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Perioperative Glucose Pragmatic (PROGRAM) Trial: Standardized Insulin Management in Surgical Patients

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ABSTRACT

Background: Perioperative hyperglycemia is associated with adverse patient outcomes including surgical site infections. This study examined whether an automated insulin dosing reminder is associated with a lower risk for postoperative hyperglycemia and other secondary and safety outcomes in patients at high risk for intraoperative hyperglycemia.

Methods: The authors conducted a pragmatic trial using a sequential and repeated crossover design between October 5, 2022, and October 26, 2023. They sequentially assigned anesthesia providers to receive either an automated insulin dosing reminder (intervention) or a glucose check reminder (routine care) periodically throughout surgery for a consecutive sample of adult patients at high risk for intraoperative hyperglycemia undergoing major surgery at their quaternary medical center. The primary outcome was hyperglycemia (glucose greater than 180 mg/dl) at the first postoperative measurement 3 h or less postoperatively. The primary analysis studied the association between automated insulin dosing reminder and postoperative hyperglycemia adjusted for demographics, surgery characteristics, preoperative glucose, time period, and the interaction of intervention and time period.

Results: A total of 4,558 cases qualified for primary analysis: 2,611 cases in the routine care group and 1,947 cases in the intervention group. A total of 970 (37%) and 675 (35%) cases, respectively, experienced the primary outcome. The authors found no evidence of an association between treatment and postoperative hyperglycemia in the overall study period (odds ratio [OR], 0.90; 95% CI, 0.78 to 1.03; $P = 0.165$). There was no evidence of difference in intraoperative glucose monitoring (OR, 0.99; 95% CI, 0.83 to 1.19; $P = 0.369$) and intraoperative insulin use (OR, 1.00; 95% CI, 0.83 to 1.20; $P = 0.995$). The odds of surgical site infections were higher in the intervention group (overall unadjusted OR, 2.52; 95% CI, 1.37 to 4.64; $P = 0.006$). No difference in safety endpoints was observed between groups.

Conclusions: Among surgical patients at high risk of intraoperative hyperglycemia, an automated insulin dosing reminder did not improve glycemic control or other outcomes compared with a glucose check reminder.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Perioperative hyperglycemia is associated with adverse patient outcomes
- Automated electronic health record reminders can improve adherence to clinical practice recommendations
- It is unclear whether an insulin dosing reminder results in better glycemic control or clinical outcomes when compared to a routine care glucose check reminder

What This Article Tells Us That Is New

- A total of 4,558 cases at high risk for hyperglycemia undergoing major surgery were enrolled in a pragmatic sequential and repeated crossover trial of an insulin dosing reminder *versus* glucose check reminder at a single academic medical center during a 1-yr period
- Of the cases, 37% (970 of 2,611) in the routine care group and 35% (675 of 1,947) in the intervention group experienced hyperglycemia at the first postoperative blood glucose measurement, which was not a clinically or statistically significant difference (odds ratio, 0.90; 95% CI, 0.78 to 1.03; $P = 0.165$)

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Abbreviations: **EHR**, electronic health record; **OR**, odds ratio; **pAUC**, perioperative area under the curve; **PROGRAM**, PeRiOperative Glucose PRAgMatic; **SSI**, surgical site infection; **VUMC**, Vanderbilt University Medical Center

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Perioperative hyperglycemia is linked to postoperative adverse events, including cardiac and noncardiac complications, urinary tract infections, surgical site infections (SSIs), and mortality.[1–4] Since intraoperative hyperglycemia has minimal immediate consequences on a patient's intraoperative status, its treatment may be overlooked or delayed due to the cognitive demands of intraoperative management. Therefore, clinical decision support reminders are valuable tools for intraoperative glucose management, as they may help mitigate delays in treatment. Notably, reminders to check intraoperative glucose have been shown to reduce SSIs.[1]

Care standardization based on evidence-based best practices improves outcomes in perioperative care.[5–7] In this work, we leveraged standardization to disseminate knowledge of appropriate treatment goals and interventions in intraoperative hyperglycemia by implementing an automated insulin dosing reminder in our institution's electronic health record (EHR). The automated insulin dosing reminder provides recommendations about blood glucose targets and insulin dosing based on clinical practice parameters (practice standards, practice guidelines, consensus statements, and practice advisories) with a focus on intraoperative glucose control and management.[8–12] To determine the effect of the integration of an automated insulin dosing reminder into the EHR, we conducted the PeRiOperative Glucose PRAgMatic (PROGRAM) trial.[13] We hypothesized that the use of the automated insulin dosing reminder would result in lower rates of hyperglycemia (primary outcome) as compared with a glucose check reminder during the first postoperative blood glucose measurement. Additionally, we evaluated secondary outcomes, including the frequency of intraoperative glucose monitoring, intraoperative insulin administration, the first postoperative blood glucose measurement, the occurrence of SSI, and the magnitude of intraoperative hyperglycemia. Finally, we assessed safety outcomes, including the occurrence of intraoperative hypoglycemia and hypokalemia, as well as hypoglycemia and hypokalemia at the first postoperative measurement.

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Materials and Methods

Study Design

We conducted a prospective, single-blinded, pragmatic and repeated crossover trial in which the use of an automated insulin dosing reminder (intervention) was compared with a glucose check reminder (routine care) in patients at high risk for perioperative hyperglycemia undergoing surgery at Vanderbilt University Hospital, Vanderbilt University Medical Center (VUMC), Nashville, Tennessee, between October 5, 2022, and October 26, 2023. The trial was approved by the institutional review board at VUMC with a waiver of written informed consent. The study was registered on clinicaltrials.gov (NCT05426096; principal investigators, Drs. Zapf and Kertai; date of registration, June 15, 2022) before initiation, and the study design including a description of relevant variables and statistical plan were published before the conclusion of enrollment.[13] The trial was overseen by an independent data and safety monitoring board. The trial was supported by departmental funding.

All patients who were deemed high-risk for hyperglycemia and underwent elective or emergency cardiac and noncardiac surgery at Vanderbilt University Hospital Main, Medical Center East, and 4 South Gynecological operating rooms were enrolled at the time of anesthesia start time (fig. 1). A patient was considered at high risk for intraoperative hyperglycemia if at least one of the two following conditions was met: (1) a documented diagnosis of diabetes mellitus type 1 or type 2 without a recorded intraoperative measurement of glucose within the last 2 h, or (2) an insulin administration within the last 12 h without a recorded measurement of blood glucose within the last hour. We included only patients without a recorded intraoperative glucose measurement within the past 2 h to identify cases where glucose monitoring may have been overlooked or delayed, rather than those in whom intraoperative glucose management was already actively addressed. Participating anesthesia providers included any in–operating room anesthesia providers caring for an eligible patient. Patients who did not meet the specified inclusion criteria were excluded from the study.[14]

The 12-month planned enrollment period was divided into four 12-week blocks. The sequence of the blocks was routine care–intervention–routine care–intervention. There was a washout period of 2 weeks at the beginning of the second, third, and fourth blocks. Some blocks were 1 to 2 weeks longer than the planned 12 weeks due to institutional policies preventing nonemergent changes to the EHR outside designated change periods. For pragmatic reasons, randomization at the provider level was not possible because our staffing model would result in combinations of attending anesthesiologists and residents, certified registered nurse anesthetists, and student registered nurse anesthetists from conflicting study groups. Randomization

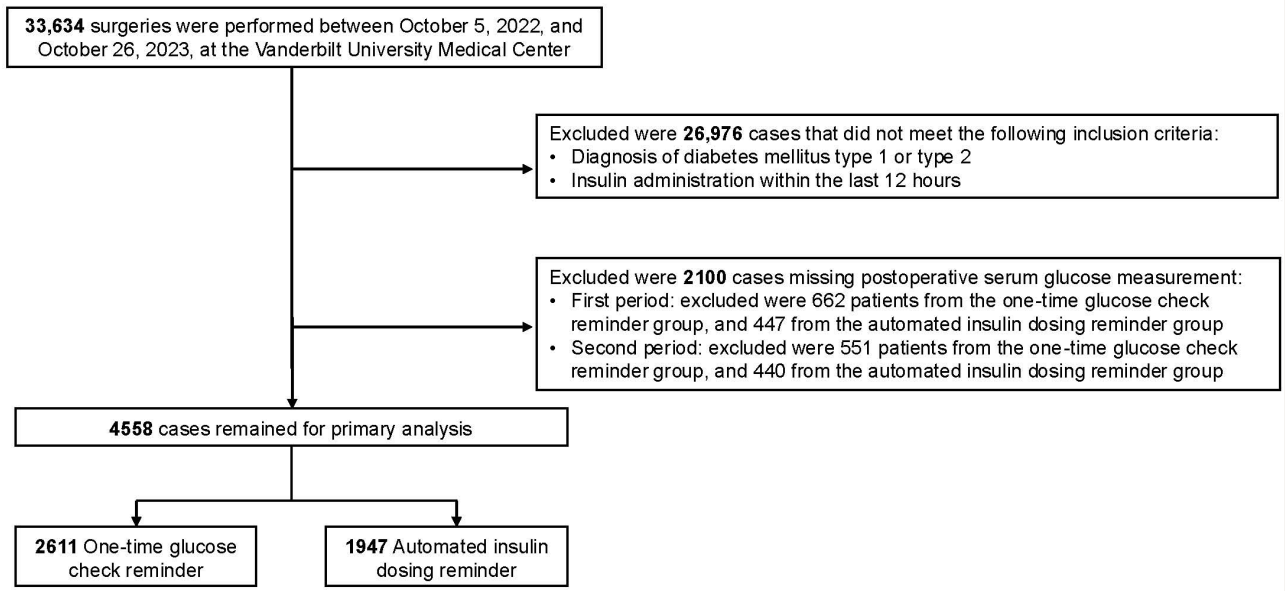

Fig. 1. Description of study population and automated insulin dosing reminder. Total surgical population during the study period, the inclusion criteria, and those cases that were included in the primary analysis.

at the patient level was not feasible out of concerns about randomly and repeatedly withholding a reminder tool on a case-by-case basis. Recognizing that providers rely on reminders to reduce cognitive burden, we minimized disruptions by limiting the removal of the reminder to a single transition between the first intervention period and the second routine care period.

Intervention

During the intervention period, the anesthesia providers periodically received the automated insulin dosing reminder at regular intervals that prompted them to measure blood glucose using either a point-of-care device or a laboratory-based test and that displayed the departmental insulin dosing guidelines (fig. 2A). In contrast, during the routine care control period, the providers received the glucose check reminder at regular intervals, prompting them to obtain a blood glucose measurement using either method, but this reminder did not include the insulin dosing guidelines (fig. 2B). Both reminder systems were designed to activate once the patient is in the operating room and the "anesthesia ready" (*i.e.*, the patient is anesthetized and surgery may begin) status had been filed, provided at least 1 h had elapsed since the "patient in room" time. The system evaluated conditions every minute from that point onward and triggered the reminder based on specific criteria: hourly if recent insulin administration had occurred or every 2 h for diabetic patients. The reminders ceased once the "anesthesia stop" status had been filed. This protocol applied to all anesthesia cases, excluding *ad hoc* records such as neuraxial blocks or labor analgesia. The logic included suppression mechanisms to reduce unnecessary alerts. If the user deferred the reminder because the glucose value had already been checked, the reminder was suppressed for 1 h for that user. If the user indicated the case would end within 30 min, the reminder was suppressed for 45 min. If the user stated they would check immediately, the reminder was suppressed for 30 min.

As part of the standard practice within the VUMC Department of Anesthesiology, the departmental insulin dosing guidelines was made available on the Departmental Center for Evidence-Based Anesthesia website. Additionally, the automated insulin dosing reminder was accessible to all anesthesia providers through a link embedded in the EHR sidebar within the intraoperative anesthesia context.

Data Collection and Outcomes

We used data collected in routine care and electronically extracted from the EHR. Our hospital uses criteria from the Centers for Disease Control and Prevention (Atlanta, Georgia) National Healthcare Safety Network for SSI identification and categorization, and reports of infection are collated by the VUMC SSI Task Force for unified reporting of SSI events across the medical center.[1]

The primary outcome of the study was the occurrence of hyperglycemia (blood glucose greater than 180 mg/dl) at the first postoperative measurement 3 h or less after surgery). Secondary outcomes were (1) the occurrence of

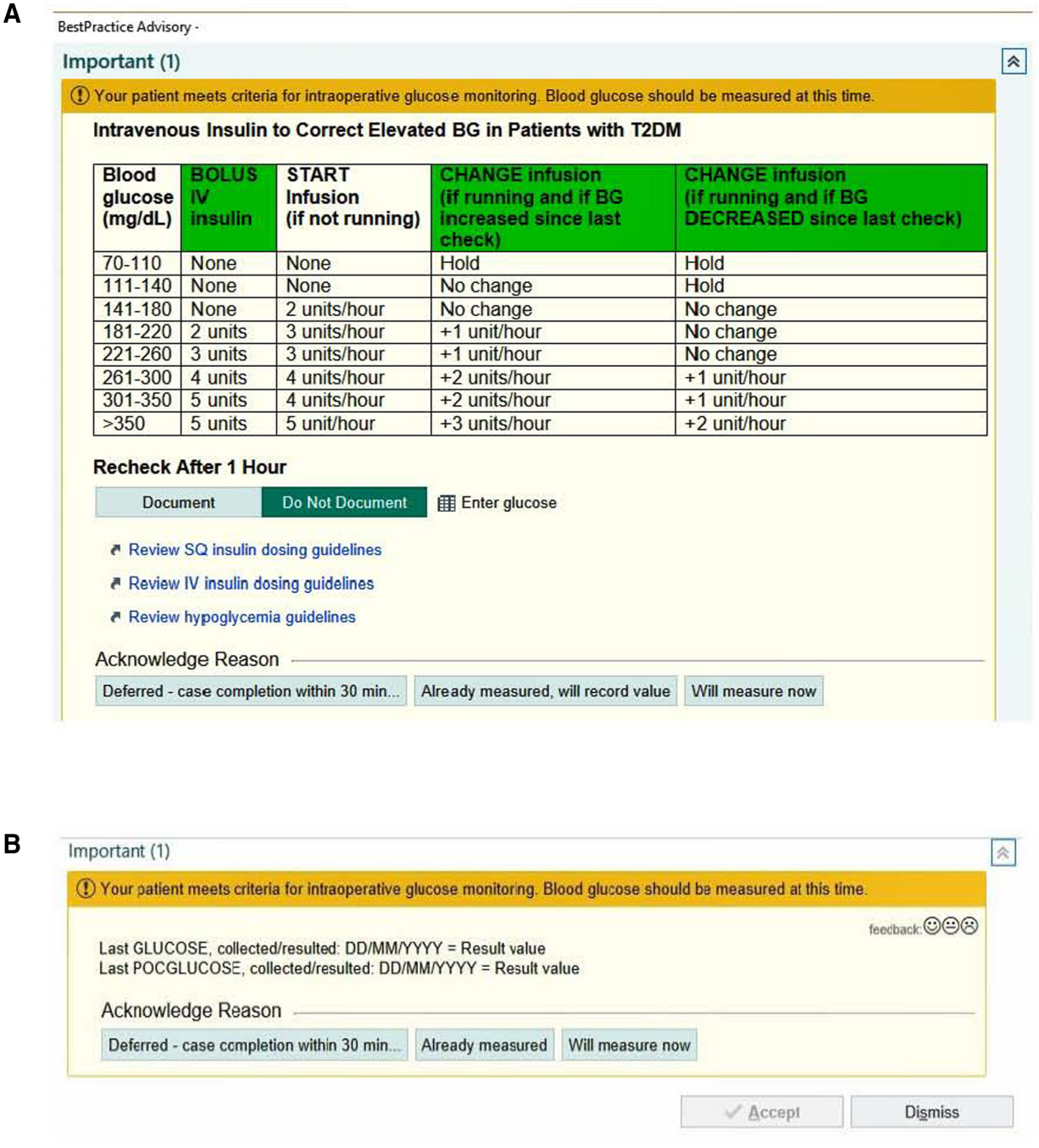

Fig. 2. (*A*) Automated insulin dosing reminder, which was used as the intervention embedded in the electronic health record for patients with high risk of hyperglycemia. The reminder displays blood glucose (BG) values as simple ranges in milligrams per deciliter to help to select the appropriate insulin dosing. (*B*) One-time glucose check reminder used in the one-time glucose check reminder period. IV, intravenous; POCGLUCOSE, point-of-care glucose; SQ, subcutaneous; T2DM, type 2 diabetes mellitus.

intraoperative glucose monitoring, (2) the administration of intraoperative insulin, (3) the first postoperative measurement of blood glucose (milligrams per deciliter at 3 h or less postoperatively), (4) the occurrence of SSI within 30 days of surgery, and (5) the magnitude of intraoperative hyperglycemia. To obtain the magnitude of hyperglycemia, we calculated the partial area under the curve (pAUC) when blood glucose was greater than 180 mg/dl (the area outside of normoglycemia) using blood glucose values and their measurement times. Specifically, we used the measured

preoperative glucose to define intraoperative time zero, intraoperative glucose measurements and the time they were measured, and the first postoperative measurement (3 h or less after surgery) as the final blood glucose at case end (supplemental fig. 1, https://links.lww.com/ALN/E15). Both laboratory-based and point-of-care glucose values were considered valid measurements.

Safety outcomes were the occurrence of intraoperative and first postoperative (3 h or less postoperatively) hypoglycemia (blood glucose less than 60 mg/dl), as well as intraoperative and first postoperative hypokalemia, with mild hypokalemia defined as potassium less than 3.5 mEq/l and severe hypokalemia defined as less than 3.0 mEq/l.

Statistical Analysis

The reporting of statistical results adhered to the proposed guidelines regarding the quality of reporting in cluster randomized crossover trials[15] and the guidelines for reporting outcomes in trial reports: Consolidated Standards of Reporting Trials (CONSORT)–Outcomes 2022 Extension (Supplemental Digital Content 1, https://links.lww.com/ALN/E14).[16]

Our prespecified analytic approach was previously described in detail.[13] To test the primary hypothesis of whether the intervention was associated with a lower rate of postoperative hyperglycemia, we fitted logistic regression with hyperglycemia (yes/no) as an outcome and intervention (routine care/intervention), time period (first/second round of routine care and intervention periods), and interaction of intervention and time period as the main covariates. The model was adjusted for the following demographic, clinical, and surgery characteristics: age, sex, body mass index, race and ethnicity (Hispanic, non-Hispanic Black, Asian, non-Hispanic White, other), American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status classification,[17] diagnosis of type 1 diabetes mellitus, diagnosis of type 2 diabetes mellitus, last preoperative hemoglobin A1C (within 3 months before surgery), the use of insulin at baseline, surgery type, surgery service line, emergent/urgent case designation, and duration of surgery. Secondary and safety outcomes, including missingness of the first postoperative glucose within 3-h measurement, were analyzed similarly using either logistic or proportional odds logistic regression as appropriate. Previously described in detail were the handling of continuous variables and missing data, sensitivity and secondary analyses (*e.g.*, analysis with matching weights, *E* value analysis), and exploratory analyses for effect modification.[13] We expected few patients to have more than one surgery; therefore, to account for multiple observations per subject, we performed sensitivity analyses using generalized estimating equations with exchangeable correlation structure.

In our study, the frequencies of secondary and safety outcomes, SSI, and intraoperative hypoglycemia were relatively low; therefore, their analyses were not adjusted for demographic and clinical characteristics to achieve model stability.[18] Measures of association were reported as odds ratios (ORs) and 95% CIs. All two-sided tests were implemented to ensure a 5% type I error rate. All statistical analyses were performed using R software (R version 4.0.2; https://www.r-project.org, accessed May 19, 2025).

Results

A total of 6,658 cases were enrolled in the trial from 5,459 unique patients, and a first postoperative blood glucose measurement within 3 h was available for 4,558 (68%) cases (3,859 [71%] unique patients), qualifying those cases for primary analysis. There was no evidence that the likelihood of missing first postoperative blood glucose measurement within 3 h was different in the intervention *versus* routine care groups ($P = 0.936$). Clinical predictors that were predictive of missing outcome data included emergency status, ASA Physical Status, home insulin use, surgical service line, preoperative glucose, and surgery duration (supplemental fig. 2, https://links.lww.com/ALN/E15). Of 3,859 patients, 3,357 (87%), 385 (10%), and 117 (3%) patients contributed one, two, and more than two cases, respectively. There were 2,611 cases in the routine care group and 1,947 cases in the intervention group. Of 4,558 cases, two (less than 1%) were missing body mass index, 96 (2.1%) were missing race, 764 (16.8%) were missing preoperative glucose, and 1,991 (43.7%) were missing A1C. The analytic sample included only three patients younger than 18 yr (three 16-yr-old patients) whose surgeries (emergency general surgery, trauma surgery, and orthopedic) were performed in the adult hospital. Demographic and clinical characteristics are summarized in table 1, and the primary, secondary, and safety outcomes are summarized in table 2.

Although our actual sample of 3,859 patients was 41 patients short of our target of 3,990, the analyses accounting for clustering induced by multiple cases per patient showed nearly identical results to those ignoring clustering (and therefore not reported); therefore, our effective sample size was closer to the number of cases than number of patients and likely larger than the target sample size.

Association between Intervention and Primary Outcome

A total of 970 cases (37%) in the routine care group and 675 cases (35%) in the intervention group experienced hyperglycemia at the first postoperative blood glucose measurement (see the unadjusted trends of the first postoperative blood glucose measurement throughout the study period in supplemental fig. 3, https://links.lww.com/ALN/E15).

The results of the primary analyses showed that during the first and second routine care–intervention periods, the odds of having hyperglycemia at the first postoperative blood glucose measurement in the intervention group compared with routine care were 0.83 (95% CI, 0.68 to 1.01) and 0.97 (95%

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristics	Missing %	One-time Glucose Check Reminder N = 2,611	Insulin Dosing Reminder N = 1,947	Absolute Standardized Mean Difference	*P* Value
Age, yr	0	63 [53; 70] (61 ± 14)	63 [53; 71] (61 ± 13)	0.032	0.390*
Sex	0			0.036	0.220†
Male		1,570 (60%)	1,136 (58%)		
BMI	0	30.4 [25.9; 35.7] (31.5 ± 7.7)	30.5 [26.1; 35.4] (31.7 ± 8.3)	0.020	0.980*
Race	2.1			0.079	0.570†
American Indian or Alaska Native		13 (1%)	12 (1%)		
Asian		24 (1%)	23 (1%)		
Black or African American		421 (16%)	283 (15%)		
Latino		48 (2%)	44 (2%)		
Middle Eastern		5 (0%)	6 (0%)		
Pacific Islander		2 (0%)	1 (0%)		
White		2,036 (78%)	1,544 (79%)		
Ethnicity	0			0.007	0.810†
Hispanic		93 (4%)	72 (4%)		
ASA Physical Status classification	0			0.080	0.068†
I or II		196 (8%)	149 (8%)		
III		1,613 (62%)	1,130 (58%)		
IV		773 (30%)	645 (33%)		
V or VI		29 (1%)	23 (1%)		
Type 1 diabetes mellitus	0	98 (4%)	54 (3%)	0.055	0.068†
Type 2 diabetes mellitus	0	1,717 (66%)	1,369 (70%)	0.098	0.001†
Preoperative hemoglobin A1c, %	43.7	6.7 [5.9; 7.9] (7.2 ± 1.9)	6.5 [5.8; 7.6] (7.0 ± 1.8)	0.120	0.002*
Preoperative glucose, mg/dl	16.8	135 [107; 173] (150 ± 64)	132 [107; 169] (145 ± 58)	0.079	0.081*
Home insulin use	0	995 (38%)	711 (37%)	0.033	0.270†
Urgent/emergent case	0	249 (10%)	156 (8%)	0.054	0.074†
Surgical service line	0			0.100	0.690†
Cardiac surgery		389 (15%)	286 (15%)		
Neurosurgery		245 (9%)	163 (8%)		
Oral and maxillofacial		41 (2%)	29 (1%)		
Gynecology		23 (1%)	8 (0%)		
Emergency surgery		252 (10%)	222 (11%)		
Trauma surgery		49 (2%)	36 (2%)		
Plastic surgery		132 (5%)	103 (5%)		
Renal/liver surgery		173 (7%)	126 (6%)		
Pulmonary/thoracic		95 (4%)	78 (4%)		
Urology		173 (7%)	137 (7%)		
Orthopedic		392 (15%)	287 (15%)		
Vascular		188 (7%)	126 (6%)		
Oncology surgery		190 (7%)	155 (8%)		
ENT		205 (8%)	145 (7%)		
Ophthalmology		64 (2%)	46 (2%)		
Length of surgery, min	0	192 [121; 308] (236 ± 153)	193 [124; 321] (243 ± 163)	0.049	0.280*

Continuous variables are summarized as median [interquartile range] and mean ± 1 SD, and the categorical variables are summarized as counts (%).

*Wilcoxon test. †Pearson chi-square test.

ASA, American Society of Anesthesiologists; BMI, body mass index; ENT, ear, nose, and throat.

CI, 0.79 to 1.18), respectively (fig. 3). Because this association was not significant ($P = 0.165$), we do not report the results of the *E* value analysis or worst-case scenario (patients with missing outcome are assigned hyperglycemia in treatment and no hyperglycemia in the routine care group) sensitivity analyses. The complete case analysis included 2,113 subjects, and the association between the intervention and hyperglycemia was not significant ($P = 0.081$) with first period with an OR of 0.74 (95% CI, 0.56 to 0.99) and second period with an OR of 0.87 (95% CI, 0.65 to 1.16). The analysis with matching weights comparing the odds of having hyperglycemia in the intervention *versus* routine care groups also showed no evidence of association with an OR of 0.98 (95% CI, 0.96 to 1.01; $P = 0.116$).

Association between Intervention and Secondary Outcomes

Secondary outcomes are summarized in figure 3. The odds of having a higher *versus* lower pAUC in the

Table 2. Primary, Secondary, and Safety Outcomes of the Study Population

Characteristics	Missing %	One-time Glucose Check Reminder N = 2,611	Insulin Dosing Reminder N = 1,947	Absolute Standardized Mean Difference	*P* Value
Primary outcome					
Hyperglycemia, glucose ≥ 180 mg/dl	0	970 (37%)	675 (35%)	0.052	0.084†
Secondary and safety outcomes					
Intraoperative					
Glucose monitoring	0	1,759 (67%)	1,327 (68%)	0.017	0.570†
Insulin administration	0	814 (31%)	616 (32%)	0.010	0.074†
Hypoglycemia, glucose < 60 mg/dl	32.3	9 (0%)	9 (1%)	0.025	0.550†
Potassium	58.6			0.028	0.720†
Normal potassium ≥ 3.5 mEq/l		766 (29%)	593 (31%)		
Moderate hypokalemia, potassium ≤ 3 and < 3.5 mEq/l		219 (8%)	154 (8%)		
Severe hypokalemia, potassium < 3.0 mEq/l		87 (3%)	66 (3%)		
Postoperative					
AUC		0.5 [0.0, 48.2] (47.2 ± 108.6)	0.0 [0.0, 42. 3] (42.6 ± 94.5)	0.046	0.050*
Blood glucose		161 [129, 200] (169 ± 56)	158 [128, 196] (166 ± 52)	0.061	0.100*
Hypoglycemia, glucose < 60 mg/dl	0	3 (0%)	1 (0%)	0.022	0.470†
Potassium	62.1			0.032	0.610†
Normal potassium ≥ 3.5 mEq/l		901 (35%)	670 (34%)		
Moderate hypokalemia, potassium ≤ 3 and < 3.5 mEq/l		85 (3%)	53 (3%)		
Severe hypokalemia, potassium < 3.0 mEq/l		11 (0%)	9 (1%)		
Surgical site infection	0	16 (1%)	30 (2%)	0.090	0.002†

Continuous variables are summarized as median [interquartile range] and mean ± 1 SD, and the categorical variables are summarized as counts (%).

*Wilcoxon test. †Pearson chi-square test.

AUC, area under the receiver operating characteristics curve.

intervention *versus* routine care group were not significant ($P = 0.282$). There was also no evidence that the intervention was associated with intraoperative glucose monitoring (68% in the intervention group *vs.* 67% in the routine care group; $P = 0.369$) or intraoperative insulin administration (32% in the intervention group *vs.* 31% in the routine care group; $P = 0.995$). Because SSIs were rare (16 cases [1%] in routine care and 30 [2%] in the intervention group), adjusted analysis could not be performed. The unadjusted association of intervention and SSI was significant ($P = 0.006$) with higher odds of having infection in the intervention *versus* routine care group in the first routine care-intervention period (OR, 4.75; 95% CI, 1.74 to 13.02) but not in the second (OR, 1.57; 95% CI, 0.71 to 3.46).

Association between Intervention and Safety Outcomes

Because postoperative hypoglycemia (3 cases in routine care and 1 in intervention group) and severe postoperative hypokalemia (11 cases in routine care and 9 in intervention group) were rare, adjusted analysis could not be performed; the unadjusted analyses showed no evidence of association with intervention. The intervention was not significantly associated with the rest of the safety outcomes (intraoperative hypoglycemia, mild/severe hypokalemia, or postoperative mild hypokalemia).

Exploratory Analyses

There was no evidence of the association of intervention and postoperative hyperglycemia in the exploratory analyses studying effect modification of the intervention by age, sex, body mass index, race or ethnicity (Hispanic, non-Hispanic Black, Asian, non-Hispanic White, other), ASA Physical Status classification,[17] diagnosis of type 1 diabetes or type 2 diabetes, last preoperative hemoglobin A1C (within 3 months before surgery), surgery type, surgery service line, emergent/urgent case designation, and duration of surgery. There was evidence that the association of intervention and hyperglycemia was modified by the use of insulin at baseline (intervention $P = 0.049$ and interaction $P = 0.046$) with no benefit of intervention for patients not receiving insulin at home (overall OR, 1.02; 95% CI, 0.85 to 2.21) and benefit for patients receiving insulin at home (overall OR, 0.76; 95% CI, 0.62 to 0.95).

Discussion

Our single-center pragmatic trial results showed no evidence that an automated insulin dosing reminder incorporated into the intraoperative portion of the EHR improved perioperative glycemic control in a cohort of surgical patients at high risk of hyperglycemia. While we found no association between using our automated insulin dosing

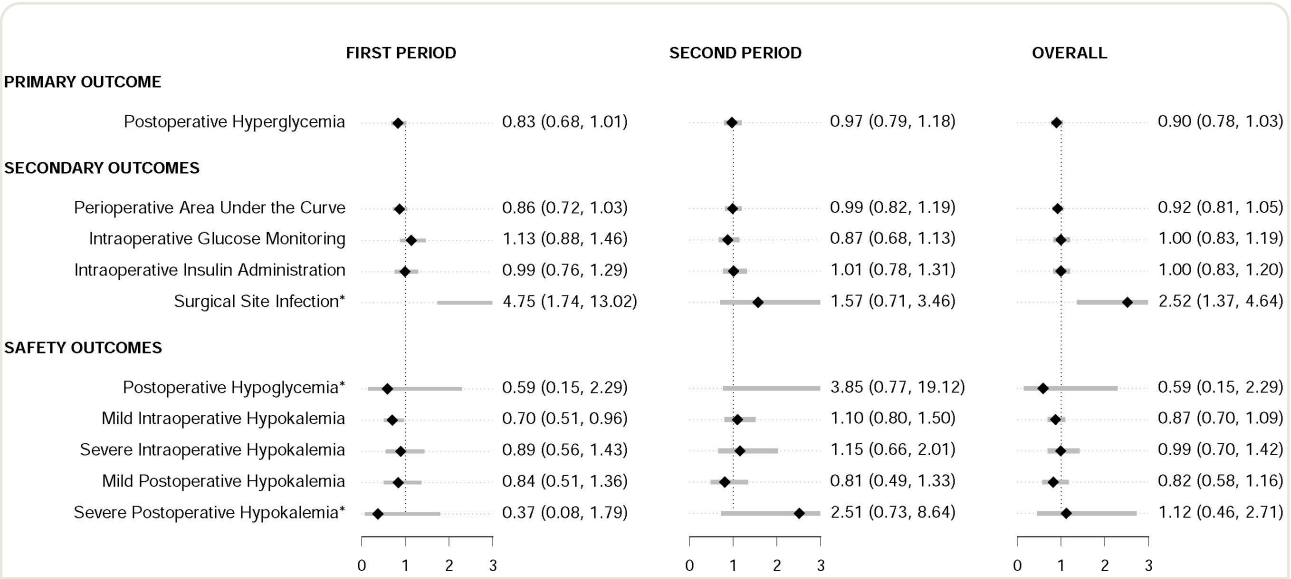

Fig. 3. Forest plots of adjusted odds ratios for primary, secondary, and safety outcomes. This figure depicts adjusted odds ratios of experiencing outcomes in the intervention *versus* one-time glucose check reminder group computed for the two study periods and overall. Both study periods had a one-time glucose reminder (control) period followed by an intervention period (first period, control–intervention; second period, control–intervention). The *left* plot shows the odds ratios for the intervention *versus* control in the first study period. The *middle* plot shows the odds ratios for the intervention *versus* control in the second study period. The *right* plot shows the overall odds ratios for the intervention *versus* control. Outcomes marked with *asterisks* had relatively low frequencies; therefore, their analyses were not adjusted for demographic and clinical characteristics, and the reported odds ratios are unadjusted.

reminder and a lower incidence of hypoglycemia, our study has important implications.

Automated insulin dosing reminder implementation represents a stepwise attempt to improve a clinical decision support tool already incorporated into our EHR. The original tool reminded clinicians to check glucose in high-risk patients and was effective in reducing SSI.[1] Not only was this glucose check reminder effective upon initiation, but, during a temporary removal of the tool during an EHR transition, glucose monitoring significantly decreased.[19] The effect was reversed upon reinitiation of the tool. Although the difference between the automated insulin dosing reminder and the glucose check reminder was not statistically significant, the results in the first period aligned with our expectations. Initially, our study aimed to detect a 4% reduction (from 42% to 38%) in hyperglycemia rates. In the first period, we observed an unadjusted reduction of 3.87% (95% CI, –0.01 to 7.67), which was close to our target. The diminished effect in the second period of 0.91% (95% CI, –3.14 to 4.69) may be attributed to learning from the intervention in the first period. The hyperglycemia rate in the intervention group remained stable across both periods, 34.7% (95% CI, 31.7 to 37.9) in the first period and 34.6% (95% CI, 31.7 to 37.6) in the second, whereas in the routine care group, it decreased from 39% (95% CI, 36 to 41) to 36% (95% CI, 33 to 38). In the first period, among patients receiving insulin at home, the proportion of hyperglycemia in the intervention group decreased from 50.3% (95% CI, 45.9 to 54.7) to 42.4% (95% CI, 37.1 to 47.9), showing an unadjusted absolute reduction of 7.9% (95% CI, 1.1 to 14.6). In the second period, this reduction was less pronounced and not significant (6.2%; 95% CI, 1.3 to 11.1).

While no significant difference was observed with the automated insulin dosing reminder compared to the glucose check reminder, our study highlighted the importance of integrating decision support directly into the workflow. Doing so reduces the cognitive burden on clinicians and reduces the potential for delays or errors. This distinction underscores that while both strategies "work" to some extent, embedding more specific, actionable prompts may better align with the demands of real-world clinical practice, especially in high-stress and complex intraoperative environments. The results of our study suggest that knowledge of appropriate insulin dosing was not the primary barrier to effective intraoperative glucose management. Rather, other factors may influence the timely process of blood glucose measurement and the prevention of hyperglycemia. These include workflow integration, system inefficiencies, and resource availability. Addressing these challenges through enhanced clinical decision support tools and streamlined workflows represents an important direction for future research and clinical innovation.

We developed a methodology to capture the severity and duration of intraoperative hyperglycemia by

examining the pAUC of blood glucose greater than 180 mg/dl. Mechanistically, pAUC may offer an insight into the dynamic interplay among glucose absorption, insulin secretion, and peripheral glucose utilization. Its potential value lies in its ability to reflect the total glycemic burden during a given period, offering a more comprehensive view of glucose metabolism.[20] This approach surpasses the static, one-time measurements of blood glucose values often used to quantify intraoperative hyperglycemia. Incremental glucose area under the receiver operating characteristics curve, also referred to as whole glucose excursion, is used in continuous glucose monitoring devices, and targeted interventions to reduce the area under the receiver operating characteristics curve have resulted in improved clinical outcomes.[21,22] In the perioperative setting, where glycemic control is critical to patient outcomes, a lower pAUC could theoretically indicate better glucose management and less variability, which may be associated with improved recovery and reduced complications. While the pAUC lacks the granularity of continuous monitoring, we believe this metric still represents an improvement compared with one-time measurements of intraoperative blood glucose values and can be used in future studies.

Our study suggests that a clinical decision support tool may facilitate the dissemination of guidelines and practice advisories in perioperative care. The data reveals a clinically significant but statistically nonsignificant reduction in postoperative hyperglycemia rate during the first intervention period (an unadjusted reduction of 3.87%; 95% CI, –0.01 to 7.67). The fact that subsequent removal of the automated insulin dosing reminder during the second period did not result in worsening of the glucose control has important implications. The insulin guidelines that underlie the automated insulin dosing reminder were available in a separate location in the EHR, where clinicians were likely accessing them during the one-time glucose control reminder period. Thereby, a temporary clinical decision support tool incorporated into the relevant phase of care may serve as a helpful mechanism to implement new perioperative guidelines and practice advisories.

We found that providing appropriate insulin dosing knowledge through the automated insulin dosing reminder did not significantly prevent hyperglycemia, suggesting that other factors may play a more critical role in intraoperative glucose monitoring and treatment. This finding may shift the focus of future research to investigating barriers such as knowledge gaps, the availability and accessibility of glucose measurement devices or insulin, and the efficiency of workflow integration. To address these barriers, automating aspects of the glucose monitoring and insulin dosing workflow could enhance performance. For instance, anesthesiology technicians could be automatically assigned to high-risk patients to perform a glucose check within the first hour of surgery. If hyperglycemia is detected, the system could trigger an automated notification to the pharmacy to prepare and deliver insulin directly to the operating room. Such interventions would require a multidisciplinary approach, involving collaboration between anesthesiologists, technicians, pharmacists, and information technology specialists to integrate workflows and optimize systems. These steps represent a promising direction for future studies and clinical workflow improvements aimed at enhancing glucose management and reducing perioperative complications.

Our study has certain limitations. First, as a single-center pragmatic trial, the findings may not be fully applicable or generalizable to other healthcare settings with different patient populations, workflows, or resources. Second, variability in the method of blood glucose measurement (laboratory-based testing *vs.* point-of-care devices) was not controlled, which could introduce variability in the timing and accuracy of glucose values. Third, approximately 2,100 cases were excluded due to missing postoperative glucose measurements, which may introduce selection bias and limit the generalizability of the findings of our study. Fourth, the potential impact of the types of anesthesia providers (*e.g.*, attending anesthesiologists, residents, certified registered nurse anesthetists, student registered nurse anesthetists) on the occurrence of postoperative hyperglycemia was not explored due to the dynamic nature of staffing during cases. Fifth, the timing of the first postoperative glucose measurement, occurring 1 to 3 h after surgery, may not fully capture the dynamic nature of glycemic fluctuations, particularly in insulin-dependent diabetes. This interval could miss hyperglycemia that develops outside this window, potentially affecting the reported rates of hyperglycemia and the interpretation of intraoperative glucose management efficacy. However, this time window was pragmatically selected to align with standard clinical workflows and to reflect real-world practice, ensuring the feasibility of the intervention within routine perioperative care. Sixth, we observed an increase in the unadjusted SSI rates during the first intervention period, which was primarily associated with a specific surgical service line. Independent quality improvement efforts were subsequently implemented to address this issue, leading to a reduction in SSI rates to baseline levels for the remainder of the study. Given that these changes were isolated to a single service line and resolved independently of the study intervention, we do not believe the increased SSI rates are attributable to the intervention itself or significantly impact the validity of our findings related to intraoperative glucose management. Finally, the study did not include patients with undiagnosed hyperglycemia, which may affect the generalizability of findings to broader patient populations, including those with obesity or other risk factors for hyperglycemia who may not have a previous diagnosis of diabetes or not on insulin administration within the last 12 h. Addressing these limitations in future research could help refine the intervention and expand its applicability to diverse healthcare environments and patient populations.

In conclusion, among adult patients at high risk of intraoperative hyperglycemia, an automated insulin dosing reminder compared with a one-time glucose check reminder did not result in a significant reduction in hyperglycemia and postoperative adverse events. Thus, future studies addressing perioperative hyperglycemia and its management should focus on other aspects of care including barriers to glucose monitoring, timely and appropriate clinical workflow integration, and management of hyperglycemia.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: miklos.kertai@vumc.org. Raw data available at: miklos.kertai@vumc.org.

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Supplemental Digital Content

PROGRAM Trial Consolidated Standards of Reporting Trials (CONSORT) Checklist, https://links.lww.com/ALN/E14
Supplemental Figures, https://links.lww.com/ALN/E15
Supplemental Figure 1. Illustration of the pAUC.
Supplemental Figure 2. Clinical predictors that were predictive of missing outcome data.
Supplemental Figure 3. First postoperative glucose trends throughout the study period.

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