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REVIEW ARTICLE

Perioperative and periprocedural management of GLP-1 receptor-based agonists and SGLT2 inhibitors: narrative review and the STOP-GAP and STOP DKA-2 algorithms

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ABSTRACT

The GLP-1 receptor-based agonists (GLP-1RAs) and SGLT2 inhibitors (SGLT2i) are major twenty first century breakthroughs in diabetes and obesity medicine but there are important safety considerations regarding the perioperative and periprocedural management of individuals who are treated with these agents. GLP-1RAs have been linked to an increased risk of retained gastric contents and pulmonary aspiration while SGLT2i can be associated with diabetic ketoacidosis. This manuscript provides a narrative review of the available evidence for perioperative and periprocedural risks in people prescribed GLP-1RAs and SGLT2i. The authors provide expert opinion-driven recommendations and algorithms on how to safely manage GLP-1RAs and SGLT2i under perioperative/periprocedural settings.

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Introduction

Glucagon-like peptide-1 receptor (GLP-1R)-based agonists (GLP-1RAs) and sodium-dependent glucose cotransporter-2 inhibitors (SGLT2i) have been transformative in the cardiorenal-metabolic space. GLP-1RAs are increasingly utilized for the treatment of type 2 diabetes mellitus (T2DM) and obesity while SGLT2i are frequently used for the management of T2DM, chronic kidney disease (CKD) and heart failure. With these agents becoming more commonplace in clinical practice, there are growing concerns on how their use should be safely adjusted prior to, during and after surgery or diagnostic/interventional procedures. Given the lack of evidence-based guideline recommendations in this regard, an expert forum was convened in November 2024 to review the evidence to date for the perioperative and periprocedural management of GLP-1RAs and SGLT2i with the overarching goal to formulate recommendations and practical algorithms that can be readily integrated into clinical practice. The expert panel comprised five endocrinologists, a gastroenterologist, an anesthesiologist/intensivist and a cardiovascular surgeon, all of whom have the relevant clinical and research experience. We reviewed reports related to the use of GLP-1RAs or SGLT2i that were published in PubMed or presented at international conferences or were in the public domain from January 1st, 2013, to October 31st, 2024. The recommendations and algorithms presented herein were unanimously approved by the panel.

GLP-1 receptor-based agonists

Background

Originally developed for T2DM and obesity because of their ability to modulate insulin and glucagon secretion, as well as reduce food intake, the GLP-1RAs have demonstrated benefits for lowering HbA1c and body weight, as well as reducing adverse cardiorenal outcomes in both T2DM and obesity settings. The epidemics of obesity and T2DM, heightened public awareness, and increasing acceptance of pharmacotherapy for weight management are together driving the use of GLP-1RAs[1].

General anesthesia, deep sedation and upper gastrointestinal (GI) endoscopy are associated with elevated risks of pulmonary aspiration[2–4]. Delayed gastric emptying (GE) is associated with retained gastric contents (RGC) which may in

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turn increase the risk for perioperative or periprocedural aspiration[4]. Delayed GE is more prevalent among people living with diabetes and especially among those whose glycemic control is poor (HbA1c >9%)[5]. Obesity, a frequent comorbidity of T2DM, may also be a risk factor for increased residual gastric volume and pulmonary aspiration[6].

GLP-1RAs have been reported to increase the risk of delayed GE[7] and GLP-1RA-associated delays in GE can culminate in RGC, in turn amplifying the risk of periprocedural pulmonary aspiration[8]. GLP-1RAs inhibit bowel motility, perhaps due to peripheral myenteric neuronal mechanisms, *via* vagal afferents or binding to GLP-1Rs in the central nervous system[8,9]. Slowed bowel motility can elevate the risk of ileus or intestinal obstruction and possibly decrease the efficacy of bowel preparation for colonoscopy[8,10–12]. Observational studies have reported conflicting results regarding GLP-1RAs and their impact on rates of bowel obstruction[10–12].

In June 2023, the American Society of Anesthesiologists (ASA) released a consensus-based guidance that raised concerns about potential increases in risk of perioperative pulmonary aspiration due to GLP-1RA use[13]. While the worries are not entirely unwarranted, it is important to note that the spectrum of risk faced by individuals undergoing surgery and diagnostic/interventional procedures can be quite variable and may therefore merit different approaches to how ongoing GLP-1RA therapy is managed. To this end, our group reviewed and discussed the published evidence and opinions surrounding GLP-1RAs and periprocedural risks and in the process, derived a pragmatic algorithm to help guide clinicians on the perioperative and periprocedural management of individuals who are being treated with GLP-1RAs.

Evidence review: gastric emptying/aspiration/bowel motility

GLP-1 receptor-based agonists and delayed gastric emptying

GE delay is more characteristic of shorter-acting GLP-1RAs (e.g. exenatide, lixisenatide) than longer-acting GLP-1RAs (e.g. dulaglutide, liraglutide, semaglutide, tirzepatide) [14]. In contrast, tachyphylaxis has been documented with longer-acting but not short-acting GLP-1RAs for at least up to 16 weeks after initiating treatment[14,15]. Studies utilizing scintigraphy, the gold standard test for GE, have shown that short treatment durations (between 8–16 weeks) with the longer-acting GLP-1RAs exenatide extended-release, liraglutide and semaglutide slowed GE delay[15–17]. A post hoc analysis of one of these bodies of work not only found that GE delay after 16 weeks of daily liraglutide 3 mg treatment was less evident than that at 5 weeks (30% vs 57% of participants, respectively) but also that half (50%) of the individuals who experienced GE delay at the 5-week timepoint demonstrated normal GE 11 weeks later[15]. Of note, tirzepatide, a GLP-1/glucose-dependent insulinotropic polypeptide co-agonist modulates GE in a similar manner to long-acting GLP-1R monoagonists[18]. To date, no study has examined the time to resolution of delayed GE upon discontinuation of a GLP-1RA.

In a meta-analysis of scintigraphy-based GE studies with GLP-1RAs, Hiramoto et al. reported a 36-minute GE delay for solids and none for liquids with the acetaminophen absorption test[19]. The 36-minute delay was deemed by the authors to be of limited magnitude relative to standard periprocedural fasting periods and the meta-analysis was considered inconclusive given the high heterogeneity (I^2=79%) of the solid-based studies[19]. Since no information on the type, dose and duration of use of the GLP-1RAs in the studies interrogated was provided, it is unknown how generalizable the results of this meta-analysis are to higher risk individuals who are more likely to experience delayed GE.

GLP-1 receptor-based agonists and retained gastric contents

Delayed gastric emptying from GLP-1RA therapy may lead to an increased likelihood of RGC. In fact, as shown in Supplementary Table 1, observational studies have consistently demonstrated greater incidence of RGC on upper GI endoscopy among individuals taking GLP-1RAs compared to non-GLP-1RA users[20–33]. Phan et al. reported that people who had their GLP-1RA withheld per the ASA guidance (1 week for weekly agents and 1 day for daily agents) were less likely to have RGC[22] while Silveira et al. did not find any difference in cessation time between those who experienced (10 days) and did not experience (11 days) RGC[23]. Many investigators have noted that consuming a liquid diet prior to upper GI endoscopy, typically in preparation for same-day colonoscopy, decreases RGC (Supplementary Table 1)[23,26–28,33]. Maselli et al. did not document any incidents of RGC in a case series of individuals with uninterrupted GLP-1RA treatment undergoing endoscopic sleeve gastrectomy and placed on a liquid diet ≥24 h prior[31]. Two independent teams did not uncover any difference in the duration of GLP-1RA therapy (median of 46–47 weeks) between those who did and did not experience RGC although notably, neither group of investigators assessed whether shorter versus longer duration of use of GLP-1RA therapy affected the outcome[23,25,34]. More studies are clearly warranted to determine if individuals who are still having their GLP-1RA titrated or have been on GLP-1RA therapy for shorter durations experience higher rates of RGC. That said, a meta-analysis of observational studies on the effects of GLP-1RAs on upper GI endoscopy demonstrated a statistically significant adjusted odds ratio (OR) of 4.2 for RGC, a 5.1-fold increased risk for aborted procedures, and very low rates of pulmonary aspiration with no statistically significant difference between GLP-1RA users and non-users (0.3% vs. 0.2%, OR 1.75, $p = 0.27$)[35].

Case reports of upper GI endoscopy have shown RGC among GLP-1RA users who had been fasting for between 10 to over 18 h, suggesting that RGC can occur after a traditional preprocedure fast[36–38]. Of further interest is that all the individuals on long-acting GLP-1RA therapy who experienced RGC had only been on their GLP-1RA for 2 months or less[37,38]. RGC has been visualized in individuals who had been on semaglutide for 6 days[39] (*via* computed tomography) and 1 month[40] (*via* point-of-care ultrasound) prior to a procedure. Observational studies using gastric ultrasonography have also found

an increase in RGC among individuals receiving weekly GLP-1RA therapy[41–44]. That RGC remained prevalent 7–10 days after the last dose of GLP-1RA had been taken suggests that the recommendation by the ASA to withhold weekly GLP-1RAs for 1 week prior to procedures is likely insufficient to prevent RGC[41–43]. A post hoc analysis by Potnuru et al. did not find any association between long-acting GLP-1RA treatment duration and RGC on gastric ultrasound[45] and when short-term (<12 weeks) GLP-1RA use was compared to long-term (≥12 weeks) use, the adjusted odds ratio for RGC was 2.48 (95% CI 0.43, 14.35; $p = 0.31$). These results should however be interpreted with caution given the small cohort size of 61 individuals of whom only 24 were in the short-term use group.

GLP-1 receptor-based agonists and pulmonary aspiration

An increase in RGC may be associated with an elevated risk of pulmonary aspiration during general anesthesia, deep sedation or upper gastrointestinal endoscopy. Observational cohort studies have reported conflicting results for how GLP-1RA use is associated with perioperative and periprocedural pulmonary aspiration occurrences (Supplementary Table 2)[46–55]. The risk of pulmonary aspiration in GLP-1RA-treated cohorts has been described as low although it is worth noting that these findings were from studies that did not include higher risk individuals and that there may have been some reporting bias. Furthermore, only three of the ten cohort studies demonstrated an increased risk of pulmonary aspiration with GLP-1RAs whereby the absolute risk increase in pulmonary aspiration was negligible in one[47], the second did not use propensity score matching[51], and even though the third did apply propensity score matching, the GLP-1RA group had higher HbA1c, fasting glucose and body mass index than the non-GLP-1RA users, potentially contributing to higher pulmonary aspiration risk among the GLP-1RA users[54]. As part of this work, we conducted a meta-analysis of 13 studies that reported on periprocedural pulmonary aspiration or pulmonary aspiration-related outcomes. The meta-analysis yielded a non-statistically significant increase in risk for pulmonary aspiration with GLP-1RA treatment (OR 1.20, 95% CI 0.92, 1.57) with low rates of overall pulmonary aspiration risk but moderate to high heterogeneity (I^2=59%; Supplementary Figure 1). It is important to reiterate that these meta-analytic results were derived from observational studies and trials with low event rates, probably in part due to underreporting of pulmonary aspiration. Given the lack of high-quality data, more studies on pulmonary aspiration risk are required to inform best treatment practices for GLP-1RA-treated individuals who are at higher risk for pulmonary aspiration.

It is worth noting that case reports of perioperative or periprocedural pulmonary aspiration or regurgitation in people taking weekly GLP-1RAs have often stemmed from individuals who had received their last GLP-1RA dose within 2–6 days of the procedure with traditional fasting recommendations[40,56–59]. Also of interest is that when the durations of GLP-1RA therapy were collected, they ranged from very recent use to up to 20 weeks[37,59,60].

GLP-1 receptor-based agonists and bowel motility

Observational studies on the impact of GLP-1RAs on the adequacy of colonoscopy preparation have yielded conflicting results, with two reporting no difference between GLP-1RA users and non-users[61,62] and three demonstrating an increase in inadequate bowel preparation amongst the GLP-1RA-treated individuals[33,63,64]. Accordingly, it is challenging to provide concrete evidence-based recommendations for bowel preparation among GLP-1RA-treated individuals who are scheduled for colonoscopy.

Summary of GLP-1 receptor-based agonist evidence review

General anesthesia, deep sedation and upper GI endoscopy are associated with an increased the risk of pulmonary aspiration. Shorter-acting GLP-1RAs and recent use (≤16 weeks or titration phase) of long-acting GLP-1RAs are associated with a higher risk for delayed GE, which may increase the risk of RGC and pulmonary aspiration. Although RGC is often more prevalent among GLP-1RA-treated individuals relative to non-GLP-1RA-treated individuals (~4-fold), its absence or presence does not appear to be predictive of increased pulmonary aspiration risk, which is notably low amongst most persons treated with GLP-1RAs. Cessation of weekly administered GLP-1RAs up to 7–10 days before procedure does not reliably minimize RGC suggesting that a longer withholding period may be necessary. Given the collective evidence from observational studies, a liquid diet one day before surgery/procedures seems appropriate and may likely reduce the risk of RGC and pulmonary aspiration. Point-of-care ultrasound can also be used pre-procedure to screen for RGC. Further investigations evaluating the impact of GLP-1RAs on the risk of pulmonary aspiration and colonoscopy preparation as well as optimal perioperative/periprocedural management strategies for GLP-1RA therapies are sorely needed. Considering the current evidence and based on our collective expert opinion, an individualized management approach with a focus on the highest-risk individuals (e.g. short-acting GLP-1RA, long-acting GLP-1RA of recent use or in titration phase, other risk factors for RGC or aspiration) is recommended.

Consensus statements and practice updates

The ASA was the first group to provide guidance for the preoperative management of patients taking GLP-1RAs[13]. It recommends withholding daily GLP-1RAs on the day of a procedure and weekly GLP-1RAs a week prior. For individuals with GI symptoms on the day of the procedure, the ASA endorses delaying the procedure. For those who have not held their GLP-1RAs, either proceed with "full stomach" precautions or utilize gastric ultrasound to screen for RGC. If RGC is not demonstrated on ultrasound, the procedure may proceed as usual but if ultrasound shows RGC or is inconclusive or not possible, then it is recommended that the procedure be delayed or if proceeding, "full stomach" precautions should be in place. The Canadian Anesthesiologists' Society has suggested that if "prolonged" holding of a GLP-1RA is not feasible, pulmonary aspiration risk reduction strategies should be considered —

these include but are not limited to case postponement, an extended "nothing by mouth" (NPO) period, clear fluid diet prior to the NPO period, avoidance of general anesthesia or deep sedation, if possible, and rapid sequence induction if general anesthesia is required[65]. A safety bulletin from the Institute for Safe Medication Practices Canada suggests similar pulmonary aspiration risk reduction strategies for those who are unable to hold a GLP-1RA for 3 half-lives, who have recently started or increased their dose or who have GI side effects[66]. Interestingly, a recent multi-society gastroenterology statement noted that there is "no data to support stopping GLP-1RAs prior to elective endoscopy" while recommending to exercise best practices[67]. This notion was reinforced in an American Gastroenterological Association Rapid Clinical Practice Update, where an individualized approach was encouraged, with attention to GI symptoms, and consideration of transgastric ultrasound and liquid diets the day prior to a procedure[68]. The Centre for Perioperative Care suggests that while GLP-1RAs can be continued perioperatively, precautions should be undertaken to avoid pulmonary aspiration[69]. A newer clinical practice guidance endorsed by the American Gastroenterological Association, American Society for Metabolic and Bariatric Surgery, American Society of Anesthesiologists, International Society of Perioperative Care of Patients with Obesity, and Society of American Gastrointestinal and Endoscopic Surgeons recommends that the management approach should be a shared decision between the patient and the care team while focusing on withholding GLP-1RAs (day of surgery for daily and a week prior for weekly agents) in individuals at higher risk of pulmonary aspiration (e.g. escalation phase, higher doses, GI symptoms, other medical conditions that may delay GE)[70]. The same group also described pulmonary aspiration risk reducing strategies such as a liquid diet 24 h prior to surgery, point-of-care gastric ultrasound and rapid sequence induction.

Editorials, commentaries and reviews

Several editorials, commentaries and review articles have analyzed the management issues related to periprocedural use of GLP-1RAs. Jones et al. have challenged the notion of withholding daily agents on the day of a procedure and weekly agents the week prior, understanding that withholding a drug for 3 half-lives allows approximately 88% clearance of the drug, which may be necessary to improve GE upon discontinuation of a GLP-1RA, although this remains unproven[71]. Bloomgarden posited that discontinuing a GLP-1RA preoperatively may cause more harm than benefit[72]. Dhatariya et al. suggested that GLP-1RAs should not be stopped in people living with diabetes and recommended pulmonary aspiration reduction strategies[73]. van Zuylen et al. and Umpierrez et al. reinforced the concept that short duration use of long-acting GLP-1RAs increases the risk of tachyphylaxis-related pulmonary aspiration and emphasized that risk decreases with long duration therapy for most GLP-1RA-treated patients[74,75]. The perioperative algorithm published by Milder et al. focused on individuals at high-risk for pulmonary aspiration and endorsed withholding GLP-1RAs for 3 half-lives, with point-of-care ultrasound recommended when the GLP-1RA is not held and rapid sequence induction or procedure delay for those with RGC[76]. The personal view article by Jalleh et al. reflected that there is insufficient data to support preprocedure cessation of GLP-1RAs in all individuals and that gastric ultrasound can help risk stratify patients[77] although no specific recommendation was offered for those who are at higher-risk for pulmonary aspiration. The same authors also proposed that weekly GLP-1RAs can be continued but that short-acting GLP-1RAs should be withheld for 48 h and liraglutide for >5 days before a procedure — this hold is notably longer than that endorsed by others[77]. For those with a preprocedure positive gastric ultrasound or if ultrasound is not available, Jalleh and colleagues recommended proceeding with "full stomach" precautions[77]. In a clinical focus review, Oprea et al. underscored that GLP-1RAs may need to be withheld among those who had only been using GLP-1RAs for a short duration of time, those in whom dose-titrating was still ongoing, and those who were experiencing GI symptoms[78]. The authors also suggested that a preprocedure liquid diet may the most important preventive intervention. Point-of-care gastric ultrasound is suggested for those on a weekly agent and if positive, consideration of a preprocedure liquid diet or intravenous erythromycin (although to the best of our knowledge, there has been no clinical study conducted to evaluate the impact of erythromycin on GE in GLP-1RA-treated patients). Wilson et al. noted that if a GLP-1RA is withheld preoperatively for a long enough time, agents that are usually titrated will have to be restarted postoperatively with the usual initiation and uptitration regimen to minimize GI side effects[79].

Summary of consensus statements and editorials/reviews

The body of evidence for what may be the best periprocedural management approach for GLP-1RAs is generally weak, predominantly due to observational study designs and absence of information. Consequently, consensus statements and expert opinions on perioperative and periprocedural management of GLP-1RA-treated patients vary widely. A liquid diet the day prior to procedures likely reduces risk of RGC and a withholding period of more than 3 half-lives for GLP-1RAs with a prolonged half-life is likely more efficacious than a one-week withholding period. Some of the important questions that require more research include: 1) Should GLP-1RAs be withheld and if so, for which operations and procedures? 2) In whom should GLP-1RAs be held and for how long before the operation or procedure? 3) What is the optimal duration of fasting? 4) What is the effect of a liquid diet the day prior? 5) Should point-of-care gastric ultrasound be utilized and how? 6) What is the impact of different dosing regimens or formulations on perioperative GLP-1RA associated pulmonary aspiration?

Recommendations for perioperative and periprocedural management of GLP-1 receptor-based agonist treated patients: The STOP-GAP algorithm

Our group has thoroughly reviewed and discussed the available and recently updated evidence on preoperative and periprocedural management of GLP-1RAs. Pending new

information, we have designed an evidence-informed and expert opinion-driven management algorithm called STOP-GAP (Figure 1), as well as practice recommendations (see below). In the absence of new information, a liquid diet is a low-risk intervention with the likelihood to reduce RGC in all GLP-1RA-treated individuals. Withholding GLP-1RAs with prolonged half-lives for 3 half-lives in individuals at higher risk for pulmonary aspiration may be more effective than withholding for only 1 half-life and not as clinically intrusive as withholding for a full 5 half-lives, after which complete elimination of the drug will occur. If withholding GLP-1RA therapy for ≥3 weeks, clinicians need to be prepared to start bridging therapy and recognize that a significant rise in glycemia and body weight can occur shortly after suspension of GLP-1RA therapy[80,81]. Withholding daily administered agents with shorter half-lives for 5 half-lives translates to a withholding period of between 1–3 days, which is a relatively safe and short period to be without GLP-1RA therapy.

Recommendations

1. Consider the individual risk of pulmonary aspiration in GLP-1RA-treated patients undergoing upper GI endoscopy or any procedures with general anesthesia or deep sedation. Discuss the risks and management options with the patient.
2. A liquid diet the day prior (with only clear fluids for ≥8–12 hours prior to NPO) and standard fasting guidelines are recommended for all who are on GLP-1RA therapy and are undergoing elective general anesthesia, deep sedation or upper GI endoscopy.
3. Most individuals do not need to have their GLP-1RA therapy withheld prior to elective surgeries or procedures since the risk of pulmonary aspiration is low in most people.
4. People at higher risk (Figure 2) for RGC or pulmonary aspiration should have their GLP-1RAs withheld prior to elective general anesthesia, deep sedation or upper GI endoscopy. Wherever possible, avoid scheduling elective surgery for individuals who have been taking a long-acting GLP-1RA for ≤16 weeks or if the GLP-1RA regimen is still in the titration phase at the time of the procedure.
5. If a GLP-1RA is to be withheld, hold it for ≥3 half-lives, to afford ~88% clearance of the drug, ahead of high-risk procedures for agents with a prolonged half-life and ≥5 half-lives for daily administered agents with shorter half-lives (Table 1). Obtain preprocedure consultation, if possible, about the appropriateness and practicality of withholding the GLP-1RA, risk of hyperglycemia and weight gain, and seek advice regarding bridging therapy if indicated.
6. Consider point-of-care gastric ultrasound, if available, for higher-risk patients who did not hold their GLP-1RA therapy before an elective procedure (e.g. withholding was deemed inappropriate or impractical), or if GI symptoms are present on the day of the procedure, or if the procedure is urgent. If an ultrasound reveals RGC or high gastric volume or is indeterminate or if an ultrasound is not conducted, "full stomach" precautions (both at the time of anesthetic induction and emergence) should be implemented or if possible, the procedure should be delayed, as long as there are no

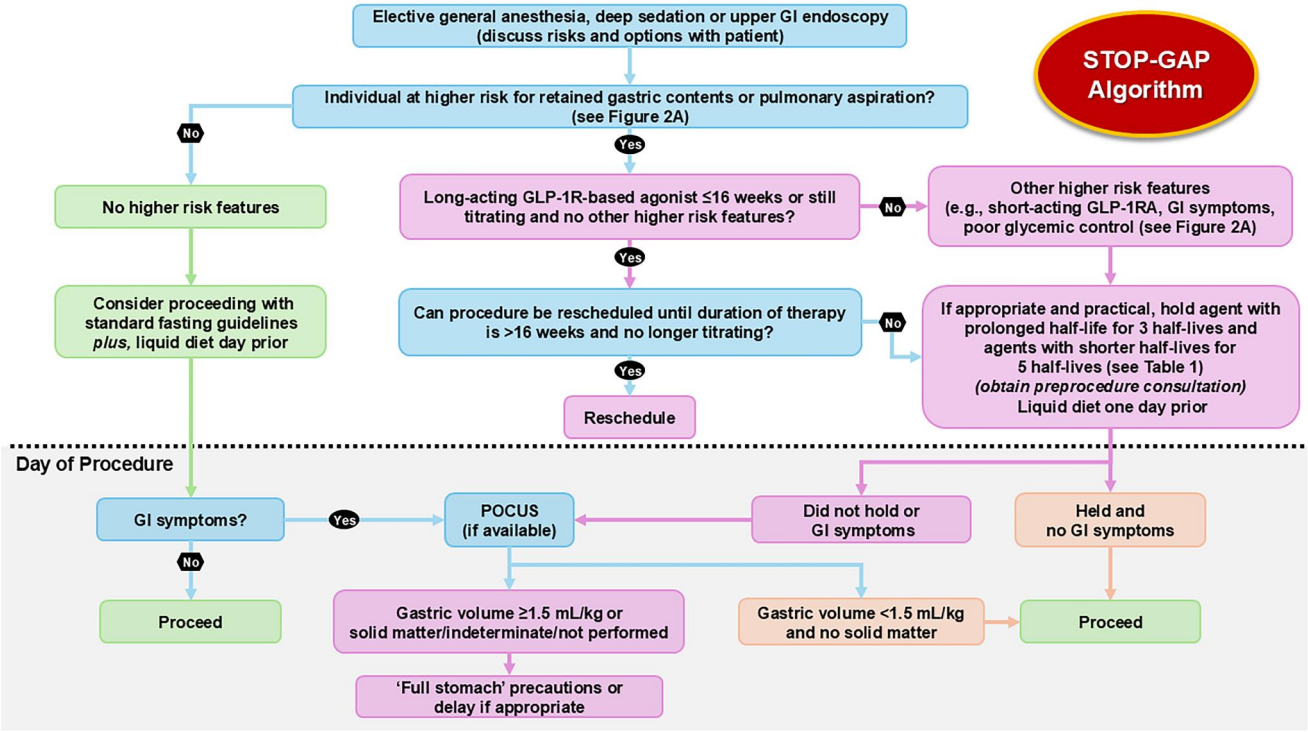

Figure 1. The STOP-GAP algorithm.
GAP, GLP-1RA related Aspiration during Procedures; GI, gastrointestinal; POCUS, point-of-care gastric ultrasound.

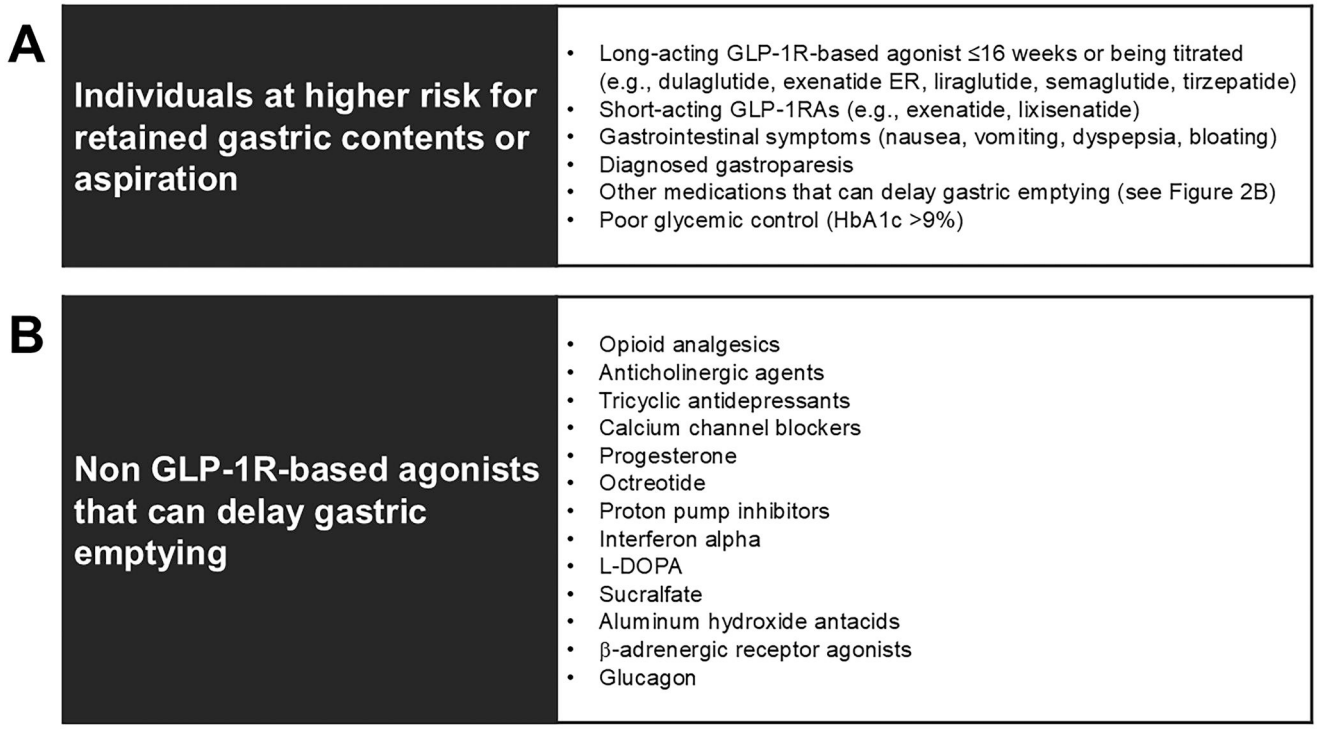

Figure 2. (A) Individuals at higher risk for retained gastric contents or pulmonary aspiration and (B) Non GLP-1R-based agonist medications that can delay gastric emptying.
ER, extended-release; GI, gastrointestinal; GLP-1(R), glucagon-like peptide-1 (receptor).
Panel B was adapted from Raven et al. 2024[7].

Table 1. Half-lives and cessation times of GLP-1 receptor-based agonists.

Generic Name	Brand Name	Indications	Route and Frequency	Half-life	Cessation Time
Administered weekly (QW) or prolonged half-life					
Dulaglutide	Trulicity®	T2DM	SC QW	~5 days	~15 days[a]
Exenatide ER	Bydureon BCise®	T2DM	SC QW	~2 weeks	~6 weeks[a]
Semaglutide (injectable)	Ozempic® / Wegovy®	T2DM / Obesity	SC QW	~7 days	~21 days[a]
Semaglutide (oral)	Rybelsus®	T2DM	SC QD	~7 days	~21 days[a]
Tirzepatide	Mounjaro® / Zepbound®	T2DM / Obesity	SC QW	~5 days	~15 days[a]
Daily administered with shorter half-lives					
Exenatide IR	Byetta®	T2DM	SC BID	2.4 h	1 day[b]
Liraglutide[c]	Victoza® / Saxenda®	T2DM / Obesity	SC QD	13 h	3 days[b]
Lixisenatide[c]	Adlyxine®	T2DM	SC QD	3.1 h	1 day[b]

[a], 3 half-lives; [b], 5 half-lives (rounded up to the nearest day); [c], also available as a fixed ratio combination (FRC) agent with basal insulin. If withholding an FRC agent, consider periprocedure use of the basal insulin component as per clinical judgement.
BID, twice daily; ER, extended-release; IR, immediate-release; QD, once daily; QW, once weekly; SC, subcutaneous; T2DM, type 2 diabetes mellitus.

unnecessarily untoward implications associated with the delay.

7. Resume GLP-1RA therapy once normal caloric intake has resumed post surgery/procedure. If the GLP-1RA has been withheld for ≥3 half-lives, titrate to previous dose as per usual recommendations for initial titration.

Sodium-glucose co-transporter inhibitors

Background

Proven benefits of SGLT2i include improved glycemic control, weight loss and blood pressure reduction in individuals living with T2DM, as well as cardiorenal risk reduction in individuals living with T2DM, CKD and heart failure[82–84]. Large randomized trials have also demonstrated lower rates of acute kidney injury (AKI) in SGLT2i-treated individuals[83]. Diabetic ketoacidosis (DKA) is a known side effect of SGLT2i that has implications for perioperative and periprocedural management, given that surgical stress along with reduced oral intake or fasting are triggers for SGLT2i-associated ketoacidosis[85].

Evidence review: Diabetic ketoacidosis and acute kidney injury

SGLT2i-associated diabetic ketoacidosis

DKA is a potentially life-threatening condition, with mortality rates of 0.65–3.3% and incidence rates in type 1 diabetes mellitus (T1DM) of between 4.6–8.0 per 1,000 patient-years and in T2DM between 0.32–2.0 per 1,000 patient-years[86]. Laboratory parameters suggestive of DKA include a pH that is ≤7.3, bicarbonate levels ≤15 mmol/L (or <18 mmol/L), anion gaps >12 mmol/L and positive serum or capillary ketone tests (≥3.0 mmol/L, β-hydroxybutyrate preferred; ≥1.5 mmol/L is an

intermediate threshold and warrants further testing). Elevated plasma glucose (≥14 or ≥11.1 mmol/L) is typical of DKA but not in euglycemic DKA with SGLT2i. Most cases of DKA are associated with a precipitant such as insulin omission or inappropriate dose reduction, surgery or invasive procedures, extensive exercise, myocardial infarction or stroke, severe infection, low carbohydrate/low calorie diets or excessive alcohol intake[86–89].

Chronic SGLT2i treatment can be associated with an asymptomatic rise in ketones, most prominent among individuals living with T1DM but also in those living with T2DM, and there can also be a blunted but small rise among people living with prediabetes[88,89]. Proposed mechanisms for perioperative SGLT2i-associated DKA include an SGLT2i-induced decline in blood glucose and surgical stress-induced rise in counterregulatory hormones, leading to a relative reduction in insulin secretion from pancreatic β-cells and an increase in glucagon secretion from pancreatic α-cells, increased lipolysis with an increase in circulating free fatty acids driving ketogenesis. Hyperglycemia can originate from counterregulatory hormone stimulation of gluconeogenesis/glycogenolysis and may be counteracted by the ongoing glycosuria and lower plasma glucose seen with SGLT2i therapy and potentially euglycemia despite the presence of ketoacidosis[85].

A meta-analysis of 13 large placebo-controlled randomized trials of SGLT2i has suggested a 2-fold increase in DKA among those living with T2DM and treated with SGLT2i[83]. While a doubling of risk seems concerning, it should be noted that the incidence rate of DKA in the SGLT2i-assigned group was 0.3% and that in the placebo group 0.14%. Furthermore, SGLT2i-associated DKA incidence was negligible among those without diabetes, with only 1 case presenting among the 7,788 SGLT2i-treated patients. In observational cohort studies of SGLT2i-treated individuals living with T2DM, another meta-analysis revealed a significant increase in DKA (hazard ratio 1.33) with absolute rates of SGLT2i-associated DKA ranging from 0.6–6.3 events per 1,000 person-years compared to 0.6–4.5 events per 1,000 person-years amongst those treated with an active comparator[90]. The risk of SGLT2i-associated DKA was much higher among those living with T1DM, with about a 3.5-fold increased risk compared to placebo-treated individuals and absolute incidences of 3.1% and 0.76% in SGLT2i- and placebo-treated individuals, respectively[91]. In the sotagliflozin trials, greater elevations in β-hydroxybutyrate levels from baseline were associated with increased events of DKA[92].

The results from observational studies of perioperative DKA in people living with diabetes and taking SGLT2i are summarized in Supplementary Table 3[93–98]. In a retrospective chart review, Auerbach et al. noted euglycemic DKA occurrences in 15.1% of SGLT2i-treated cardiac surgery patients. They did not report on the cessation of SGLT2i prior to surgery and there was no DKA risk mitigation protocol in place[93]. Brekke et al. reported a 41% incidence of post-cardiac surgery anion gap metabolic acidosis in SGLT2i-treated individuals without kidney failure compared to only 8% in non-SGLT2i-treated patients[98]. In this study, SGLT2i was held for ≥3 days in 16% of the patients and only 42% received an insulin infusion from the onset of surgery. In a matched cohort study where SGLT2i was not held prior to elective surgery, euglycemic DKA developed in 23% of the SGLT2i-treated group and in 8% of the no SGLT2i group ($p = 0.047$) [94]. In another retrospective cohort study, the incidence rate ratio was 6.3 for SGLT2i users compared to non-users, with a higher incidence among those who were not counselled on SGLT2i withdrawal, in emergency or major surgery, among insulin-treated individuals and those with a high HbA1c[95]. Mehta et al. found that 7 of 8 cases of euglycemic DKA occurred when the SGLT2i was not held preoperatively[96]. Zero cases of DKA were reported in a study by Seki et al.[97] where a DKA risk mitigation strategy with insulin administration and glucose infusions was utilized in 759 individuals living with diabetes and undergoing surgery with general anesthesia. These results are notable given that 35% of the patients received an SGLT2i within one day of surgery.

In a systematic review of 99 perioperative SGLT2i-associated DKA case reports, 8 cases were euglycemic incidents, 83 were reported for individuals living with T2DM, 10 for diabetes of unknown type, 3 among people living with T1DM, 1 in an individual without diabetes but with heart failure and a prolonged fast (>24 h) and volume depletion, and 2 with unknown diabetes status[99]. Among the 58 cases where the cessation time of SGLT2i was reported, all 58 had their SGLT2i stopped <3 days preoperatively. DKA was associated with various triggers, among which were fasting or reduced caloric intake ($n = 27$), bariatric surgery ($n = 24$), emergency surgery ($n = 19$), coronary artery bypass graft surgery ($n = 18$), cholecystectomy ($n = 5$) and inadequate insulin dosing ($n = 4$) [99]. In a case series describing colonoscopy-related SGLT2i-associated DKA, all 8 cases were living with T2DM and two were using insulin. None of the cases had their SGLT2i withheld for ≥3 days, all had euglycemia and their serum ketone levels ranged from 2.0–5.2 mmol/L. Interestingly, 7 of the 8 cases were diagnosed after bowel preparation but before the colonoscopy procedures began[100]. A cross-sectional study demonstrated that bowel preparation with a liquid diet can raise ketone levels up to 1.7 mmol/L, even in those without diabetes[101]. The upper limit of 1.7 mmol/L is similar to the 1.5 mmol/L value that is used for defining "at risk" individuals living with diabetes and warranting further testing for DKA.

There is little data on the optimal cessation time for SGLT2i prior to surgery or procedures. In a case report, Osafehinti et al. observed that stopping the SGLT2i 48 h before surgery did not prevent DKA[102]. Furthermore, there appears to be an inverse relationship between SGLT2i hold time and postoperative anion-gap[103]. With cessation of a drug for 5 half-lives, close to 100% of the drug is eliminated from the body[104]. Since the average half-life of an SGLT2i is between 11–13 h, stopping the SGLT2i for about 3 days pre-procedure should translate to negligible circulating levels of the SGLT2i by the time of the procedure[104]. Clinical case reports suggest that the pharmacologic activity of SGLT2i may be prolonged under certain circumstances, with glycosuria and ketonuria persisting for up to 14 days[105]. While cessation of SGLT2i intake for 3 days will reduce the rates of

DKA, the drug effect may continue well beyond 5 half-lives[105]. Accordingly, clinicians need to have ongoing clinical suspicion for ketosis/DKA postprocedure and this should be considered as part of a risk mitigation strategy, especially among those individuals who are at higher risk[105].

Although almost all cases of SGLT2i-associated DKA have been reported in individuals living with diabetes, the risk of SGLT2i-associated DKA occurring in individuals without diabetes is negligible but not zero. Fasting or reduced caloric intake may be a precipitating factor for perioperative SGLT2i-associated DKA in those living with or without diabetes[106]. There are rare reports of SGLT2i-associated DKA in people without diabetes and taking SGLT2i for heart failure; DKA in these incidences were triggered by fasting ~12 hrs or reduced caloric intake over 3–7 days due to acute illness[105,106]. Postoperative SGLT2i-associated DKA has been reported in individuals without diabetes and were associated with fasting ≥12 h with low postoperative carbohydrate intake or dehydration[104,107]. Although risk is low among those without diabetes, it may be prudent to withhold SGLT2i in people who do not have diabetes and who require bowel preparation or have reduced caloric intake (e.g. bariatric surgery, liquid diets, or anticipated prolonged NPO period).

SGLT2i and acute kidney injury

AKI correlates with elevated mortality rates and longer hospital stays[108]. Major surgery is associated with an increased risk of AKI, especially cardiac, vascular, transplantation, intraperitoneal, thoracic, orthopedic and urologic surgery[109,110]. Diabetes is a known risk factor for postoperative AKI after major surgery[108,109]. In a large prospective international observational multicenter study of individuals undergoing major surgery (requiring admission to the intensive care unit or high dependency unit care), AKI occurred in 18.4% of the overall cohort, 24.3% of the people living with diabetes (OR 1.27, $p < 0.001$ for diabetes vs. no diabetes) and 40.7% of those living with CKD and with an eGFR <60 mL/min/1.73 m^2 (OR 2.0, $p < 0.001$ for CKD vs. no CKD) [111]. In a meta-analysis, an eGFR <60 mL/min/1.73 m^2 before major surgery was associated with an increased risk of AKI (relative risk [RR] 3.1; 95% CI 2.2, 4.4) [112].

Contrast-associated AKI is a major complication after contrast exposure[113]. Diabetes is a risk factor for contrast-associated AKI, with the incidence ranging from 5.7–29.4% compared to approximately 13% in those without diabetes[114]. In a meta-analysis of 1.1 million contrast exposed patients, the presence of diabetes was associated with a higher risk of contrast-associated AKI (OR 1.58, 95% CI 1.48, 1.70) compared to those without diabetes[113]. Among individuals living with CKD, the presence of diabetes was associated with a 2.3-fold increase in the risk of contrast-associated AKI compared to those without diabetes[113]. The risk of contrast-associated AKI reportedly rose with each stepwise increase in CKD stage — a 15% increase in risk with eGFR <45 mL/min/1.73 m^2 and 30% at eGFR <30 mL/min/1.73 m^2[115].

Postoperative AKI can be triggered by reduced kidney blood flow along with increased kidney oxygen demand[116]. Contrast-associated AKI can occur due to cytotoxic effects on kidney tubular and endothelial cells, intra-kidney vasoconstriction, increased oxidative stress and medullary hypoxia[117]. SGLT2i have the potential to increase AKI due to osmotic diuresis and volume depletion as well as uricosuria, which can lead to local tubular injury[118]. In contrast, there is also the potential for SGLT2i therapy to reduce the risk of AKI by stimulating pathways that can reduce kidney ischemia[119].

Clinical studies suggest that SGLT2i may protect against AKI. Indeed, a meta-analysis of 13 large placebo-controlled randomized trials revealed a reduction in AKI among SGLT2i-treated individuals (RR 0.77; 95% CI 0.70, 0.84), with similar benefits observed among people living with and without diabetes[83]. The incidence of AKI was approximately 2% among the SGLT2i-treated patients and up to 3% in the placebo group[83]. A meta-analysis of observational cohort studies also showed fewer AKI events in the SGLT2i-treated group versus the control group (OR 0.50, 95% CI 0.38, 0.66) [120].

A single center retrospective cohort study analyzed the effect of withholding versus not withholding SGLT2i on perioperative AKI as a component of a composite adverse events outcome[121]. Among the 16 individuals who had their SGLT2i held for ≥3 days preoperatively, there were 3 cases of AKI (18.8%). Among the 66 individuals who did not hold their SGLT2i, there were 5 cases of AKI (4.6%). There was only 1 case of DKA in this study and interestingly, it was in the group that withheld their SGLT2i. Although the number of AKI cases was small and the p-value was 0.05, this study suggests a potential protective effect of SGLT2i on AKI during the perioperative period[121]. Given the potentially grave consequences, more research on how withholding an SGLT2i preoperatively affects the risk of AKI is merited.

There are few randomized studies of the impact of SGLT2i on periprocedural AKI. The MERCURI-1 (MEtabolic and Renal outcomes in Cardiac sUrgery patients Receiving SGLT2 Inhibitors) trial was an open-label randomized pilot study comparing empagliflozin 10 mg to standard of care in 55 individuals undergoing cardiac surgery (9% of whom were living with T2DM) [122]. Empagliflozin was started 3 days prior to surgery and continued to 2 days after surgery. There were 5 cases of AKI among the 25 empagliflozin-treated participants (20%) and 20 cases of AKI among the 30 individuals in the control arm (66.7%) with an absolute risk reduction of 46.7%. Of note, a DKA risk mitigation strategy was in place during this trial (perioperative blood gas and ketone monitoring, glucose/insulin infusions for suspected DKA) and there was no difference in serum ketone levels between the groups nor any occurrences of DKA[122]. The open-label POST-CABGDM study compared empagliflozin 25 mg to usual treatment in 145 individuals living with T2DM and undergoing coronary artery bypass surgery[123]. Empagliflozin was given for 3 months prior to surgery and discontinued 3 days prior to surgery, resulting in a 55% relative reduction in the incidence of AKI within 7 days of surgery[123]. The ongoing MERCURI-2 (proMoting Effective Renoprotection in Cardiac sURgery Patients by Inhibition of SGLT-2; $N = 784$)[124] and VERTIGO (EValuating the Effect of periopeRaTIve

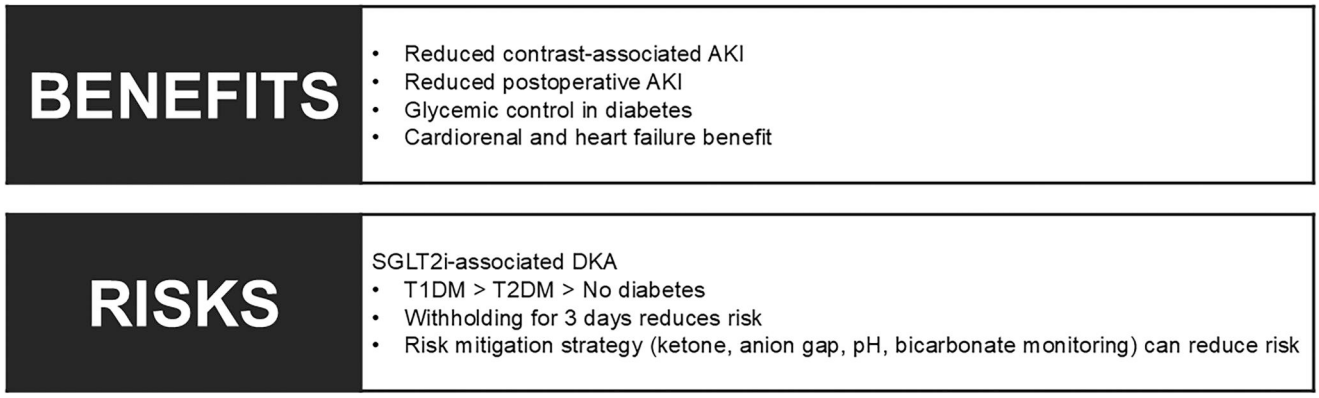

Figure 3. Perioperative and periprocedural benefits versus risks of SGLT2 inhibitors.
AKI, acute kidney injury; DKA, diabetic ketoacidosis; SGLT2i, sodium-glucose co-transporter type 2 inhibitors; HF, heart failure; T1DM, type 1 diabetes mellitus; T2DM; type 2 diabetes mellitus.

empagliflozin; $N = 608$)[125] randomized trials are comparing perioperative SGLT2i therapy to placebo in cardiac surgery patients.

The effect of chronic SGLT2i treatment on AKI after percutaneous intervention (PCI) or coronary angiography in individuals living with T2DM has been reviewed in a meta-analysis of 8 bodies of work (7 observational studies and 1 randomized trial) [126]. The meta-analysis demonstrated a 52% reduction in AKI with SGLT2i treatment (RR 0.48; 95% CI 0.39, 0.59; I^2=0%). Observational evidence thus suggests that chronic SGLT2i regimens should generally not be discontinued prior to intravenous contrast. The small randomized trial by Feitosa et al. ($N = 42$) was neutral for the effect of chronic SGLT2i for T2DM on post-contrast AKI, but it was notably underpowered with only 5 events[127]. A prospective study in a cohort without diabetes demonstrated lower rates of AKI with dapagliflozin (0.3%) versus placebo (6%) after PCI/angiography[128]. Nardi et al. showed a reduction in post-contrast AKI with chronic SGLT2i treatment for heart failure with reduced or mildly reduced ejection fraction[129]. Cai et al. demonstrated a reduction in AKI with acute dapagliflozin treatment post-myocardial infarction[130] while Zang et al. suggested an increase in AKI after coronary angiography in the setting of T2DM with acute SGLT2i treatment[131]. Randomized trials are studying the effect of acute SGLT2i treatment on post-contrast AKI but the results are not yet available[132,133].

During the management of SGLT2i-treated individuals who are undergoing procedures or surgery, one must consider the benefits of ongoing SGLT2i treatment (reduced risk of contrast associated AKI, reduced risk of postoperative AKI, glycemic control and cardiorenal/heart failure benefits) versus the risks of postoperative DKA (T1DM > T2DM > no diabetes). Withholding SGLT2i for 3 days and implementing a periprocedural risk mitigation strategy (ketone, anion gap, pH and bicarbonate monitoring and insulin/dextrose infusions as indicated) can help reduce SGLT2i-associated DKA risk (Figure 3).

Summary of evidence review: diabetic ketoacidosis and acute kidney injury

SGLT2i are associated with an increased risk of DKA in individuals living with diabetes (T1DM > T2DM) but the risk is negligible in those without diabetes. Surgery, invasive procedures or colonoscopy are known risk factors for SGLT2i-associated DKA, but the absolute risk is low. Other SGLT2i-associated DKA risk factors relevant to surgery include low calorie/low carbohydrate intake or prolonged fasting prior to or after surgery in those living with or without diabetes. Withholding SGLT2i by about 3 days in individuals living with diabetes prior to surgery or invasive procedures or reduced perioperative oral intake can reduce the risk of postoperative SGLT2i-associated DKA. Among those without diabetes, there is generally no need to hold the SGLT2i, unless one is concerned about reduced caloric intake (e.g. bariatric surgery, liquid diets, or anticipated prolonged NPO period). A perioperative risk mitigation strategy (ketone, pH and anion-gap monitoring; insulin and dextrose infusions) can help in mitigating risk of DKA.

Major surgery and procedures using contrast media convey a significant risk of AKI, especially if the eGFR is <60 mL/min/1.73m^2 prior to major surgery or <45 mL/min/1.73m^2 prior to contrast media. Diabetes, especially in the presence of CKD, further increases the risk of postsurgical and post-contrast AKI. The rates of postsurgical and post-contrast AKI in higher risk individuals appear to be greater than those of SGLT2i-associated DKA. SGLT2i have been shown to reduce AKI in randomized trials and observational studies. Chronic SGLT2i therapy likely protects against postoperative AKI, even when withheld for 3 days prior to surgery. Finally, chronic SGLT2i treatment has been shown to reduce the risk of contrast-associated AKI in observational studies.

Consensus statements, guidelines and bulletins: diabetic ketoacidosis

Consensus statements, guidelines and bulletins have offered different recommendations for the perioperative/periprocedural management of individuals treated with SGLT2i. The 2016 position statement from the American Association of Clinical Endocrinologists endorsed stopping SGLT2i $\geq$24 h prior to elective surgery or invasive procedures, a cessation period that is much shorter than the typical 5 half-lives recommendation[134]. In 2022, the U.S. Food & Drug Administration updated a drug safety communication by recommending that SGLT2i be stopped at least 3–4 days before scheduled surgery[135]. This is the current recommendation of the

American Diabetes Association[136]. Health Canada recommends stopping SGLT2i ≥3 days before surgery or invasive procedures requiring prolonged fasting[137]. The British Obesity & Metabolic Surgery Society has suggested discontinuing SGLT2i 48 h before any preoperative diet[138]. In a May 2023 Alert Update, a multi-society group from Australia and New Zealand recommended that SGLT2i be omitted for ≥3 days before surgery and procedures requiring ≥1 day(s) in hospital or requiring a bowel preparation with carbohydrate restriction[139]. They also suggested that for day-stay procedures that do not require bowel preparation, SGLT2i could be halted just on the day of the procedure (i.e. no holding period in the days leading up to the procedure); and for those who had not held their SGLT2i as recommended, a perioperative ketone and acidosis monitoring strategy was recommended[139]. In a peer-reviewed narrative "guideline" from the University of Pennsylvania, a 3-day holding period was recommended for patients living with diabetes with monitoring for DKA starting preoperatively if the SGLT2i had not been held. They also provided intraoperative and postoperative treatment instructions based on ketone levels and anion-gap monitoring and that considered patient characteristics and procedure-related risk factors for DKA[140].

Expert opinions, editorials and reviews: diabetic ketoacidosis

In a clinical practice systematic review article by Thiruvenkatarajan et al. it was noted that when the risk for DKA is low, such as short-stay or minor surgical procedures where resumption of caloric intake will be within hours of the intervention, SGLT2i do not need a withholding period and if held, the SGLT2i therapy can be resumed the day following the procedure[141]. When oral intake is likely to be delayed postoperatively, a longer holding period should be considered[141]. Verdone et al. have suggested a DKA risk mitigation algorithm for SGLT2i-treated patients who did not discontinue therapy prior to elective procedures, with a focus on serum ketone measurements as well as anion-gap or pH if DKA is suspected[142]. Some experts have recognized the negligible risk of SGLT2i-associated DKA in individuals without diabetes. Raven et al. suggested that perioperative recommendations in guidelines should differentiate between patients living with and without diabetes[143]. In an editorial on the risk of perioperative discontinuation of SGLT2i among individuals living with heart failure, it was suggested that a strategy for prevention of DKA by early detection and treatment of ketosis and acidosis may be preferred over discontinuation of SGLT2i, given that cardiovascular status may deteriorate after discontinuation of the SGLT2i[144]. Although SGLT2i are traditionally stopped during an acute illness, a clinical review by Khunti et al. has suggested that continuation of the SGLT2i may be considered alongside regular assessment for DKA with a focus on ketone monitoring[145]. Our group feels that for some SGLT2i-treated patients, a ketone-based monitoring strategy can be applied to a periprocedural strategy while continuing SGLT2i therapy, especially if the benefits of continuing the SGLT2i therapy outweigh the risks of SGLT2i withdrawal (see below for more details). Of note, there are a limited number of meters capable of measuring capillary blood ketones using dry-chemistry methodologies, and versions of these meters are currently available for inpatient monitoring, with connectivity[146].

Warnings, editorials and reviews: acute kidney injury

There is limited contemporary guidance on the management AKI risk among SGLT2i-treated patients in the setting of surgical or procedural situations. In 2016, based on post-marketing reports of AKI in individuals treated with SGLT2i, the U.S. Food & Drug Administration issued an updated drug safety communication risk with warnings about AKI[147]. Subsequently, as summarized in detail above, clinical data suggested that SGLT2i are protective against AKI. Sridhar et al. has published an editorial entitled "We Can Finally Stop Worrying About SGLT2 Inhibitors and Acute Kidney Injury", recognizing that these drugs are in fact "kidney safe" and do not predispose to AKI[148]. Finally, in a discussion of the observational evidence that SGLT2i may prevent contrast-induce AKI in individuals undergoing PCI, it has been suggested that withdrawal of SGLT2i be discouraged before PCI[149].

Summary of consensus statements and editorials/reviews

Recommendations for the perioperative and periprocedural management of SGLT2i-treated patients vary across guidelines, consensus statements, bulletins and expert opinions. Arising from the discussions at our expert forum, we recognized the need for a practical, safe and easily implemented management algorithm that takes into consideration the following:

- Patient profile (diabetes versus no diabetes) and procedure characteristics that are associated with an increased risk of DKA
- Benefits versus risks of withholding SGLT2i
- Duration of SGLT2i withholding
- Perioperative monitoring for DKA and treatment with insulin/glucose
- When to resume SGLT2i post-procedure

The STOP DKA-2 algorithm and ketone monitoring protocol described below is evidence informed with expert opinion where further studies may be required.

Recommendations for perioperative and periprocedural management of SGLT2itreated patients: STOP DKA-2 Algorithm and STOP DKA-2 Ketone Monitoring Protocol

Recommendations

1. Individuals living with or without diabetes who are undergoing elective procedures with a lower risk for DKA (Figure 4(A)) do not need to hold their SGLT2i. Procedures should be booked early in morning to minimize the fasting duration. Early postprocedure caloric intake should be encouraged. If total perioperative NPO time extends to >12 hours or if the individual is not tolerating postprocedure oral intake with carbohydrates, begin the STOP DKA-2 ketone monitoring protocol (Figure 4(B)).

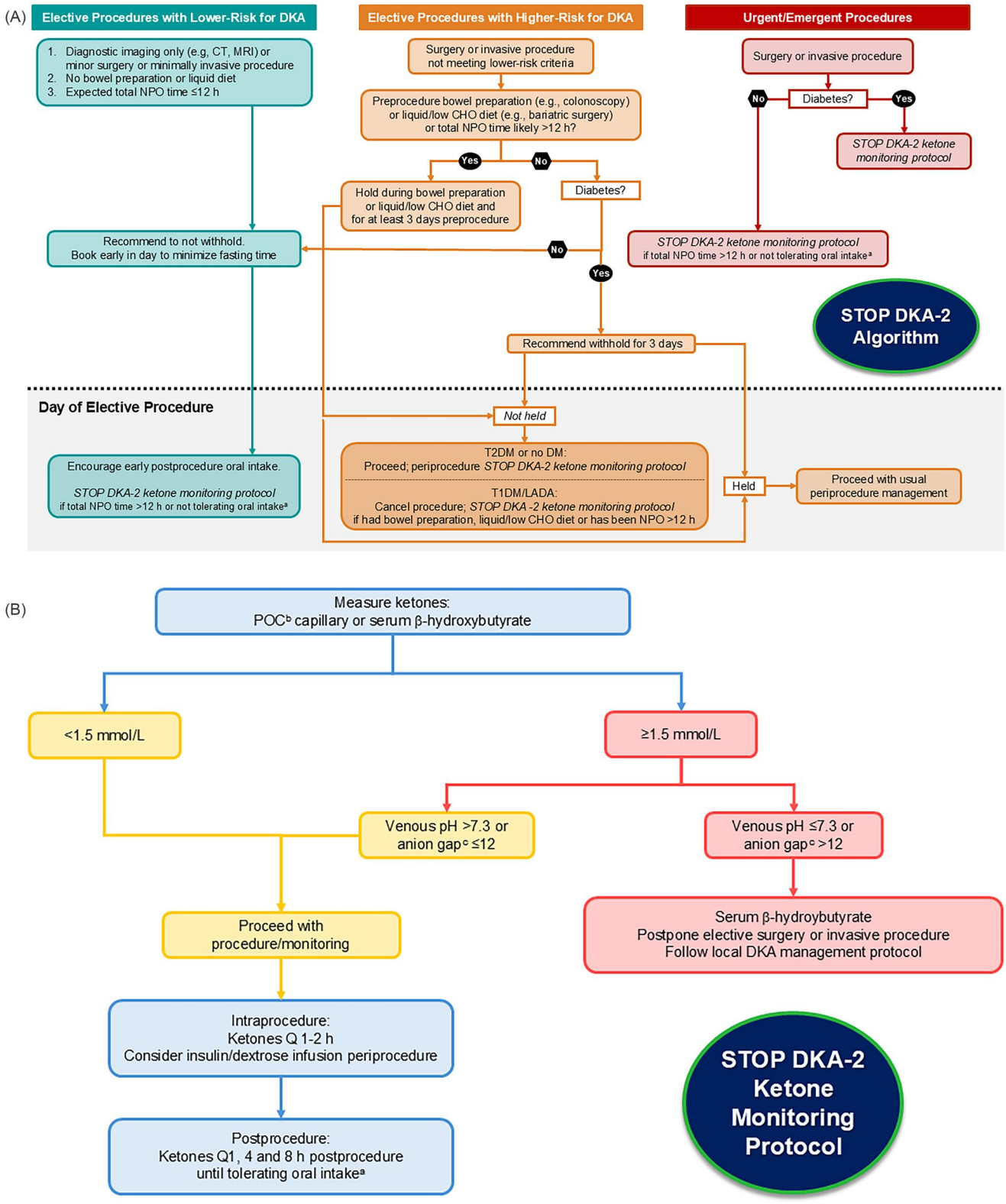

Figure 4. The (A) STOP DKA-2 algorithm and (B) STOP DKA-2 ketone monitoring protocol.
[a], oral intake includes liquid diet, if it contains carbohydrates; [b], point-of-care testing recommended if available and approved locally, otherwise order serum β-hydroxybutyrate; [c], anion gap = (sodium + potassium) − (chloride + bicarbonate).
CHO, carbohydrate; CT, computed tomography; DM, diabetes; DKA, diabetic ketoacidosis; LADA, latent autoimmune diabetes; MRI, magnetic resonance imaging; NPO, nothing by mouth; POC, point-of-care; T1DM, type 1 diabetes mellitus.

2. Individuals living with or without diabetes who are booked for elective procedures requiring bowel preparation, are following a liquid/low carbohydrate diet prior to the procedure or are likely to experience a perioperative NPO duration that is >12 hours, should have their SGLT2i held during the bowel preparation or liquid/low carbohydrate diet and for ≥3 days preprocedure. If the individual has not held the SGLT2i upon

arrival at the surgical site and is living with either T2DM or no diabetes, proceed with the procedure and utilize the STOP DKA-2 ketone monitoring protocol (Figure 4(B)). If the individual is living with either T1DM or latent autoimmune diabetes (LADA), cancel the procedure and utilize the STOP DKA-2 ketone monitoring protocol if they had a bowel preparation, liquid/low carbohydrate diet or have been NPO for >12 hours.

3. Individuals without diabetes who are undergoing elective procedures with a higher risk for DKA (Figure 4(A)), and who do not require a bowel preparation or liquid/low carbohydrate diet and the expected perioperative NPO time is ≤12 hours, do not need to withhold their SGLT2i. Procedures should be booked early in morning to minimize the fasting duration. Early postprocedure caloric intake should be encouraged. If the total perioperative NPO time extends beyond 12 hours or the individual is not tolerating postprocedure caloric intake, begin the STOP DKA-2 monitoring protocol (Figure 4(B)).
4. Individuals living with diabetes who are undergoing elective procedures with a higher risk for DKA (Figure 4(A)), and who do not require a bowel preparation or liquid/low carbohydrate diet and the expected perioperative NPO time is ≤12 hours, should have their SGLT2i withheld for 3 days. If the SGLT2i was not held prior to the procedure, consider proceeding with the procedure and utilizing the STOP DKA-2 ketone monitoring protocol for individuals with T2DM and cancel the procedure for individuals with T1DM or LADA and use the STOP DKA-2 monitoring (Figure 4(B)) protocol if they have been NPO for over 12 hours (Figure 4(B)).
5. For individuals requiring urgent/emergent surgery or invasive procedures, proceed in those without diabetes and utilize the STOP DKA-2 monitoring protocol (Figure 4(B)) if the total periprocedure NPO time is >12 hours or if they are not tolerating oral intake with carbohydrates. For those living with diabetes, proceed with the STOP DKA-2 ketone monitoring protocol.
6. Periprocedure glucose management for individuals with diabetes should continue as per local practice. All individuals living with diabetes treated with insulin should continue with periprocedure insulin dosing, and reduction in dosage should be done with caution because of the risk of DKA. Utilize insulin and dextrose infusions and treat DKA as per local practice.
7. SGLT2i therapy should be resumed as soon as the individual can tolerate oral intake and there is no clinical evidence for ketosis/ketoacidosis. Caloric intake includes a liquid diet if it contains carbohydrates.

Conclusions

With the growing utility of GLP-1RAs and SGLT2i across different disease types, clinicians need to become more familiar with how to manage their use in perioperative and periprocedural settings. Despite the gaps in knowledge, the available evidence supports the contention that there is no "one size fits all" approach to adjusting these agents perioperatively and periprocedurally. We hope that the STOP-GAP and STOP DKA-2 algorithms described herein will be of assistance to our colleagues and their patients in deciding how to safely individualize perioperative and periprocedural management of GLP-1RAs and SGLT2i.

Transparency

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Author contributions

RMG conceived the work and drafted the original versions of the text, tables and figures. All authors conducted the literature search and critically revised the manuscript. The final version of the manuscript was reviewed and approved by every author, all of whom agreed to act as guarantors of the work.

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