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Preoperative SGLT2 Inhibitor Use and Postoperative Diabetic Ketoacidosis

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IMPORTANCE Case reports of postoperative diabetic ketoacidosis in patients using sodium-glucose cotransporter 2 inhibitor (SGLT2i) medications underlie guidance by the US Food and Drug Administration to withhold SGLT2i medication for at least 3 days prior to surgery. Given the potential negative consequences associated with preoperative medication withholding, a large-scale evaluation of the risk of diabetic ketoacidosis in this population is needed.

OBJECTIVE To estimate the association between preoperative SGLT2i medication use and postoperative diabetic ketoacidosis in a population of patients who underwent a variety of emergency surgeries. Emergency surgery was chosen given the assumption that a patient would be unable to withhold their SGLT2i medication per the current guidance.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study was conducted among a nationwide sample of patients aged 18 years or older with type 2 diabetes who were enrolled in commercial or Medicare fee-for-service insurance plans and who underwent 1 of 13 emergency surgeries between January 1, 2016, and December 15, 2022. Emergency surgeries were defined as those occurring on the same day or the 1 to 2 days after an emergency department claim. Data were analyzed from November 2023 through December 2024.

EXPOSURE SGLT2i medication use.

MAIN OUTCOMES AND MEASURES Diabetic ketoacidosis, defined by diagnosis codes, in the 0 to 14 days after surgery.

RESULTS Among 34 671 patients with type 2 diabetes who underwent emergency surgery (mean [SD] age, 63.9 [14.0] years; 19 175 female [55.3%] and 15 496 male [44.7%]), the most common surgeries were laparoscopic cholecystectomy (9385 patients) and transurethral procedures (12 246 patients). There were 2607 patients (7.5%) who used SGLT2i medications and 32 064 patients (92.5%) who did not. Unadjusted incidence of diabetic ketoacidosis was 127 patients (4.9%) for those exposed to SGLT2i medications and 1115 patients (3.5%) for those unexposed. After accounting for covariates, including demographic characteristics, indicators of diabetic severity, comorbidities, and surgery type, the incidence of the outcome was 3.8% for those exposed to SGLT2i medications and 3.5% for those unexposed. The average treatment effect [ATE] was 0.2% (95% CI, −1.7% to 2.2%). Results were robust to alternate specifications (eg, intensive care unit–level care as the outcome: ATE, −1.0%; 95% CI, −2.9% to 1.1%).

CONCLUSIONS AND RELEVANCE This study found that preoperative use of SGLT2i medications in patients undergoing emergency surgery was not associated with an increased risk for postoperative diabetic ketoacidosis compared with no use of SGLT2i medications. These findings may justify liberalizing current guidance on preoperative SGLT2i medication withholding periods.

Invited Commentary

Supplemental content

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Sodium-glucose cotransporter 2 inhibitor (SGLT2i) medications are a class of oral antiglycemic agents that prevent kidney glucose reabsorption and promote glucosuria. They are typically used as second-line pharmacotherapy for patients with type 2 diabetes and atherosclerotic cardiovascular disease and are also indicated in some patients with heart failure and chronic kidney disease. While SGLT2i medications have substantial cardioprotective, kidney-protective, and quality of life benefits,[1-3] they are associated with an increased risk of diabetic ketoacidosis relative to other antidiabetic agents.[4-6] Given this risk, as well as case reports of life-threatening ketoacidosis in the setting of perioperative fasting,[7] the US Food and Drug Administration (FDA) issued guidance in 2020 for patients to withhold SGLT2i medications for at least 3 days prior to surgery.[8] However, this guidance was not based on any large-scale evaluations of risk of diabetic ketoacidosis in the context of perioperative fasting.

Although medication withholding guidelines can avert complications, they can also lead to adverse outcomes, such as suboptimal perioperative glycemic control on the day of surgery. Perioperative hyperglycemia is associated with increased risk of surgical site infections, end-organ injury, and death,[9] as well as longer hospitalizations given the potential need for preoperative intravenous insulin therapy. Furthermore, medication withholding guidelines can be logistically burdensome for patients and health care systems given that patients who do not appropriately withhold medications may have their surgery delayed or canceled, resulting in patient harm[10] and significant financial losses due to inefficient use of operating room time and resources.[11] Thus, despite the FDA's 2020 recommendations on perioperative SGLT2i withholding, this guidance remains controversial and some international societies have endorsed less conservative withholding guidelines.[12] Given the increasing use of SGLT2i medications,[13] in line with recommendations from the American Diabetes Association and the American College of Cardiology,[14,15] a large-scale evaluation of the perioperative risks associated with SGLT2i medications is needed and could facilitate evidence-based updates to clinical medication withholding guidelines.

Based on these considerations, we used a large, nationally representative claims database to evaluate the risk of postoperative diabetic ketoacidosis in patients with diabetes who underwent a variety of emergency surgeries, comparing those who used SGLT2i medications against those who used other antidiabetic agents. This approach leveraged a natural experiment given that patients undergoing emergency surgery would likely not have been able to withhold their SGLT2i medications in accordance with guidance. We hypothesized that the risk of diabetic ketoacidosis would not differ between those who did or did not use SGLT2i medications.

Key Points

Question Is preoperative use of sodium-glucose cotransporter 2 inhibitor (SGLT2i) medication associated with postoperative occurrence of diabetic ketoacidosis?

Findings In this cohort study of 34 671 patients with type 2 diabetes who underwent an emergency surgery and therefore were unlikely to withhold their SGLT2i medication per current guidance, preoperative use of SGLT2i medication was not associated with postoperative diabetic ketoacidosis.

Meaning This finding suggests that current guidance on 3-day preoperative medication withholding periods for SGLT2i medications may be unnecessary.

Methods

Data and Sample

This cohort study was approved by the Stanford University Institutional Review Board with a waiver of informed consent because the data were deidentified. The study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. We conducted a retrospective cohort study using the Merative MarketScan Commercial and Medicare Supplemental Databases,[16,17] a combination of databases representing approximately 250 million individuals nationwide in the following 2 groups: (1) younger than 65 years and enrolled in employer-sponsored or other commercial health insurance plans as primary subscribers or dependents and (2) ages 65 and older and enrolled in Medicare fee-for-service plans. These datasets provide enrollment data and inpatient, outpatient, and pharmaceutical claims that can be linked to provide a longitudinal understanding of each patient's health care and outcomes.

Patients were included in our study if they were aged 18 years or older; had undergone any of 13 emergency surgeries between January 1, 2016, and December 15, 2022; and were continuously enrolled in a MarketScan plan for 180 days before and 15 days after the date of surgery. Emergency surgeries were defined using Current Procedural Terminology codes that occurred on the same day or the 1 to 2 days after an emergency department (ED) visit with a relevant *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) diagnosis code (eTable 1 in Supplement 1). This approach restricted the sample to patients who would not have been able to withhold their SGLT2is in accordance with the FDA-recommended 3-day withholding period before surgery.[8] We applied this same logic in a 2024 study evaluating the use of other antidiabetic agents.[18] We further limited the sample to patients with type 2 diabetes, defined as having at least 1 *ICD-10* diagnosis code for type 2 diabetes plus a prescription fill for at least 1 oral antidiabetic medication or evidence of insulin use[19] in the 180 days preceding the date of surgery (eFigure and eMethods 1 in Supplement 1). No patients underwent more than 1 surgery.

Exposure

The exposure was defined as patients with prescription fills for an SGLT2i medication with days-supply overlapping with the date of surgery. The unexposed group, therefore, comprised patients with type 2 diabetes treated with non-SGLT2i antidiabetic agents, restricted to those who had not filled any prescriptions for SGLT2i medications in the previous 180 days.

Outcome

We defined the outcome as diabetic ketoacidosis in the 0 to 14 days after the date of surgery given that the vast majority of reported cases of diabetic ketoacidosis in patients who used SGLT2is have been diagnosed within this time frame.[7] We categorized patients as having diabetic ketoacidosis if they had any of several diagnosis codes for diabetic ketoacidosis, a code for acidosis (*ICD-10* E87.2), or both, as others have done (eTable 2 in Supplement 1).[20-22] Given that there is no *ICD-10* code specific to SGLT2i-related euglycemic diabetic ketoacidosis, this approach captures patients who may have experienced the outcome of interest but were not identified as having diabetic ketoacidosis because they were not hyperglycemic. We further conducted a sensitivity analysis, described subsequently, focused on a narrower set of codes.

Additional Variables

Covariates included age, sex, Diabetes Complications Severity Index score,[23] number of pharmacologic classes used to treat diabetes, use of insulin, Elixhauser comorbidities,[24] insurance type (ie, commercially insured vs insured by Medicare fee-for-service), year fixed effects, surgical procedure fixed effects, and fixed effects for the number of days between the last ED claim and date of surgery (ie, 0, 1, or 2 days). See additional details on Elixhauser comorbidities in eMethods 1 in Supplement 1.

Statistical Analysis

We first calculated absolute standardized mean differences (SMDs) between patients exposed vs unexposed to SGLT2is across all covariates and surgical procedure fixed effects listed previously. We considered an SMD greater than 0.1 to be a meaningful difference in prevalence between groups.

Next, we estimated the association between SGLT2i and postoperative complications using targeted maximum likelihood estimation (TMLE).[25] This is a doubly robust method that is preferred to traditional multivariable logistic regression methods given that TMLE is an efficient estimator and offers 2 opportunities to control for confounding. TMLE is useful in pharmacoepidemiologic studies using large datasets given the complex associations that may exist between exposure, outcome, and other variables, particularly because it allows incorporation of machine learning methods to estimate the treatment and outcome models. We applied TMLE using the SuperLearner,[26] an ensemble machine learning method with 10-fold cross-validation.[26,27] We included a combination of learners (ie, standard logistic regression, with and without interaction terms, and elastic net regularization) to estimate treatment and outcome models, allowing for covariate selection with reduction of multicollinearity and overfitting (eMethods 2 in Supplement 1). We implemented TMLE to estimate the average treatment effect (ATE), which represented the mean difference in risk of diabetic ketoacidosis if all patients in the cohort were exposed vs unexposed to SGLT2is. We calculated the 95% CI for the ATE based on the standard error using 1000 bootstrap resamples with replacement. All analyses were conducted using R statistical software version 4.2.3 (R Project for Statistical Computing). Data were analyzed from November 2023 through December 2024.

Sensitivity Analyses

As checks of robustness, we conducted several sensitivity analyses. First, we respecified our outcome to a composite binary outcome encompassing diabetic ketoacidosis, admission to the intensive care unit (ICU) based on ICU-specific revenue codes, or both in the 0 to 14 days after the date of surgery (eTable 2 in the Supplement). We added this sensitivity analysis because patients with diabetic ketoacidosis (whether euglycemic or with elevated glucose levels) would likely require ICU-level care and treatment with an insulin infusion. We restricted this analysis to the commercially insured population because patients enrolled in Medicare fee for service undergoing emergency general surgery have high rates of ICU admission,[28] and thus inclusion of this group would likely have low specificity for diabetic ketoacidosis. Second, we respecified the comparison group to include only patients with non-SGLT2i antidiabetic medications overlapping with the date of surgery. Third, we respecified the outcome to a narrower set of codes for diabetic ketoacidosis by excluding code E87.2 for acidosis (eTable 2 in Supplement 1), as others have done.[5] Fourth, we respecified the outcome period to days 1 to 14 after the date of surgery (omitting day 0) to exclude the possibility of the patient having ketoacidosis prior to surgical intervention. Finally, we compared results from our primary analysis, which used TMLE, with results using a multivariable logistic regression model, adjusting for all covariates and fixed effects listed previously.

Subgroup Analyses

We conducted 4 subgroup analyses. These analyses restricted the cohort to (1) patients who underwent any of 3 surgeries considered lower risk for postoperative complications (laparoscopic appendectomy, laparoscopic cholecystectomy, and transurethral interventions), (2) those who underwent surgery on the same day as a claim for the ED given evidence for a dose-dependent association between time from last SGLT2i dose and diabetic ketoacidosis,[29] (3) those who underwent surgery in the 1 to 2 days after their last ED claim (rather than on the same day as their last ED claim) assuming that most of these patients would be appropriately fasting and would have withheld their SGLT2i medications starting from presentation to the ED until date of surgery (this approach approximated outcomes in an elective surgical population following standard preoperative fasting times and SGLT2i medication withholding guidance), and (4) those who underwent intra-abdominal or pelvic surgery given the possibility that these individuals may have had prolonged periods of low oral intake during the perioperative period.

Results

Our final sample included 34 671 patients who underwent emergency surgery (mean [SD] age, 63.9 [14.0] years; 19 175 female [55.3%] and 15 496 male [44.7%]), among whom

2607 patients (7.5%) used SGLT2i medications and 32 064 patients (92.5%) did not (**Table 1**). The most common surgeries were laparoscopic cholecystectomy (9385 patients) and transurethral procedures (12 246 patients). Patients using SGLT2i medications were more likely to be female (1636 female [62.8%] vs 17 539 female [54.7%]) and commercially insured (1843 patients [70.7%] vs 15 782 patients [49.2%]) and used a higher mean (SD) number of antidiabetic agents (2.7 [1.0] vs 1.2 [0.9] agents). They were less likely to have a diagnosis of kidney failure. The unadjusted incidence of the outcome was 127 patients (4.9%) for those exposed to SGLT2i medications and 1115 patients (3.5%) for those unexposed.

After adjustment using TMLE, the incidence of the outcome was 3.8% for patients exposed and 3.5% for those unexposed (**Table 2**). The ATE was 0.2% (95% CI, −1.7% to 2.2%). Results were robust to alternate specifications, with all sensitivity analyses estimating the ATE as 0.4% or lower and all

Table 1. Characteristics of the Study Population

Characteristic	Patients, No. (%) (N = 34 671)		SMD[a]
	SGLT2i use (n = 2607)	No SGLT2i use (n = 32 064)	
Demographic characteristics			
Age, mean (SD), y	59.6 (11.1)	64.3 (14.1)	0.37
Sex			
Female	1636 (62.8)	17 539 (54.7)	0.16
Male	971 (37.2)	14 525 (45.3)	0.16
Insurance type			
Commercial	1843 (70.7)	15 782 (49.2)	0.45
Medicare	764 (29.3)	16 282 (50.8)	0.45
Severity of diabetes			
Preoperative use of insulin	628 (24.1)	6923 (21.6)	0.06
Total No. of agents used to treat diabetes, mean (SD)	2.7 (1.0)	1.2 (0.9)	1.49
Diabetes Complications Severity Index score, mean (SD)[b]	1.5 (1.7)	1.8 (2.0)	0.20
Elixhauser comorbidities[c]			
AIDS or HIV	15 (0.6)	62 (0.2)	0.06
Alcohol abuse	33 (1.3)	470 (1.5)	0.02
Blood loss anemia	49 (1.9)	954 (3.0)	0.07
Other anemia	154 (5.9)	2879 (9.0)	0.12
Cardiac arrhythmia	496 (19.0)	8428 (26.3)	0.17
Congestive heart failure	221 (8.5)	4389 (13.7)	0.17
Coagulopathy	139 (5.3)	2005 (6.3)	0.04
Chronic pulmonary disease	344 (13.2)	5557 (17.3)	0.12
Depression	327 (12.5)	4654 (14.5)	0.06
Drug abuse	28 (1.1)	469 (1.5)	0.04
Fluid or electrolyte disorder	516 (19.8)	7747 (24.2)	0.11
Hypertension, complicated	330 (12.7)	5887 (18.4)	0.16
Hypertension, uncomplicated	2123 (81.4)	25 870 (80.7)	0.02
Hyperthyroidism	414 (15.9)	5842 (18.2)	0.06
Liver disease	567 (21.7)	5861 (18.3)	0.09
Lymphoma	17 (0.7)	352 (1.1)	0.05
Metastatic cancer	39 (1.5)	672 (2.1)	0.05
Obesity	997 (38.2)	10 829 (33.8)	0.09
Other neurologic disorder	95 (3.6)	2631 (8.2)	0.19
Paralysis	22 (0.8)	398 (1.2)	0.04
Psychosis	<11	182 (0.6)	0.07
Chronic peptic ulcer disease	62 (2.4)	925 (2.9)	0.03
Pulmonary circulation disorder	81 (3.1)	1202 (3.7)	0.04
Kidney failure	264 (10.1)	5658 (17.6)	0.22
Rheumatoid arthritis	93 (3.6)	1279 (4.0)	0.02
Solid tumor	200 (7.7)	3336 (10.4)	0.10
Valvular disease	192 (7.4)	3481 (10.9)	0.12
Weight loss	72 (2.8)	1551 (4.8)	0.11

(continued)

Table 1. Characteristics of the Study Population (continued)

Characteristic	Patients, No. (%) (N = 34 671)		SMD[a]
	SGLT2i use (n = 2607)	No SGLT2i use (n = 32 064)	
Type of surgery			
Laparoscopic appendectomy	506 (19.4)	3373 (10.5)	0.25
Laparoscopic cholecystectomy	825 (31.6)	8560 (26.7)	0.11
Operative management of traumatic hip fracture	138 (5.3)	3137 (9.8)	0.17
Colectomy for diverticulitis	11 (0.4)	226 (0.7)	0.04
Operative management of adhesive small bowel obstruction	28 (1.1)	223 (0.7)	0.04
Operative management of ovarian torsion[d]	<11	60 (0.2)	0.03
Operative management of testicular torsion[d]	<11	11 (0.0)	0.03
Operative management of ectopic pregnancy[d]	<11	69 (0.2)	0.04
Operative management of incarcerated or strangulated hernia	227 (8.7)	2808 (8.8)	0.00
Laparoscopic or open repair of perforated peptic or duodenal ulcer[d]	<11	47 (0.1)	0.04
Transurethral intervention for urolithiasis or nephrolithiasis	696 (26.7)	11 550 (36.0)	0.20
Upper endoscopy for management of bleeding peptic or duodenal ulcer	79 (3.0)	1168 (3.6)	0.03
Upper endoscopy for foreign body removal	102 (3.9)	1005 (3.1)	0.04
Days between ED claim and surgery			
0	1924 (73.8)	25 628 (79.9)	0.15
1	474 (18.2)	4516 (14.1)	0.11
2	209 (8.0)	1920 (6.0)	0.08

Abbreviations: ED, emergency department; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SMD, standardized mean difference.

[a] An SMD greater than 0.1 was considered reflective of meaningful differences between groups.

[b] The Diabetes Complications Severity Index is a severity score ranging from 0 to 13 and validated for use with *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) diagnosis codes in administrative data. It is based on the sum of individual scores of 0 to 2 for diabetes-related complications in 7 categories (cardiovascular, cerebrovascular and peripheral vascular disease, metabolic disease, nephropathy, retinopathy, and neuropathy).

[c] Among 30 Elixhauser comorbidities, 28 comorbidities were included, with 2 Elixhauser comorbidities (diabetes with and without complications) excluded to avoid collinearity with the Diabetes Complications Severity Index.

[d] Some cell sizes in this row have been suppressed for patient privacy in accordance with the data use agreement with Merative MarketScan.

Table 2. Primary Adjusted Model, Sensitivity, and Subgroup Analyses

Analysis	Adjusted incidence of diabetic ketoacidosis, % (95% CI)[a]		ATE, % (95% CI)
	Exposed to SGLT2i medication	Unexposed to SGLT2i medication	
Targeted maximum likelihood estimation[b]	3.8	3.5	0.2 (−1.7 to 2.2)
Sensitivity analyses			
1: Outcome respecified to include ICU-level care	4.6	5.6	−1.0 (−2.9 to 1.1)
2: Comparison group restricted to patients with antidiabetic medications with days-supply overlapping date of surgery	3.7	3.4	0.2 (−1.6 to 2.1)
3: Outcome respecified to more restrictive definition of ketoacidosis	0.6	0.5	0.1 (−1.7 to 1.9)
4: Outcome period respecified to exclude date of surgery	3.0	2.6	0.4 (−1.6 to 2.4)
5: Multivariable logistic regression	0.6	1.0	0.4 (0.1 to 0.8)[c]
Subgroup analyses			
1: Sample restricted to low-risk surgeries	3.2	3.2	0.0 (−2.1 to 2.1)
2: Sample restricted to same-day surgeries	4.3	3.5	0.9 (−2.7 to 4.5)
3: Sample restricted to surgeries occurring 1-2 d after ED claim	2.6	3.8	−1.2 (−5.7 to −0.3)
4: Sample restricted to intra-abdominal and pelvic surgeries	3.0	3.4	−0.4 (−3.0 to 2.3)

Abbreviations: ATE, average treatment effect; ED, emergency department; ICU, intensive care unit; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

[a] Results are presented for the primary analysis and additional sensitivity and subgroup analyses estimating the risk of postoperative complications in patients undergoing emergency surgery who were exposed preoperatively to SGLT2is.

[b] The area under the receiver operating characteristic curve was 0.95 for the model estimating the probability of treatment and 0.84 for the model estimating the probability of the outcome.

[c] This value represents an average marginal effect. The odds ratio was converted to estimated probabilities and the average marginal effect by calculating the mean estimated probability of the outcome if all patients in the study population had or had not received an SGLT2i medication, keeping all other covariates and fixed effects as they were.

subgroup analyses estimating the ATE as 0.9% or lower. For example, in sensitivity analysis 1 (ICU-level care as the outcome), the ATE was −1.0% (95% CI, −2.9% to 1.1%). All sensitivity and subgroup analyses are presented in Table 2.

Discussion

In this cohort study, preoperative use of SGLT2i medications in patients undergoing emergency surgery was not associated with an increased risk for postoperative diabetic ketoacidosis compared with not using SGLT2i medications after adjusting for relevant confounders. The primary analysis estimated a near-zero ATE with narrow CIs, and findings were replicated in all sensitivity and subgroup analyses. The absolute adjusted risk of diabetic ketoacidosis in our cohort of patients who underwent emergency surgery, more than 20% of whom used insulin, was in line with results of other studies. Estimates of the incidence of postoperative diabetic ketoacidosis range from approximately 1% to 15% in patients who underwent emergency surgery, major intra-abdominal or major intrathoracic surgery, or both, with a more pronounced risk for patients who were insulin dependent.[30-33]

SGLT2i medications have been linked to life-threatening cases of diabetic ketoacidosis, often in the context of illness or perioperative fasting and likely due to an imbalance in insulin-to-glucagon ratios. A retrospective study[34] of patients who presented to the hospital with diabetic ketoacidosis or who developed diabetic ketoacidosis during an inpatient admission found an increased risk in those who had used SGLT2i medications. A systematic review of case reports[7] identified 59 patients undergoing surgery who developed ketoacidosis after using SGLT2i medications in the 0, 1, or 2 days before surgery, with no cases identified in those who used SGLT2i medications in the 3 days or longer before surgery. Both of these studies were restricted to patients diagnosed with diabetic ketoacidosis and therefore could not be used to assess population-level risk of this outcome across all patients using SGLT2i medications; furthermore, these studies may have been confounded by other factors, such as underlying medical reasons for inpatient admission. Additionally, a single-center study[29] found a dose-dependent association between shorter SGLT2i medication withholding times and increased postoperative anion gap, implying that most patients using SGLT2i medications develop increased serum ketoacids postoperatively regardless of whether this metabolic state progresses to diabetic ketoacidosis. That study also found that undergoing emergency surgery was associated with increased risk of having an elevated anion gap postoperatively.[29] While the study provided evidence that use of SGLT2i medications within the few days preceding surgery may be associated with increased risk of postoperative metabolic derangements, it did not establish the magnitude of clinically significant diabetic ketoacidosis across the population of patients undergoing surgery who use SGLT2i medications. Finally, a high-quality meta-analysis[35] that pooled results from multiple large randomized clinical trials of patients with type 2 diabetes found that those who used SGLT2i medications had approximately 2 times the odds of diabetic ketoacidosis compared with those receiving no treatment, active placebo, or other active antidiabetic agents, with an estimated risk difference of 1.7 more events per 1000 patients over 5 years. While this meta-analysis showed a clear, statistically significant increase in the risk of diabetic ketoacidosis in patients using SGLT2i medications, it also found that the absolute incidence of this outcome was low. Furthermore, it did not include patients undergoing surgery and therefore could not be used to evaluate risk during the specific, relatively short perioperative time frame.

Our study used a large, nationwide population of patients with type 2 diabetes who underwent emergency surgery to advance this literature, providing a population-level risk estimate for identified, clinically meaningful postoperative complications, as defined by claims for management of diabetic ketoacidosis, in patients with type 2 diabetes who used SGLT2i medications and underwent surgery. Our study was designed to isolate patients who were most likely unable to adhere to a 3-day medication withholding period for their SGLT2i medications. Findings from this study may provide reassurance that the absolute incremental risk of clinically meaningful postoperative diabetic ketoacidosis in the population of patients using SGLT2i medications undergoing surgery, including a subgroup of those who likely followed standard preoperative fasting guidelines, is extremely low.

SGLT2i medications provide a variety of clinical benefits in addition to glycemic control, including blood pressure control and improved cardiac and kidney function, in patients with and without diabetes.[36,37] Withholding these medications prior to surgery, therefore, could plausibly be associated with poor glycemic control, worsened hypertension, and suboptimal cardiac and kidney function on the day of surgery, all of which are independent risk factors associated with adverse postoperative outcomes.[9,38,39] These risks associated with withholding SGLT2i medications, in addition to patient harms and financial losses caused by canceled surgeries,[10,11] must be weighed against the low risks of diabetic ketoacidosis estimated by this large-scale study.

Limitations

This study has important limitations. First, although we included a large number of potential confounders, including those specific to severity of diabetes, we did not have access to laboratory values and cannot rule out the possibility of residual confounding from unmeasured variables. Second, we assumed that patients would have continued taking their SGLT2i medication and would not be fasting prior to presentation to the ED. If patients skipped their medication doses prior to presentation, a behavior that is not possible to identify using claims data, the exposure would be misclassified and would likely skew results toward the null. However, if patients had prolonged periods of fasting prior to or after surgery, the incidence of the outcome would likely be overestimated. We addressed this potential limitation with a subgroup analysis focused on patients undergoing only intra-abdominal or pelvic surgery, which corroborated the main findings. Third, we used a claims-based definition for diabetic ketoacidosis drawing on multiple other studies that investigated diabetic ketoacidosis using *ICD-10*-based definitions.[5,20-22] However, no studies to our knowledge have reported the sensitivity or specificity of these definitions. We therefore conducted sensitivity analyses using more restrictive (ie, exclusion of the E87.2 code) and more liberal (ie, inclusion of ICU-level care) inclusion criteria

than the primary analysis and found results that corroborated those of the primary analysis. Fourth, our population may not reflect the glucose homeostasis of an elective surgical population with specific fasting guidance prior to their procedure. However, a sensitivity analysis approximating characteristics of an elective surgical population also found no association between SGLT2i medication use and diabetic ketoacidosis; the risk of diabetic ketoacidosis in patients undergoing elective surgery is much lower than that in patients undergoing emergency surgery, meaning that the effect size estimated by this study was likely higher than would be found in an elective population; and findings from this study may help justify more expeditious care for patients who require urgent surgery within the subsequent 1 to 2 days (ie, less than the 3-day waiting period recommended by the FDA). Fifth, our analysis focused on patients with type 2 diabetes and excluded patients without diabetes using SGLT2i medications for management of heart failure or chronic kidney disease. Future research should evaluate this growing population, although patients without diabetes likely would have a lower risk of ketoacidosis in the setting of perioperative fasting given that their insulin-glucagon regulation is less likely to be impaired. Sixth, while we used standard methodology to define medication adherence, we do not have specific information on when the last dose of the SGLT2i was taken prior to surgery. Seventh, our analysis was retrospective and limited to patients who underwent the selected emergency surgeries and were enrolled in commercial and Medicare fee-for-service plans, and findings may not apply to other populations.

Conclusions

In this retrospective cohort study, we compared the occurrence of postoperative diabetic ketoacidosis in patients undergoing emergency surgery who had type 2 diabetes and used SGLT2i medications compared with those who used other antidiabetic medications. We found that use of SGLT2i medications was not associated with an increased risk of postoperative diabetic ketoacidosis. Given that these patients undergoing emergency surgery were unlikely to withhold their SGLT2i medications in line with current guidance, our findings suggest that recommended 3-day medication withholding periods for SGLT2i medications could be liberalized. Future research based on more precise SGLT2i inhibitor and perioperative fasting times is warranted to corroborate these results. Furthermore, additional evaluations may focus on other populations, including patients without diabetes using SGLT2i medications for management of heart failure or chronic kidney disease.

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Concept and design: Dixit, Bateman, Sun.
Acquisition, analysis, or interpretation of data: Dixit, Bateman, Hawn, Odden, Sun.
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Critical review of the manuscript for important intellectual content: All authors.
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Supervision: Sun.

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