Noniatrogenic hypoglycemia: A universal marker for poor outcomes

Hannah Rando, MD, MPH, Matthew Acton, MD, Ifeanyi Chinedozi, MD, Zachary Darby, MD, Jin Kook Kang, MD, and Glenn Whitman, MD

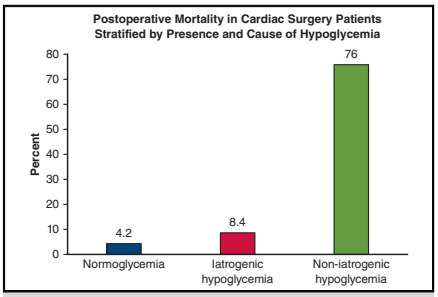
ABSTRACT

Objective: Previous retrospective studies have established a relationship between postoperative hypoglycemia and adverse outcomes after cardiac surgery, but none have accounted for the cause of hypoglycemia.

Methods: A retrospective review was performed of patients who underwent cardiac surgery at a single institution between 2016 and 2021. Patients were categorized as hypoglycemic if they had 1 or more postoperative blood glucose measurement less than 70 mg/dL and normoglycemic otherwise. Hypoglycemia was subcategorized as noniatrogenic (underlying liver failure, adrenal insufficiency, sepsis, or shock) or iatrogenic (insulin infusion continued while nil per os or infusion protocol violated) via manual chart review. Baseline characteristics were compared between groups using Pearson χ^2, analysis of variance, and Kruskal-Wallis testing, and outcomes were compared using multivariable logistic regression.

Results: In total, 5373 patients and 183,346 glucose measurements were included. Hypoglycemia occurred in 5% (267) of patients, of whom 63% (169) were iatrogenic and 37% (98) were noniatrogenic. In a multivariate analysis adjusting for age, sex, case urgency, pre-existing diabetes, and bypass time, both iatrogenic and noniatrogenic hypoglycemia were associated with greater odds of renal failure, prolonged ventilation, and prolonged intensive care unit length of stay relative to normoglycemia, but the magnitude was substantially lower in iatrogenic hypoglycemia. Patients with noniatrogenic hypoglycemia had 68.6 times greater odds of mortality relative to patients who were normoglycemic (odds ratio, 68.6; confidence interval, 39.5-119), but patients with iatrogenic hypoglycemia had no increased odds of mortality (odds ratio, 1.45; confidence interval, 0.77-2.73).

Conclusions: When excluding patients with conditions known to cause hypoglycemia from the analysis, the morbidity and mortality of iatrogenic hypoglycemia from tight postoperative glycemic control is dramatically attenuated. (JTCVS Open 2024;22:323-31)



Postoperative outcomes in cardiac surgery stratified by presence and cause of hypoglycemia.

CENTRAL MESSAGE

When compared with normoglycemia, iatrogenic hypoglycemia is associated with increased perioperative adverse outcomes, but these are dramatically attenuated relative to noniatrogenic hypoglycemia.

PERSPECTIVE

In this study, postoperative hypoglycemia carried an increased odds of morbidity, but the magnitude was substantially lower in iatrogenic hypoglycemia relative to noniatrogenic hypoglycemia. This suggests that the adverse outcomes previously attributed to tight glycemic control may have been partially caused by a failure to exclude comorbid patients with noniatrogenic hypoglycemia from the analysis.

The importance of glycemic control in the perioperative period is well recognized, with a variety of retrospective studies demonstrating adverse outcomes in both patients who are hypoglycemic and hyperglycemic.[1-5] Within cardiac surgery specifically, glycemic control carries additional importance, in part because of the high prevalence of pre-existing diabetes within the patient population[6] and also because of the physiologic stress response

From the Division of Cardiac Surgery, Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Md.

Read at the 103rd Annual Meeting of The American Association for Thoracic Surgery, Los Angeles, California, May 6-9, 2023.

Received for publication Jan 4, 2024; revisions received May 5, 2024; accepted for publication May 9, 2024; available ahead of print June 20, 2024.

Address for reprints: Hannah Rando, MD, MPH, Division of Cardiac Surgery, Department of Surgery, Johns Hopkins University School of Medicine, 600 N Wolfe St, Blalock 1259, Baltimore, MD 21287 (E-mail: hrando1@jh.edu).

2666-2736

https://doi.org/10.1016/j.xjon.2024.05.005

Abbreviations and Acronyms

CI = confidence interval
ECMO = extracorporeal membrane oxygenation
IABP = intra-aortic balloon pump
ICU = intensive care unit
OR = odds ratio
STS = Society of Thoracic Surgeons

that follows cardiopulmonary bypass and results in more challenging glycemic control.[7-10] Both observational studies and clinical trials have established a causal relationship between hyperglycemia and surgical-site infections.[11-13] The well-established risks of hyperglycemia have resulted in inclusion of glycemic control as a quality metric in the Society of Thoracic Surgeons (STS) guidelines and the routine initiation of postoperative insulin infusions to maintain blood glucose levels less than 180 mg/dL.[14] Conversely, other studies have cautioned against hypoglycemia in cardiac surgery by demonstrating increased mortality, renal failure, and prolonged intensive care unit (ICU) stay in patients with hypoglycemic events,[5,15] but the literature on hypoglycemia has been inconsistent and is primarily retrospective.[15,16]

As the clinician is tasked with balancing the relative risks of hypoglycemia and hyperglycemia in the patient after cardiac surgery, a more thorough evaluation of patients with hypoglycemia at risk for adverse outcomes would be of value. Our objective was to elucidate the relationship between postoperative hypoglycemia and outcomes by accounting for the underlying cause of hypoglycemia. We hypothesized that patients who had noniatrogenic and iatrogenic hypoglycemia would have vastly different baseline characteristics and postoperative outcomes, and that patients with purely iatrogenic hypoglycemia would have no increased risk of postoperative morbidity and mortality relative to patients who were normoglycemic.

METHODS

Study Design and Patient Population

We performed a retrospective review of all adult cardiac surgery patients at a single institution between the years of 2016 and 2021. Patients were excluded if they were not admitted to the cardiovascular ICU or had no linked record in the institutional STS database. Blood glucose measurements for the duration of each patients' ICU stay were analyzed, and patients were dichotomized into 2 groups: hypoglycemic if they had 1 or more blood glucose measurement less than 70 mg/dL at any point during their ICU stay and normoglycemic otherwise. Manual chart review of the hypoglycemic cohort was then undertaken to identify erroneous glucose measurements and identify the underlying source of hypoglycemia. Measurements were considered to be erroneous if another blood glucose measurement was taken within 30 minutes of the hypoglycemic measurement, was greater than 70 mg/dL, and differed by at least 15 mg/dL from the initial sample. Hypoglycemia was considered to be noniatrogenic if the patient had evidence of underlying liver failure, adrenal insufficiency, sepsis, or shock. Hypoglycemia was considered to be iatrogenic in instances in which the insulin infusion was continued while the patient was nil per os or had enteric feeds held, where the insulin infusion protocol was violated, or if none of the criteria for noniatrogenic hypoglycemia was met. The study design and methods for data collection were approved by the Johns Hopkins Institutional Review Board (IRB00309193, December 14, 2021), and need for informed consent was waived because of the retrospective nature of the study.

Data Definitions and Outcomes

Patient demographics were collected, including age, sex, and race. Comorbidities were collected and were analyzed as binary variables, including hypertension, dyslipidemia, diabetes, heart failure, liver disease, and peripheral artery disease. In order to establish baseline renal and cardiac function, preoperative creatinine, ejection fraction, and the presence or absence of previous myocardial infarction were all collected. Need for perioperative mechanical circulatory support (extracorporeal membrane oxygenation [ECMO], intra-aortic balloon pump [IABP]) and presence or absence of infective endocarditis were collected as surrogate markers of critical illness. Operative metrics, including case urgency (elective, emergent, emergent salvage, urgent), procedure category (coronary artery bypass grafting, valve, coronary artery bypass grafting/valve, aorta), and cardiopulmonary bypass time were also included.

The primary outcome of interest was in-hospital mortality. All STS major morbidities were collected and analyzed as secondary outcomes, including prolonged ventilation (intubation longer than 24 hours), deep sternal wound infection, permanent stroke, renal failure, and reoperation (for any cardiac reason). Additional outcomes of interest included hospital and ICU (initial and total) length of stay, pneumonia, and sepsis.

Statistical Methods

Demographics, comorbidities, operative details, and outcomes were compared between patients who were normoglycemic, iatrogenic hypoglycemic, and noniatrogenic hypoglycemic using Pearson χ^2, analysis of variance, or Kruskal-Wallis testing, as appropriate. For variables with significant differences on the omnibus test, pairwise comparisons were subsequently performed using the Pearson χ^2test for categorical variables and Student *t* test or Dunn's test for continuous variables. Multivariable logistic regression was then used to separately analyze the relationship between iatrogenic hypoglycemia and major morbidity or mortality and between noniatrogenic hypoglycemia and major morbidity or mortality, with patients who were normoglycemic as the reference group. Covariates were selected a priori based on clinical knowledge and a literature review of potential confounders. Performance was assessed by the c-statistic and goodness of fit was tested using the Hosmer-Lemeshow method. All statistical analysis was performed using STATA/IC 17.0 (StataCorp LLC).

RESULTS

A total of 5373 patients were included (Figure 1), of whom 5106 (95%) were normoglycemic and 267 (5%) were hypoglycemic. Most patients who were hypoglycemic (63%) had an iatrogenic cause. Compared with patients with noniatrogenic hypoglycemia, patients with iatrogenic hypoglycemia were more likely to be undergoing elective surgery (25.9% vs 18.8%, $P = .045$), were less likely to have a previous myocardial infarction (37.4% vs 48.9%, $P = .022$), less likely to require ECMO (8.0% vs 49.3%, $P < .001$), less likely to require IABP placement (22.0% vs 55.6%, $P < .001$), and had shorter cardiopulmonary bypass times (median 126 vs

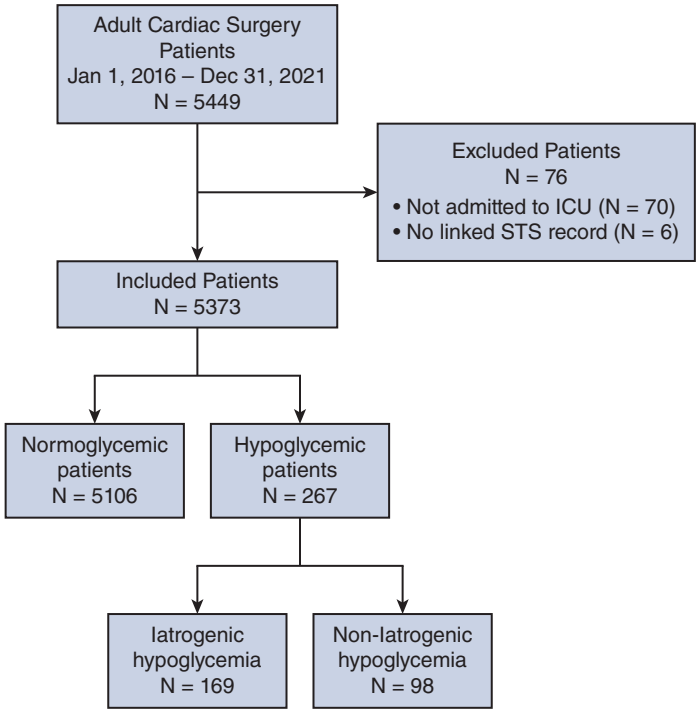


FIGURE 1. Consolidated Standards of Reporting Trails (*CONSORT*) flow diagram of the study population. *ICU*, Intensive care unit; *STS*, Society of Thoracic Surgeons.

141 minutes, $P < .001$) compared with patients with noniatrogenic hypoglycemia.

When compared with patients with normoglycemia, patients with iatrogenic hypoglycemia were less likely to be White (62.7% vs 70.9%, $P = .001$), more likely to be Black (30.1% vs 18.7%, $P = .002$), and were more comorbid, with a greater prevalence of diabetes (43.4% vs 33.4%, $P = .007$) and peripheral artery disease (13.3% vs 8.4%, $P = .027$). Pre-existing renal and myocardial dysfunction were more likely to be present in the iatrogenic hypoglycemia cohort, with a slightly greater preoperative creatinine (1.2 vs 1.0, $P < .001$), lower preoperative ejection fraction (55% vs 58%, $P < .001$), and greater prevalence of baseline heart failure (66% vs 38.4%, $P < .001$) than in patients who were normoglycemic. Case urgency was more likely to be emergent (13.3% vs 5.9%, $P < .001$) or urgent (59.6% vs 45.1%, $P < .001$), and cardiopulmonary bypass time was longer (126 vs 106 minutes, $P < .001$).

When we compared patients with noniatrogenic hypoglycemia with patients with normoglycemia (Table 1), patients with noniatrogenic hypoglycemia had a similar pattern to the iatrogenic cohort. They were less likely to be White (59.6% vs 70.9%, $P = .014$) and more likely to be Black (27.7% vs 18.7%, $P = .028$). They were also more likely to have preexisting diabetes (46.3% vs 33.4%, $P = .008$) or peripheral artery disease (16.8% vs 8.4%, $P = .003$) and had worse underlying renal, hepatic, and cardiac function, as evidenced by a greater median preoperative creatinine (1.1 vs 1.0, $P = .004$), greater prevalence of baseline liver disease (14.6% vs 4.8%, $P < .001$), and lower preoperative ejection fraction (54% vs 58%, $P = .002$). Case urgency was less likely to be elective (18.8% vs 47.8%, $P < .001$), patients were more likely to require ECMO (49.3% vs 5.5%, $P < .001$) or IABP (55.7% vs 14.1%, $P < .001$) support, and bypass time was significantly longer (141 vs 106 minutes, $P < .001$).

In unadjusted bivariate analysis, outcomes were worse for both patients with noniatrogenic and iatrogenic hypoglycemia when compared with patients who were normoglycemic (Table 2). Patients with noniatrogenic hypoglycemia had a greater prevalence of stroke (11.5% vs 5.3%, $P = .009$), pneumonia (18.8% vs 7.3%, $P < .001$), prolonged ventilation (90.6% vs 26.7%), renal failure (55.2% vs 9.4%, $P < .001$), and wound infection (5.3% vs 1.8%, $P = .015$). They also had longer initial (174 vs 45, $P < .001$) and total (201 vs 46, $P < .001$) ICU length of stay and greater 30-day mortality (76% vs 4.2%, $P < .001$). Patients with iatrogenic hypoglycemic exhibited the same patterns, with the exception of stroke (7.9% vs 5.3%, $P = .20$) and wound infection (3.7% vs 1.8%, $P = .090$), which showed no significant difference between the 2 groups. When directly comparing outcomes between patients with iatrogenic and noniatrogenic hypoglycemia, however, the magnitude of major morbidity and mortality was less severe in those with iatrogenic hypoglycemia (Figure 2); although both groups had worse

TABLE 1. Baseline characteristics of patients who underwent cardiac surgery stratified by the presence and cause of ICU hypoglycemia

Variables	Normoglycemic (n = 5106)	Iatrogenic hypoglycemia (n = 169)	Noniatrogenic hypoglycemia (n = 98)	*P* value
Age, y	63 (54-71)	62 (51-71)	66 (55-73)	.093
Female	1608 (31.5)	50 (30.1)	38 (39.6)	.19
Body mass index*	28.0 (24.5-32.1)	26.7 (23.4-31.0)	28.2 (24.2-34.0)	.04†
Race*‡				.01†
White	3605 (70.9)	96 (62.7)	56 (59.6)	
Black	949 (18.7)	46 (30.1)	26 (27.7)	
Asian	254 (5.0)	10 (6.5)	8 (8.5)	
Native American	19 (0.4)	1 (0.6)	0 (0.0)	
Other	260 (5.1)	10 (6.5)	4 (4.3)	
Comorbidities				
Hypertension	3661 (71.9)	118 (71.1)	75 (78.1)	.54
Heart failure*‡	1270 (38.4)	66 (66.0)	44 (69.8)	<.001†
Dyslipidemia*	2620 (65.7)	79 (52.3)	44 (58.7)	<.001†
Diabetes*‡	1701 (33.4)	72 (43.4)	44 (46.3)	.003†
Liver disease*‡	244 (4.8)	17 (11.3)	12 (14.6)	<.001†
Peripheral artery disease*‡	426 (8.4)	22 (13.3)	16 (16.8)	.002†
Preoperative creatinine*‡	1.0 (0.9-1.2)	1.2 (1.0-1.6)	1.1 (0.9-1.8)	<.001†
Ejection fraction*‡	58 (48-63)	55 (37-63)	54 (33-63)	<.001†
Previous myocardial infarction‡§	1614 (32.6)	61 (37.4)	44 (48.9)	.006†
Endocarditis*	223 (4.4)	24 (15.9)	6 (7.3)	<.001†
Status*‡§				<.001†
Elective	2441 (47.8)	43 (25.9)	18 (18.8)	
Emergent	302 (5.9)	22 (13.3)	13 (13.5)	
Emergent salvage	60 (1.2)	2 (1.2)	5 (5.2)	
Urgent	2302 (45.1)	99 (59.6)	60 (62.5)	
Procedure				
CABG	2686 (52.7)	72 (47.7)	48 (58.5)	.27
Valve*	1701 (33.4)	70 (46.4)	31 (37.8)	.003†
CABG/valve*‡	393 (7.7)	23 (15.2)	16 (19.5)	<.001†
Aorta	484 (9.5)	19 (12.6)	10 (12.2)	.33
Bypass time, min*‡§	106 (78-146)	126 (85-171)	141 (93.5-187.5)	<.001†
Mechanical circulatory support				
ECMO‡§	222 (5.5)	11 (8.0)	37 (49.3)	<.001†
IABP*‡§	583 (14.1)	31 (22.0)	45 (55.6)	<.001†
Lowest glucose*‡	100 (87-114)	62 (52-68)	55 (45-62)	<.001†
Number of glucose measurements*‡§	21 (13-39)	69 (41-138)	127 (78-22)	<.001†

Data are presented as mean (standard deviation), median (interquartile range), or n (%). *CABG*, Coronary artery bypass grafting; *ECMO*, extracorporeal membrane oxygenation; *IABP*, intra-aortic balloon pump; *ICU*, intensive care unit. *Comparison of patients who were normoglycemic and iatrogenic hypoglycemic ($P < .05$). †$P < .05$. ‡Comparison of patients who were normoglycemic and noniatrogenic hypoglycemic ($P < .05$). §Comparison of patients who were iatrogenic and noniatrogenic hypoglycemic ($P < .05$).

postoperative outcomes compared with patients who were normoglycemic, patients with iatrogenic hypoglycemia had a lower prevalence of prolonged ventilation (54.3% vs 90.6%, $P = .032$), renal failure (24.4% vs 55.2%, $P = .015$), and sepsis (15.7% vs 41.7%, $P = .007$) compared with patients with noniatrogenic hypoglycemia. Patients with iatrogenic hypoglycemia also had a shorter initial and total ICU length of stay (initial: 118 vs 174 hours, $P < .001$; total: 133 vs 201 hours, $P < .001$) and a shorter total length of stay (19 vs 29 days, $P < .001$).

After we adjusted for age, case urgency, cardiopulmonary bypass time, preoperative diabetes, and preoperative creatinine, most of these relationships persisted (Table 3). Both iatrogenic and noniatrogenic hypoglycemia were associated with greater odds of renal failure, prolonged ventilation, reoperation, and prolonged ICU and total length of stay. Even so, patients with noniatrogenic hypoglycemia had a substantially greater odds of these major morbidities relative to patients with iatrogenic hypoglycemia. For example, whereas patients with noniatrogenic hypoglycemia had 25.9 times

TABLE 2. Postoperative outcomes of patients who underwent cardiac surgery stratified by the presence and cause of ICU hypoglycemia

Outcomes	Normoglycemic (n = 5106)	Iatrogenic hypoglycemia (n = 169)	Noniatrogenic hypoglycemia (n = 98)	*P* value
Mortality, 30-d*†‡	215 (4.2)	14 (8.4)	75 (76.0)	<.001§
Stroke†	270 (5.3)	13 (7.9)	11 (11.5)	.010§
Pneumonia*†	373 (7.3)	27 (15.7)	18 (18.8)	<.001§
Reoperation*†	232 (4.6)	42 (17)	11 (40.7)	<.001§
Prolonged ventilation*†‡	1363 (26.7)	92 (54.3)	89 (90.6)	<.001§
Renal failure*†‡	480 (9.4)	41 (24.4)	54 (55.2)	<.001§
Renal failure requiring dialysis*†‡	357 (7.0)	37 (22.0)	51 (52.1)	<.001§
Wound infection†	92 (1.8)	6 (3.7)	5 (5.3)	.022§
Deep*†	21 (0.4)	3 (1.8)	2 (2.1)	.022§
Superficial	46 (0.9)	2 (1.2)	2 (2.1)	.52
Sepsis*†‡	194 (3.8)	26 (15.7)	41 (41.7)	<.001§
Initial ICU hours*†‡	45 (24-89)	118 (64-180)	174 (95-426)	<.001§
Total ICU hours*†‡	46 (24-93)	133 (77-263)	201 (116-529)	<.001§
ICU readmission*†‡	286 (5.6)	36 (21.7)	15 (15.6)	<.001§
Total LOS*†‡	9 (6-14)	19 (10-34)	29 (11-62)	<.001§

Data are presented as median (interquartile range) or n (%). *ICU*, Intensive care unit; *LOS*, length of stay. *Comparison of patients who were normoglycemic and iatrogenic hypoglycemic ($P < .05$). †Comparison of patients who were normoglycemic and noniatrogenic hypoglycemic ($P < .05$). ‡Comparison of patients who were iatrogenic and non-iatrogenic hypoglycemic ($P < .05$). §$P < .05$.

greater odds of prolonged ventilation (odds ratio [OR], 25.9; confidence interval [CI], 12.6-53.3), patients with iatrogenic hypoglycemia had only 2.8 times greater odds of prolonged ventilation (OR, 2.79; CI, 1.87-4.16) relative to patients with normoglycemia. Furthermore, although patients with noniatrogenic hypoglycemia had 68.6 times greater odds of 30-day mortality than patients who were normoglycemic (OR, 68.6; CI, 39.5-119), the odds of mortality in iatrogenic hypoglycemia were not statistically significantly greater than patients who were normoglycemic in an adjusted analysis (OR, 1.45; CI, 0.77-2.73).

DISCUSSION

Our objective was to elucidate the relationship between postoperative hypoglycemia and adverse outcomes in cardiac surgery after accounting for the underlying source of hypoglycemia. We found that both patients with noniatrogenic and iatrogenic hypoglycemia are profoundly different from patients who were normoglycemic at baseline, with more comorbidities, longer cardiopulmonary bypass times, and greater case urgency. Hypoglycemia was associated with increased postoperative morbidity regardless of etiology, but the morbidity and mortality of patients with purely

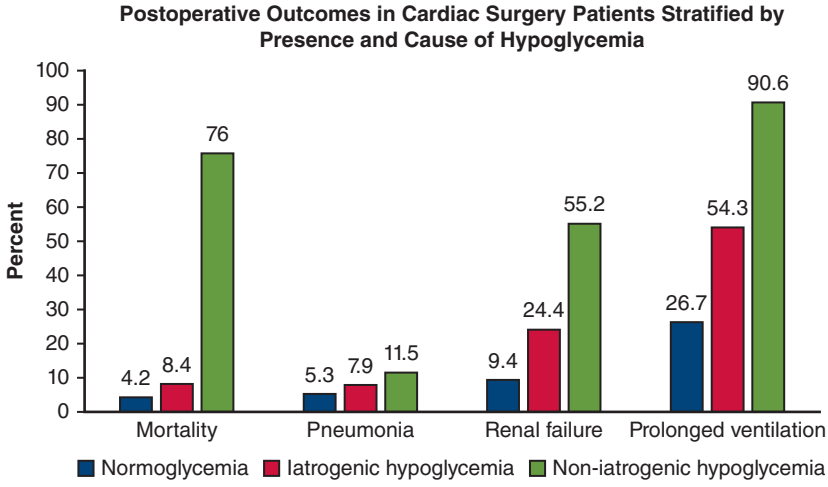


FIGURE 2. Postoperative outcomes in cardiac surgery stratified by the presence and cause of hypoglycemia.

TABLE 3. Regression analysis of postoperative outcomes stratified by presence and cause of ICU hypoglycemia

Outcome	Iatrogenic hypoglycemia	Noniatrogenic hypoglycemia
Mortality	1.5 (0.8-2.7)	68.6 (39.5-119.0)*
Renal failure	3.2 (2.0-5.2)*	13.3 (8.2-21.6)*
Prolonged ventilation	2.8 (1.9-4.2)*	25.9 (12.6-53.3)*
Deep sternal wound infection	3.6 (1.0-12.9)*	3.8 (0.8-18.2)
Reoperation for bleeding	2.0 (1.3-3.2)*	3.0 (1.8-4.9)*
ICU readmission	3.5 (2.3-5.2)*	1.7 (0.9-3.2)
Prolonged ICU LOS	6.0 (4.1-8.9)*	18.0 (8.2-39.7)*
Prolonged total LOS	3.7 (2.6-5.3)*	9.4 (5.2-17.2)*
Stroke	1.4 (0.7-2.8)	1.6 (0.8-3.3)

Data are presented as odds ratio (95% confidence interval). Adjusted for age, case urgency, cardiopulmonary bypass time, preoperative diabetes, and preoperative creatinine. *ICU*, Intensive care unit; *LOS*, length of stay. *$P < .05$.

iatrogenic hypoglycemia was dramatically attenuated compared with patients with noniatrogenic hypoglycemia (Figure 3). These findings emphasize the importance of excluding confounding conditions such as liver disease and sepsis when evaluating the association between hypoglycemia and postoperative outcomes and suggest that the risks of tight postoperative glycemic control in the average cardiac surgery patient may be less substantial than previously thought.

Risk Factors for Postoperative Hypoglycemia

We hypothesized that patients with iatrogenic hypoglycemia would have comparable baseline characteristics and postoperative outcomes compared with patients who were normoglycemic, but this was not the case. Even before their postoperative recovery, patients with iatrogenic hypoglycemia were fundamentally different than patients who were normoglycemic. Patients with iatrogenic hypoglycemia had lower body mass index, a greater prevalence of diabetes and peripheral artery disease, worse baseline renal and myocardial function, and a greater prevalence of IABP placement. Similarly, previous single-institutional analyses of patients who were hypoglycemic versus normoglycemic undergoing cardiac surgery have noted a greater incidence of diabetes, renal failure, older age, and hypertension in patients who were hypoglycemic.[5,16] These findings collectively suggest that patients with comorbidity or patients with greater disease acuity have a greater predisposition to postoperative hypoglycemia on insulin infusions that are otherwise appropriately protocoled, even if they do not progress to overt cardiogenic shock, liver failure, or sepsis.

Further supporting this hypothesis, we noted a substantially greater prevalence of reoperation in the hypoglycemic cohorts, with a shocking 41% of patients with

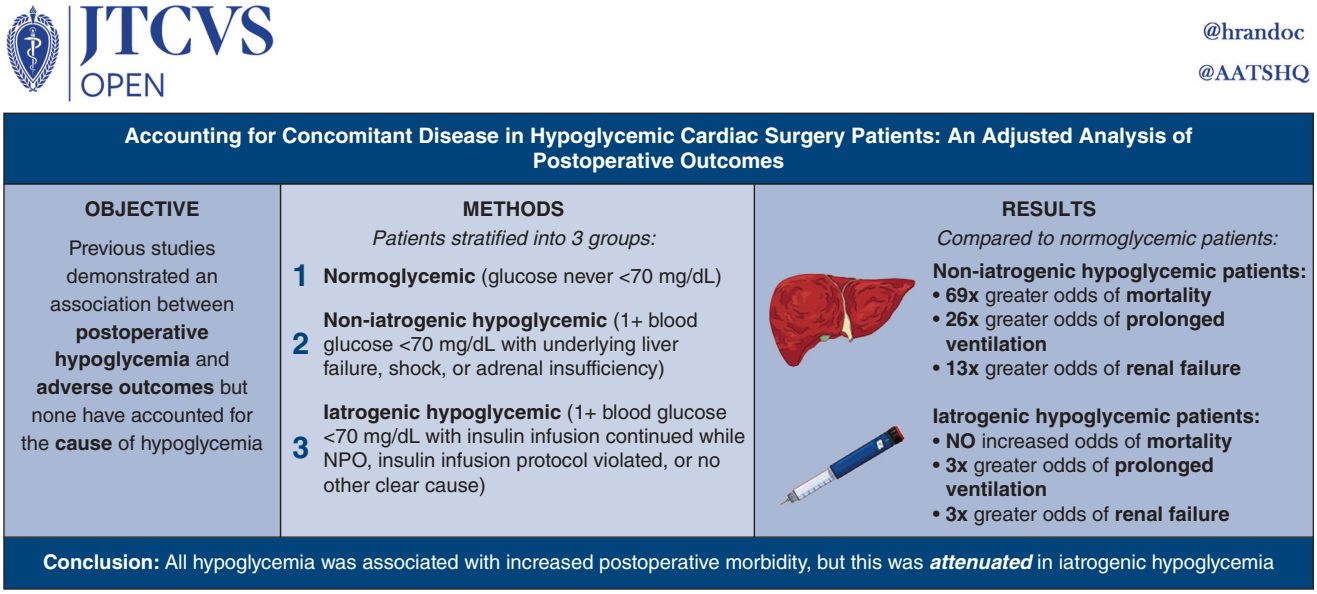


FIGURE 3. Summary of study design and results in an analysis of cardiac surgery patients with and without postoperative hypoglycemia. *NPO*, Nil per os.

noniatrogenic hypoglycemia and 17% of patients with iatrogenic hypoglycemia undergoing reoperation for bleeding during their index hospitalization, compared with less than 5% of patients with normoglycemic. It is possible that the hypoglycemic events noted in these patients are a marker of their underlying critical illness and reflect insulin hyperresponsiveness and glycemic lability from glucose dysregulation. Indeed, multiple studies have described the dysregulation of endogenous glucose production that occurs in times of stress,[17-19] with worse outcomes noted in critically ill patients with high glycemic variability.[20-22]

OUTCOMES OF PATIENTS WITH POSTOPERATIVE HYPOGLYCEMIA

Similar to the existing literature,[5,15,16] we observed substantial differences in postoperative morbidity and mortality for patients who were hypoglycemic as a whole when compared with patients who were normoglycemic. Regardless of the cause, there was a greater incidence of mortality and nearly all major morbidities for patients who were hypoglycemic in an unadjusted analysis. However, after we adjusted for confounders and accounting for the underlying cause of hypoglycemia, there was no increased mortality in patients with iatrogenic hypoglycemia compared with patients who were normoglycemic. This observation is corroborated by a retrospective study performed by Stamou and colleaugues,[16] wherein the authors demonstrated similar postoperative survival in patients who were hypoglycemic after propensity score matching. A nonpropensity score–matched analysis performed by Johnston and colleagues[5] demonstrated greater mortality in patients who were hypoglycemic, but this relationship was minimal in patients with only 1 hypoglycemic episode, as opposed to being substantially greater in patients with more than 1 hypoglycemic episode. Given the pervasiveness of hypoglycemia in sepsis and liver failure compared with the transient process of iatrogenic hypoglycemia from insulin infusion,[23-25] our noniatrogenic hypoglycemia population is likely comparable with the population with more than 1 hypoglycemic episode in the study from Johnston and colleagues.[5] The collective implication of these studies is that although hypoglycemia is associated with increased mortality, this relationship is unlikely to be causal in nature.

We expected that patients with purely iatrogenic hypoglycemia would have comparable risks of major morbidity relative to patients who were normoglycemic, but this was not the case. Even after adjusting for potential confounders, both iatrogenic and noniatrogenic hypoglycemia were associated with greater odds of renal failure, prolonged ventilation, deep sternal wound infection, reoperation, prolonged ICU length of stay, and prolonged total length of stay. These results are consistent with the existing literature, which has reliably demonstrated a relationship between hypoglycemia and postoperative morbidity.[5,15,16] It is worth mentioning, however, that the incidence of major morbidity was substantially lower in patients with iatrogenic hypoglycemia when compared with those with noniatrogenic hypoglycemia, suggesting that the independent risks of tight postoperative glycemic control with insulin infusion may be lower than previously thought.

IMPLICATIONS AND FUTURE DIRECTIONS

These findings have important implications for the glycemic management of cardiac surgery patients in the postoperative period. The ideal blood glucose target continues to be elusive, as clinicians balance the risks of both hypo- and hyperglycemia. At our institution, nearly 14% of blood glucose values are greater than 180 mg/dL, despite targeting a blood glucose range of 100 to 140 mg/dL (Figure 4). Furthermore, despite this target, 68% of patients have at least 1 blood glucose greater than 180 mg/dL, and 46% have at least 1 blood glucose greater than 200 mg/dL. Hyperglycemia is associated with an increased risk of mortality, deep sternal wound infections, renal failure, postoperative stroke, and prolonged hospital stay,[11-13,26-28] and in our trepidation toward hypoglycemia, we may be inadvertently increasing our incidence of hyperglycemic events.

Tight postoperative glycemic control has fallen out of favor since publication of the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, which demonstrated increased mortality for patients with a blood glucose target of 80 to 110 mg/dL compared with a blood glucose target of <180 mg/dL.[29] The generalizability of the NICE-SUGAR study to the cardiac surgery population is questionable, however; patients were only included in the NICE-SUGAR trial if their expected ICU length of stay was 3 or more consecutive days, which does not describe most of the cardiac surgery population. Within cardiac surgery specifically, the most robust evidence for tight glycemic control comes from the Randomized Controlled Trial of Intensive Versus Conservative Glucose Control in Patients

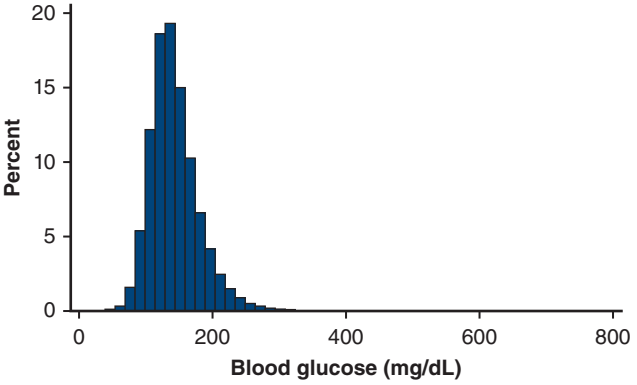


FIGURE 4. Histogram of blood glucose values for patients who underwent cardiac surgery in the intensive care unit. *NPO*, Nil per os.

Undergoing Coronary Artery Bypass Graft Surgery (GLUCO-CABG) trial, which demonstrated fewer postoperative complications in patients without diabetes who were managed with a target glucose of 100 to 140 mg/dL compared with a target glucose of 141 to 180 mg/dL,[27] a benefit that incidentally was not observed in the population with diabetes in this study.

The selective benefit of tight glucose control in the GLUCO-CABG trial coupled with the observations from our study suggest that insulin infusion protocols that target specific blood glucose ranges might improve outcomes if they were more patient-specific. Given the predisposition to hypoglycemia observed in patients with lower body mass index, greater case urgency, and baseline renal dysfunction, perhaps these patients would benefit from a more liberal blood glucose target. Similarly, given the high risk for hypoglycemia in patients with sepsis and/or liver failure, there may be benefit to adjusting their blood glucose targets when facing these complications. Indeed, in the noncardiac surgery population, Waeschle and colleagues[24] have demonstrated greater rates of hypoglycemia and increased mortality in septic patients with tight glycemic control. As we venture further into the era of personalized medicine, predictive studies aimed at identifying patients at greatest risk of postoperative hypoglycemia and prospective studies investigating the ideal blood glucose range based on these patient-specific factors would be of great value.

LIMITATIONS

This study had several limitations. First of all, determination of the cause of hypoglycemia was based on a manual chart review and was therefore susceptible to miscategorization. In some cases, documentation of the clinical scenario surrounding the hypoglycemic episode was unclear. In these instances, the reviewer used their best clinical judgment to determine the most likely underlying cause of hypoglycemia. Second, we did not separately analyze patient outcomes on the basis of presence and quantity of hyperglycemic events, which limits the conclusions we can draw regarding ideal postoperative blood glucose range. Furthermore, this was a purely retrospective study and is inherently susceptible to unmeasured confounders. Finally, this was a single-institutional study and may be limited in its generalizability to other institutions.

Despite these limitations, this study is the first attempt to describe preoperative characteristics and postoperative outcomes of patients who are hypoglycemic on the basis of the underlying source of hypoglycemia. When diseases or conditions that are known to cause hypoglycemia are excluded, the morbidity and mortality from iatrogenic hypoglycemia resulting from therapeutic glycemic control after cardiac surgery appear to be substantially less. Therefore, when attempting to evaluate the risks and benefits of tight glycemic control for reducing postoperative morbidity and mortality, future studies should exclude patients with diseases or conditions that may directly result in hypoglycemia and therefore hypoglycemic episodes that are not a consequence of therapeutic glycemic control. Iatrogenic hypoglycemia was not associated with increased mortality in this analysis, suggesting that the risks of tight glycemic control may not be as substantial as previously thought.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

References

1. Puskas F, Grocott HP, White WD, Mathew JP, Newman MF, Bar-Yosef S. Intraoperative hyperglycemia and cognitive decline after CABG. *Ann Thorac Surg*. 2007;84(5):1467-1473. https://doi.org/10.1016/j.athoracsur.2007.06.023
2. Bochicchio GV, Sung J, Joshi M, et al. Persistent hyperglycemia is predictive of outcome in critically ill trauma patients [published correction appears in *J Trauma*. 2005;59(5):1277-1278]. *J Trauma*. 2005;58(5):921-924. https://doi.org/10.1097/01.ta.0000162141.26392.07
3. Ouattara A, Lecomte P, Le Manach Y, et al. Poor intraoperative blood glucose control is associated with a worsened hospital outcome after cardiac surgery in diabetic patients. *Anesthesiology*. 2005;103(4):687-694. https://doi.org/10.1097/00000542-200510000-00006
4. Badawi O, Waite MD, Fuhrman SA, Zuckerman IH. Association between intensive care unit-acquired dysglycemia and in-hospital mortality. *Crit Care Med*. 2012;40(12):3180-3188. https://doi.org/10.1097/CCM.0b013e3182656ae5
5. Johnston LE, Kirby JL, Downs EA, et al. Postoperative hypoglycemia is associated with worse outcomes after cardiac operations. *Ann Thorac Surg*. 2017;103(2):526-532. https://doi.org/10.1016/j.athoracsur.2016.05.121
6. Navaratnarajah M, Rea R, Evans R, et al. Effect of glycaemic control on complications following cardiac surgery: literature review. *J Cardiothorac Surg*. 2018;13(1):10. https://doi.org/10.1186/s13019-018-0700-2
7. Lehot JJ, Piriz H, Villard J, Cohen R, Guidollet J. Glucose homeostasis. Comparison between hypothermic and normothermic cardiopulmonary bypass. *Chest*. 1992;102(1):106-111. https://doi.org/10.1378/chest.102.1.106
8. Schricker T, Lattermann R, Schreiber M, Geisser W, Georgieff M, Radermacher P. The hyperglycaemic response to surgery: pathophysiology, clinical implications and modification by the anaesthetic technique. *Clin Intensive Care*. 1998;9(3):118-128. https://doi.org/10.3109/tcic.9.3.118.128
9. Clarke RS. The hyperglycaemic response to different types of surgery and anaesthesia. *Br J Anaesth*. 1970;42(1):45-53. https://doi.org/10.1093/bja/42.1.45
10. Kuntschen FR, Galletti PM, Hahn C. Glucose-insulin interactions during cardiopulmonary bypass. Hypothermia versus normothermia. *J Thorac Cardiovasc Surg*. 1986;91(3):451-459.
11. Talbot TR. Diabetes mellitus and cardiothoracic surgical site infections. *Am J Infect Control*. 2005;33(6):353-359. https://doi.org/10.1016/j.ajic.2004.10.008
12. Zukowska A, Zukowski M. Surgical site infection in cardiac surgery. *J Clin Med*. 2022;11(23):6991. https://doi.org/10.3390/jcm11236991
13. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345(19):1359-1367. https://doi.org/10.1056/NEJMoa011300
14. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2011;124(25):e957]. *Circulation*. 2011;124(23):e652-e735. https://doi.org/10.1161/CIR.0b013e31823c074e
15. Lowden E, Schmidt K, Mulla I, et al. Evaluation of outcomes and complications in patients who experience hypoglycemia after cardiac surgery. *Endocr Pract*. 2017;23(1):46-55. https://doi.org/10.4158/EP161427.OR
16. Stamou SC, Nussbaum M, Carew JD, et al. Hypoglycemia with intensive insulin therapy after cardiac surgery: predisposing factors and association with mortality.

J Thorac Cardiovasc Surg. 2011;142(1):166-173. https://doi.org/10.1016/j.jtcvs.2010.09.064
17. Al-Yousif N, Rawal S, Jurczak M, Mahmud H, Shah FA. Endogenous glucose production in critical illness. *Nutr Clin Pract*. 2021;36(2):344-359. https://doi.org/10.1002/ncp.10646
18. Thorell A, Nygren J, Ljungqvist O. Insulin resistance: a marker of surgical stress. *Curr Opin Clin Nutr Metab Care*. 1999;2(1):69-78. https://doi.org/10.1097/00075197-199901000-00012
19. Hanna M, Balintescu A, Glassford N, et al. Glycemic lability index and mortality in critically ill patients—a multicenter cohort study. *Acta Anaesthesiol Scand*. 2021;65(9):1267-1275. https://doi.org/10.1111/aas.13843
20. Hryciw BN, Ghossein J, Rochwerg B, et al. Glycemic variability as a prognostic factor for mortality in patients with critical illness: a systematic review and meta-analysis. *Crit Care Explor*. 2024;6(1):e1025. https://doi.org/10.1097/CCE.0000000000001025
21. Bansal B, Carvalho P, Mehta Y, et al. Prognostic significance of glycemic variability after cardiac surgery. *J Diabetes Complications*. 2016;30(4):613-617. https://doi.org/10.1016/j.jdiacomp.2016.02.010
22. Takahashi H, Iwahashi N, Kirigaya J, et al. Glycemic variability determined with a continuous glucose monitoring system can predict prognosis after acute coronary syndrome. *Cardiovasc Diabetol*. 2018;17(1):116. https://doi.org/10.1186/s12933-018-0761-5
23. Kushimoto S, Abe T, Ogura H, et al. Impact of blood glucose abnormalities on outcomes and disease severity in patients with severe sepsis: an analysis from a multicenter, prospective survey of severe sepsis. *PLoS One*. 2020;15(3):e0229919. https://doi.org/10.1371/journal.pone.0229919
24. Waeschle RM, Moerer O, Hilgers R, Herrmann P, Neumann P, Quintel M. The impact of the severity of sepsis on the risk of hypoglycaemia and glycaemic variability. *Crit Care*. 2008;12(5):R129. https://doi.org/10.1186/cc7097
25. Honda F, Hiramatsu A, Hyogo H, et al. Evaluation of glycemic variability in chronic liver disease patients with type 2 diabetes mellitus using continuous glucose monitoring. *PLoS One*. 2018;13(4):e0195028. https://doi.org/10.1371/journal.pone.0195028
26. Umpierrez G, Cardona S, Pasquel F, et al. Randomized controlled trial of intensive versus conservative glucose control in patients undergoing coronary artery bypass graft surgery: GLUCO-CABG trial. *Diabetes Care*. 2015;38(9):1665-1672. https://doi.org/10.2337/dc15-0303
27. Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2003;125(5):1007-1021. https://doi.org/10.1067/mtc.2003.181
28. Guvener M, Pasaoglu I, Demircin M, Oc M. Perioperative hyperglycemia is a strong correlate of postoperative infection in type II diabetic patients after coronary artery bypass grafting. *Endocr J*. 2002;49(5):531-537. https://doi.org/10.1507/endocrj.49.531
29. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-1297. https://doi.org/10.1056/NEJMoa0810625

Key Words: cardiac surgery, hypoglycemia, postoperative, outcomes