,11</sup>
Cardiac	Suggested through several case reports. <sup>16</sup>
Other perioperative considerations	
Pre- and Postoperative hypovolemia	Suggested as it can mask the usual hyperglycemia induced polyuria. <sup>11</sup>
Postoperative nutrition	Supported by current guidelines, reviews and meta-analyses; inadequate nutrition can worsen postoperative catabolic state and worsen metabolic complications. <sup>19</sup>
Infection/sepsis	Suggested as it can impair adequate glycemic control and cause physiological stress. <sup>7,11</sup>
Glucocorticoid use	Suggested as it can promote hyperglycemia and insulin resistance. <sup>11</sup>

T2DM: Type 2 Diabetes Mellitus; DKA: Diabetic Ketoacidosis

approach to developing an algorithm to guide the management of high-risk euglycemic ketoacidosis cases for anesthesia providers taking care of patients on SGLT2i.

Finally, it is important to highlight that for certain patients, SGLT2i cessation in the perioperative setting may be more harmful. At the end of EMPEROR trials that demonstrated cardioprotective benefit of empagliflozin, the patients who were prospectively withdrawn from treatment had increased risk of cardiovascular death and hospitalization for heart failure within 30 days of discontinuation back to pretreatment baseline.<sup>18</sup> Given the rapid reversal of the cardioprotective benefits of SGLT2i, some advocate for early detection and treatment of ketoacidosis (e.g., intraoperative lab monitoring for acidosis and insulin infusion use) rather than perioperative discontinuation of SGLT2i in heart failure patients.<sup>19,20</sup> There also has never been a case of euglycemic ketoacidosis in patients taking SGLT2i for cardiorenal indications in the absence of T2DM, so SGLT2i should be continued in this population.<sup>17</sup>

We suggest a perioperative algorithm for patients on SGLT2i (Figure 1, next page). Given the lack of evidence in current literature, this algorithm may not apply to every case. However, we highlight the most significant perioperative considerations supported by current data, such as emergent procedures and other

confounding risk factors for diabetic ketoacidosis.<sup>7,11,14,16,19</sup> For emergent or urgent procedures, we recommend proceeding with surgery with close perioperative monitoring for acidosis and early initiation of insulin infusion, as the risk of delaying surgery may outweigh the risk of diabetic ketoacidosis. While data are lacking, the current FDA and other institutional guidelines suggest holding SGLT2i for all scheduled surgeries, including outpatient procedures with expected rapid return to preoperative state.<sup>1,8,9</sup> Therefore, for elective procedures, if the patient is considered high risk, we recommend rescheduling surgery, but if the patient is considered low risk, we recommend assessing other patient and surgical factors.<sup>17</sup> For non-diabetic patients taking SGLT2i for heart failure or cardiorenal protection, we do not believe this algorithm applies; based on current data, they should continue SGLT2i and are considered at low risk for diabetic ketoacidosis. However, depending on other confounding risk factors, they too may require close perioperative monitoring for acidosis.

In summary, we believe that SGLT2i pose an increased risk for diabetic ketoacidosis and other morbidities in the perioperative setting. However, the optimal preoperative hold time for SGLT2i and how cases should be handled if the hold time is not met remains controversial.

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The latter is particularly important for anesthesia professionals as many patients currently do not adhere to a universal hold time. While further research is needed, we encourage clinicians to consider the currently reported risk factors, along with other patient and surgical factors, to risk-stratify and individualize the management of patients taking SGLT2i, from case cancellation consideration to enhanced postoperative monitoring.

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## Perioperative SGLT2-Inhibitor Management Recommendations

**HOLD** SGLT2i for 3 days\* prior to elective surgery, **except** for patients with significant history of heart failure or patients without T2DM taking SGLT2i for cardiorenal protection.<sup>1</sup>

\*4 days for ertugliflozin

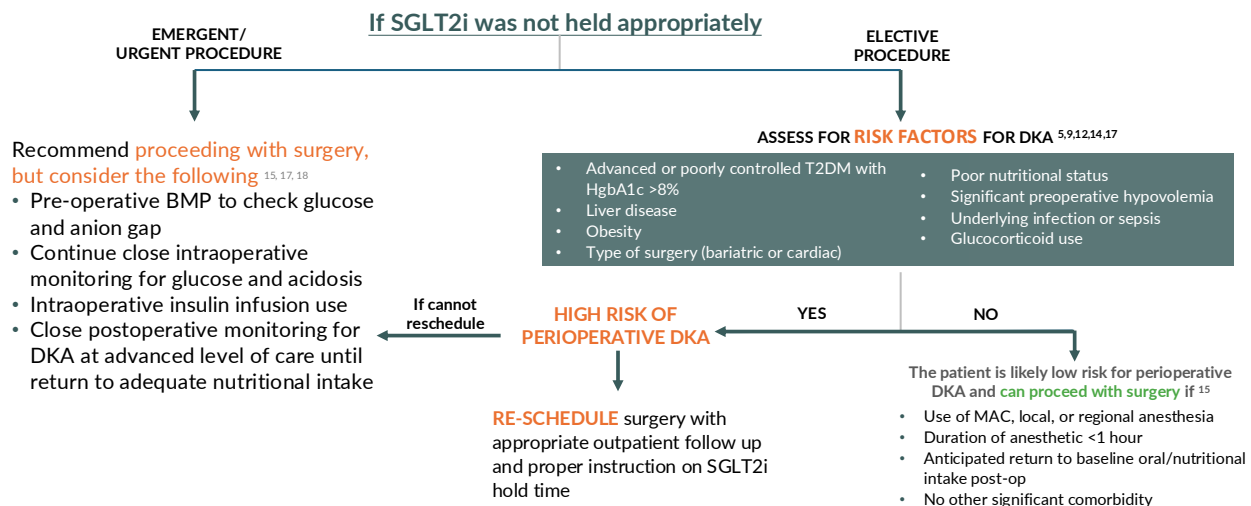


Figure 1: Recommendations for perioperative management of SGLT2i. Management pathways are influenced by the urgency of surgery and other significant patient or surgical factors that may increase risk of perioperative diabetic ketoacidosis. This algorithm does not apply to nondiabetic patients taking SGLT2i for heart failure or cardiorenal protection, as data suggest they should continue SGLT2i. Note that there are no Class 1 evidence for the perioperative management of SGLT2i. SGLT2i: Sodium-Glucose Cotransporter-2 Inhibitor; BMP: Basic Metabolic Panel; T2DM: Type 2 Diabetes Mellitus; DKA: Diabetic Ketoacidosis; MAC: Monitored Anesthesia Care.

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