

Intensive Intraoperative Insulin Therapy versus Conventional Glucose Management during Cardiac Surgery

A Randomized Trial

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Background: It is not known whether rigorous intraoperative glycemic control reduces death and morbidity in cardiac surgery patients.

Objective: To compare outcomes of intensive insulin therapy during cardiac surgery with those of conventional intraoperative glucose management.

Design: A randomized, open-label, controlled trial with blinded end point assessment.

Setting: Tertiary care center.

Patients: Adults with and without diabetes who were undergoing on-pump cardiac surgery.

Measurements: The primary outcome was a composite of death, sternal infections, prolonged ventilation, cardiac arrhythmias, stroke, and renal failure within 30 days after surgery. Secondary outcome measures were length of stay in the intensive care unit and hospital.

Intervention: Patients were randomly assigned to receive continuous insulin infusion to maintain intraoperative glucose levels between 4.4 (80 mg/dL) and 5.6 mmol/L (100 mg/dL) ($n = 199$) or conventional treatment ($n = 201$). Patients in the conventional treatment group were not given insulin during surgery unless glucose levels were greater than 11.1 mmol/L (>200 mg/dL). Both groups were treated with insulin infusion to maintain normoglycemia after surgery.

Results: Mean glucose concentrations were statistically significantly lower in the intensive treatment group at the end of surgery (6.3 mmol/L [SD, 1.6] [114 mg/dL [SD, 29]] in the intensive treatment group vs. 8.7 mmol/L [SD, 2.3] [157 mg/dL [SD, 42]] in the conventional treatment group; difference, -2.4 mmol/L [95% CI, -2.8 to -1.9 mmol/L] [-43 mg/dL {CI, -50 to -35 mg/dL}]). Eighty two of 185 patients (44%) in the intensive treatment group and 86 of 186 patients (46%) in the conventional treatment group had an event (risk ratio, 1.0 [CI, 0.8 to 1.2]). More deaths (4 deaths vs. 0 deaths; $P = 0.061$) and strokes (8 strokes vs. 1 stroke; $P = 0.020$) occurred in the intensive treatment group. Length of stay in the intensive care unit (mean, 2 days [SD, 2] vs. 2 days [SD, 3]; difference, 0 days [CI, -1 to 1 days]) and in the hospital (mean, 8 days [SD, 4] vs. 8 days [SD, 5]; difference, 0 days [CI, -1 to 0 days]) was similar for both groups.

Limitations: This single-center study used a composite end point and could not examine whether outcomes differed by diabetes status.

Conclusions: Intensive insulin therapy during cardiac surgery does not reduce perioperative death or morbidity. The increased incidence of death and stroke in the intensive treatment group raises concern about routine implementation of this intervention.

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Hyperglycemia occurs frequently in patients with and without diabetes during cardiac surgery, especially during cardiopulmonary bypass surgery (1, 2). In a study by Van den Berghe and colleagues (3), intensive insulin therapy after surgery reduced morbidity and death in critically ill patients, most of whom underwent cardiac surgery. As a result, professional organizations have recommended rigorous glycemic control in hospitalized patients (4) and strict glycemic control is now routine practice during the postoperative period in cardiac surgical patients.

However, no consensus exists on the optimal management of intraoperative hyperglycemia in cardiac surgical patients because of the lack of evidence from randomized trials. Researchers are increasingly extrapolating evidence from studies that assess the role of strict postoperative glycemic control in critically ill patients to advocate for intravenous insulin therapy for patients in the operating room (3, 5–7). Evidence, strictly from observational studies, suggests that tight intraoperative glycemic control may reduce postoperative complications (8–10). We recently reported, in a retrospective, observational study of 409 cardiac sur-

gical patients, that intraoperative hyperglycemia was an independent risk factor for perioperative complications, including death, after adjustment for postoperative glucose concentrations. Each 1.1-mmol/L (20 mg/dL) increase in glucose concentration greater than 5.6 mmol/L (>100 mg/dL) during surgery was associated with a 34% increase in the likelihood of postoperative complications (8).

An association between intraoperative hyperglycemia

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Context

Intensive insulin therapy used to maintain normoglycemia during intensive care after cardiac surgery improves perioperative outcomes. Its effect during cardiac surgery is unknown.

Contributions

The authors randomly assigned 400 cardiac surgical patients to tight glycemic control (blood glucose level, 4.4 to 5.6 mmol/L [80 to 100 mg/dL]) during surgery or usual intraoperative care. All patients received tight glycemic control in the cardiac intensive care unit. The groups had the same risk for perioperative adverse events (risk ratio, 1.0 [95% CI, 0.8 to 1.2]). The intensive treatment group had more strokes (8 vs. 1) and more deaths (4 vs. 0) than the conventional treatment group.

Caution

The authors performed the study at a single center.

Implications

Maintaining normoglycemia during cardiac surgery does not improve outcomes and might worsen them.

—The Editors

and adverse outcomes based on observational studies does not prove causality. Because hyperglycemia can adversely affect immunity, wound healing, and vascular function, the concept that normoglycemia be maintained during the relatively brief duration of cardiac surgery seems plausible (11–16). On the other hand, the degree of intraoperative hyperglycemia may merely reflect the severity of underlying “stress.” If so, prevention of hyperglycemia might not reduce perioperative complications, and the risks and costs of intensive intraoperative glycemic management may outweigh the benefits. Simple, safe, and effective insulin infusion algorithms that achieve rigorous intraoperative glycemic control are lacking. To address these questions, we conducted a randomized, controlled trial at 1 center to determine whether maintenance of near normoglycemia during cardiac surgery by using intraoperative intravenous insulin infusion reduced perioperative death and morbidity when added to rigorous postoperative glycemic control.

METHODS**Design Overview**

This was a randomized, open-label, controlled trial with blinded assessment. We randomly assigned patients to receive intensive insulin therapy to maintain intraoperative glucose levels between 4.4 (80 mg/dL) and 5.6 mmol/L (100 mg/dL) or conventional treatment. By design, both groups were postoperatively treated with strict glycemic control to ensure that the observed difference in outcome could be attributed to the effects of intraoperative glycemic control.

Setting

We performed the study at St. Marys Hospital, Rochester, Minnesota, which is a tertiary care teaching hospital with 1157 beds and an average of more than 41 000 admissions per year.

Participants

Adults undergoing elective cardiac surgery between July 2004 and April 2005 were eligible for enrollment in our study. We excluded patients who had off-pump cardiopulmonary bypass procedures. The Mayo Foundation Institutional Review Board, Rochester, Minnesota, approved the protocol.

Randomization and Interventions

Before we enrolled patients in our randomized trial, we enrolled 20 patients in a 2-week pilot trial to ensure that the anesthesiologists in the operating room and the nursing staff in the intensive care units (ICUs) had adequate experience with the study insulin infusion algorithm. The 20 patients received intensive insulin therapy during surgery and for 24 hours after surgery. The pilot period data allowed us to modify the graded insulin infusion to achieve desired glucose concentration goals. We built safety features into our infusion protocol to minimize hypoglycemia. We discontinued the infusion when glucose levels were less than 4.4 mmol/L (<80 mg/dL) and initiated dextrose infusion. When glucose levels decreased to less than 3.3 mmol/L (<60 mg/dL), we treated hypoglycemia according to a standardized hypoglycemia protocol. Per protocol, patients treated in the pilot phase were not included in the analyzed cohort.

Study coordinators obtained written informed consent from all patients who met eligibility criteria. We randomly assigned patients to receive intensive or conventional intraoperative insulin therapy. Randomization was computer-generated with permuted blocks of 4, with stratification according to surgeon, surgical procedure (coronary artery bypass grafting [CABG] with or without other procedures and no CABG), and diabetes. The randomization assignments were concealed in opaque, sealed, tamper-proof envelopes that were opened sequentially by study personnel after participants signed the patient consent form. We could not possibly know, before obtaining consent, the few patients who would not have intraoperative hyperglycemia (glucose concentration of 5.6 mmol/L or more [≥ 100 mg/dL]). Therefore, per protocol, patients who gave consent were randomly assigned, and those whose glucose levels were less than 5.6 mmol/L (<100 mg/dL) during surgery were not included in the final analyses.

Intraoperative Period**Intensive Treatment**

Patients in the intensive treatment group received a continuous intravenous insulin infusion, 250 units of NovoLin R (Novo Nordisk, Princeton, New Jersey) in 250 mL of 0.45% sodium chloride, when their blood glucose levels exceeded 5.6 mmol/L (>100 mg/dL). We adjusted

the infusions to maintain blood glucose levels between 4.4 (80 mg/dL) and 5.6 mmol/L (100 mg/dL). We adjusted the dose according to a standardized algorithm used by anesthesiologists (Appendix Table 1, available at www.annals.org).

Conventional Treatment

Patients in the conventional treatment group did not receive insulin during surgery unless their glucose levels exceeded 11.1 mmol/L (≥ 200 mg/dL). If glucose concentration was between 11.1 (200 mg/dL) and 13.9 mmol/L (250 mg/dL), patients received an intravenous bolus of 4 units insulin every hour until the glucose concentration was less than 11.1 mmol/L (< 200 mg/dL). If the intraoperative glucose concentration was greater than 13.9 mmol/L (> 250 mg/dL), patients received an intravenous infusion of insulin that was continued until the glucose level was less than 8.3 mmol/L (< 150 mg/dL).

In both study groups, we measured arterial plasma glucose concentration every 30 minutes, starting just before anesthetic induction by using hexokinase method on a Double P Modular System (Roche Diagnostics, Indianapolis, Indiana). Intraoperative procedures, including cardiopulmonary bypass, monitoring, laboratory testing, and treatment, were left to the discretion of anesthesiologists and cardiac surgeons. There was no standard protocol for monitoring and managing intraoperative potassium levels.

Postoperative Period

Intravenous insulin infusion was started in patients in the conventional treatment group on their arrival in the ICU. Thereafter, both study groups were treated identically, with the intravenous insulin infusion rates adjusted by a nursing staff that was not involved with the study according to a standard protocol. The target blood glucose range was 4.4 (80 mg/dL) to 5.6 mmol/L (100 mg/dL) (Appendix Table 1, available at www.annals.org). Arterial blood glucose levels were measured every 1 to 2 hours by using the Accu-Check Inform blood glucose monitoring system (glucometer) (Roche Diagnostics). During the first 24 hours after surgery, patients were given only clear liquids by mouth; we did not administer subcutaneous insulin or oral diabetic medications during this time. Thereafter, the hospital diabetes consulting service saw all patients and provided individualized recommendations for ongoing care.

Outcomes and Measurements

The primary outcome variable was a composite of death, sternal wound infections, prolonged pulmonary ventilation, cardiac arrhythmias (new-onset atrial fibrillation, heart block requiring permanent pacemaker, or cardiac arrest), stroke, and acute renal failure within 30 days after surgery. Secondary outcome measures were length of stay in the ICU and hospital. Trained study personnel identified the occurrence of a complication through chart abstraction by using confirmable, objective criteria in ac-

cordance with standardized definitions from the Society of Thoracic Surgeons (STS) database committee (17). Personnel who assessed outcomes were not aware of patient treatment assignment or of the study hypothesis.

Follow-up Procedures

We contacted patients by telephone and used a standardized telephone survey at 30 days after surgery to assess outcomes that occurred after discharge. We considered patients to be lost to follow-up if we could not contact them within 10 days of the initial attempt. If patients returned to our institution for care, we reviewed their medical records and confirmed their complications.

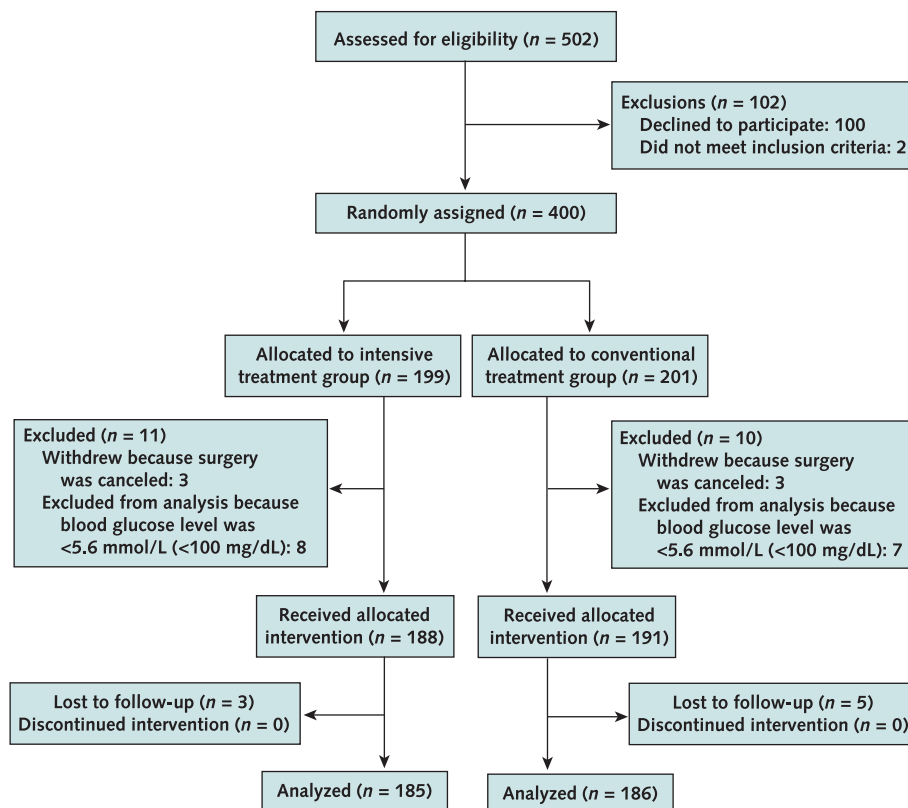
Statistical Analysis

On the basis of our previous study (8), we expected a composite outcome rate of 40% in the conventional treatment group. We needed to enroll 177 patients per treatment group to have 90% power (2-sided α level of 0.05) of finding a 40% decrease in the composite outcome with intensive insulin therapy (decrease from 40% to 24%). Because we expected that approximately 10% of patients would not experience hyperglycemia during surgery, we randomly assigned 200 patients per treatment group to ensure a sufficient number with outcome information. As specified in the protocol, we intended to treat only patients who experienced hyperglycemia (but logistical concerns required that we treat all patients), so these patients are included in the intention-to-treat analyses. We performed a single interim analysis with respect to the primary outcome after one half of prespecified patients had reached the 30-day follow-up. For that analysis, we used an O'Brien-Fleming stopping rule with a P value less than 0.005 (2-sided) as the criterion for stopping early (18). Results from the interim test were not statistically significant, and the data and safety monitoring board recommended continuing the trial. In our final analysis, we used a P value threshold of 0.048 to judge statistical significance. We compared baseline patient characteristics and outcome variables across treatment groups, categorical variables by using chi-square or Fisher exact tests, and continuous variables by using t -tests or Wilcoxon rank-sum tests. We estimated odds ratios according to multivariate logistic regression analyses. We performed the primary analysis on an intention-to-treat basis as described. We did not specify a hierarchy of events for the composite outcome. The occurrence of any composite event indicated that the composite occurred. For the components of the composite, we report all such events so that the total events for the components exceed the number of composite events. We considered 2-sided P values less than 0.05 to be statistically significant. We used SAS, version 6.12 (SAS Institute, Inc., Cary, North Carolina) for analyses.

Role of the Funding Sources

Novo Nordisk, Princeton, New Jersey, and Mayo Foundation and Mayo Clinic College of Medicine, Rochester, Minnesota funded the study. The funding sources

Figure 1. Study flow diagram.



were not involved in the study design and conduct; collection, management, analysis and interpretation of data; and preparation, review, or approval of the manuscript. The authors had full access to study data.

RESULTS

Study Patients and Treatment

Of the 502 patients who were assessed for eligibility, 400 were randomly assigned to intensive treatment ($n = 199$) or conventional treatment ($n = 201$) (Figure 1). We excluded 15 randomly assigned patients (8 in the intensive treatment group and 7 in the conventional treatment group) from the final intention-to-treat analyses (see statistical analysis) because their glucose levels were less than 5.6 mmol/L (<100 mg/dL) during surgery. We withdrew 3 patients in each group after randomization because surgery was canceled. Among the patients who received study interventions, 3 of 188 patients in the intensive treatment group and 5 of 191 patients in the conventional treatment group were lost to follow-up after being discharged from the hospital. Because we do not have follow-up data on these patients, we could not include them in our primary efficacy analyses. Baseline characteristics did not differ significantly between the 8 patients who were lost to follow-up and the remaining study patients, with the excep-

tion of age. Patients lost to follow-up were significantly younger than the remaining patients (mean age, 51 years [SD, 17] vs. 63 years [SD, 15]; $P = 0.023$). Table 1 provides clinical and demographic characteristics of study patients who were included in subsequent analyses (185 patients in the intensive treatment group and 186 patients in the conventional treatment group). These patients had intraoperative glucose levels that exceeded 5.6 mmol/L (>100 mg/dL), their surgery was not canceled, and they provided follow-up information by telephone at 30 days after surgery. Baseline characteristics did not differ statistically significantly between the 2 study groups. Clinical and demographic characteristics of all randomly assigned patients (201 in the conventional treatment group and 199 in the intensive treatment group) were also similar (Appendix Table 2, available at www.annals.org). Approximately 20% of patients in each group had known diabetes. The groups did not differ in mean surgical time (221 minutes [SD, 77] for the intensive treatment group vs. 231 minutes [SD, 82] for the conventional treatment group; difference, -10 minutes [95% CI, -6.24 to 26.24 minutes]). The groups also had similar inotropic use for more than 48 hours perioperatively (34 of 185 patients [18%] vs. 32 of 186 patients [17%]; risk ratio, 1.1 [CI, 0.7 to 1.7]).

Table 1. Baseline Characteristics*

Characteristic	Intensive Treatment Group (n = 185)	Conventional Treatment Group (n = 186)
Mean age at surgery (SD), y	63 (15)	63 (16)
Male, n (%)	134 (72)	123 (66)
White, n (%)	178 (96)	179 (96)
Mean body mass index (SD), kg/m ²	30 (6)	29 (6)
Diabetes, n (%)	37 (20)	36 (19)
Diabetes treatment, n (%)		
Insulin only	8 (22)	10 (28)
Oral diabetic medications only	20 (54)	11 (31)
Insulin and oral diabetic medications	6 (16)	7 (19)
Mean hemoglobin A _{1c} level (SD)†, %	7 (2)	7 (2)
Smoking history, n (%)‡		
Current	13 (7)	20 (11)
Past	90 (49)	84 (46)
Never	81 (44)	80 (43)
Chronic renal failure, n (%)	2 (1)	3 (2)
History of myocardial infarction, n (%)	20 (11)	30 (16)
Stroke or transient ischemic attack, n (%)	20 (11)	13 (7)
Angiotensin-converting enzyme inhibitor use, n (%)	65 (35)	72 (39)
β-Blocker use, n (%)	96 (52)	103 (55)
Antiarrhythmic use, n (%)	17 (9)	18 (10)
Aspirin use, n (%)	89 (48)	112 (60)
ASA classification, n (%)§		
2	3 (2)	2 (1)
3	161 (88)	163 (88)
4	19 (10)	20 (11)
Type of surgery, n (%)		
CABG with or without other procedures	86 (46)	91 (49)
No CABG	99 (54)	95 (51)

* Data are summarized for patients included in the outcome analyses. The 8 patients (3 in the intensive treatment group and 5 in the conventional treatment group) who were randomly assigned but were lost to follow-up are not included. ASA = American Society of Anesthesiologists; CABG = coronary artery bypass grafting.

† Only measured in patients with diabetes.

‡ We were unable to ascertain the smoking status of 3 patients.

§ We were unable to ascertain the ASA class for 3 patients.

Glycemic Control

The groups had similar mean glucose levels at the time of anesthetic induction (6.2 mmol/L [SD, 1.2] [111 mg/dL {SD, 223}] vs. 6.2 mmol/L [SD, 1.7] [111 mg/dL {SD, 31}]) (Table 2). After cardiopulmonary bypass, glucose concentrations were lower in the intensive treatment group (6.8 mmol/L (SD, 1.3) [123 mg/dL {SD, 24}]) than in the conventional treatment group (8.2 mmol/L [SD, 1.9] [148 mg/dL {SD, 35}]). Glucose concentrations were also lower on arrival in the ICU in the intensive treatment group (6.3 mmol/L [SD, 1.6] [114 mg/dL {SD, 29}]) than in the conventional treatment group (8.7 mmol/L [SD, 2.3] [157 mg/dL {SD, 42}]) (Figure 2). All patients in the intensive treatment group and 28 of 186 patients (15%) in the conventional treatment group received insulin infusion during surgery. Per protocol, insulin was infused intravenously in all patients in the ICU, resulting in a mean glucose concentration at the end of the first 24 hours of 5.7 mmol/L (SD, 0.9) (103 mg/dL [SD, 17]) in the intensive treatment group and 5.8 mmol/L (SD, 1.2) (104 mg/dL [SD, 22]) in the conventional treatment group (Table 2 and Figure 2). At 24 hours in the ICU, glucose measurements were available for 126 patients in the intensive treatment group and 129 patients in the conventional treatment group. Most patients with missing data at 24 hours

had their final glucose measurement obtained between 20 and 24 hours after arrival in the ICU. The ICU nursing staff terminated insulin infusion at approximately 24 hours in the ICU depending on when patients arrived in the ICU. To investigate the potential influence of missing data, we compared 20-hour ICU glucose values (available in 178 patients in the intensive treatment group and 175 patients in the conventional treatment group) with 24-hour ICU glucose values. Mean glucose levels were 5.7 mmol/L (SD, 1) (102 mg/dL [SD, 18]) in the intensive treatment group and 5.7 mmol/L (SD, 1.2) (103 mg/dL [SD, 22]) in the conventional treatment group (mean difference, 0 mmol/L [CI, -0.3 to 0.2 mmol/L] [-1 mg/dL {CI, -5 to 3 mg/dL}]; $P = 0.57$).

Mean glucose levels for patients with diabetes (36 patients in the conventional treatment group and 37 patients in the intensive treatment group) were higher at induction of anesthesia in both groups (7.7 mmol/L [SD, 1.7] [139 mg/dL {SD, 31}] vs. 7.8 mmol/L [SD, 3] [141 mg/dL {SD, 53}]). Mean glucose concentrations after cardiopulmonary bypass were lower in the intensive treatment group (7.3 mmol/L [SD, 1.6] [132 mg/dL {SD, 29}]) than in the conventional treatment group (9.4 mmol/L [SD, 2.7] [169 mg/dL {SD, 49}]). Mean glucose concentrations after car-

Table 2. Glycemic Control in Study Patients*

Characteristic	Intensive Treatment Group	Conventional Treatment Group	Mean Difference (95% CI)	P Value†
Intraoperative				
Baseline glucose level				
Patients, n‡	185	186		
Mean level (SD)				
mmol/L	6.2 (1.2)	6.2 (1.7)	0 (−0.3 to 0.3)	0.98
mg/dL	111 (22)	111 (31)	0 (−5 to 6)	
Post-CPB glucose level				
Patients, n‡	184	184		
Mean level (SD)				
mmol/L	6.8 (1.3)	8.2 (1.9)	−1.4 (−1.8 to −1.1)	<0.001
mg/dL	123 (24)	148 (35)	−25 (−32 to −19)	
Mean total amount of insulin, U	19 (16)	2 (5)	17 (15 to 20)	<0.001
ICU				
Baseline glucose level				
Patients, n‡	185	186		
Mean level (SD)				
mmol/L	6.3 (1.6)	8.7 (2.3)	−2.4 (−2.8 to −1.9)	<0.001
mg/dL	114 (29)	157 (42)	−43 (−50 to −35)	
24-h glucose level				
Patients, n‡	126	129		
Mean level (SD)				
mmol/L	5.7 (0.9)	5.8 (1.2)	−0.1 (−0.3 to 0.2)	0.72
mg/dL	103 (17)	104 (22)	−1 (−6 to 4)	
Mean total amount of insulin (SD), U	72 (41)	73 (37)	−1 (−9 to 7)	0.83

* Variables are compared across treatment groups using *t*-test or Wilcoxon rank-sum test. CPB = cardiopulmonary bypass; ICU = intensive care unit.
 † P values are unadjusted.
 ‡ Number of patients with data available. The 8 patients (3 in the intensive treatment group and 5 in the conventional treatment group) who were randomly assigned but were lost to follow-up are not included in the analyses.

diopulmonary bypass were also lower on arrival in the ICU in the intensive treatment group (7.2 mmol/L [SD, 1.6] [130 mg/dL {SD, 29}]) than in the conventional treatment group (10 mmol/L [SD, 2.8] [180 mg/dL {SD, 50}]). At the end of the first 24 hours in the ICU, mean glucose concentrations were similar in both groups (5.9 mmol/L [SD, 1] [106 mg/dL {SD, 18}]) vs. 5.8 mmol/L [SD, 1.4] [105 mg/dL {SD, 25}]) (Appendix Tables 3 and 4, available at www.annals.org).

The frequency of hypoglycemia (defined as blood glucose concentration <3.3 mmol/L [<60 mg/dL]) was low

in both groups. One patient in each group experienced hypoglycemia during surgery, and 8 patients in the intensive treatment group and 14 patients in the conventional treatment group had hypoglycemic episodes during the first 24 hours in the ICU (Table 3). In all instances, hypoglycemia was mild and caused no clinically significant adverse consequences.

Outcomes

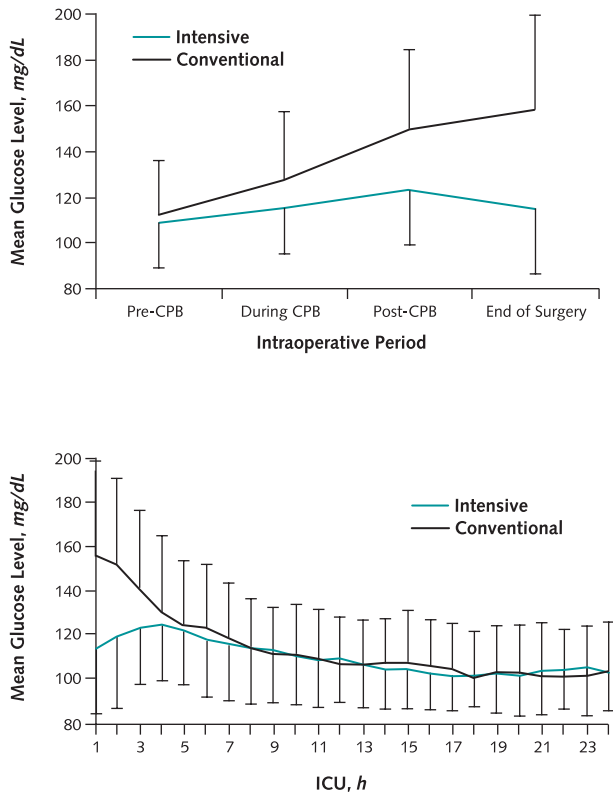
The 2 treatment groups did not statistically significantly differ in the primary composite end point: 82 of 185

Table 3. Comparison of Glycemic Control and Length of Stay*

Outcome	Intensive Treatment Group (n = 185)	Conventional Treatment Group (n = 186)	P Value†
Intraoperative hypoglycemia (glucose level <3.3 mmol/L [<60 mg/dL]), n (%)‡	1 (1)	1 (1)	1.00
Intraoperative hyperglycemia (glucose level >13.9 mmol/L [>250 mg/dL]), n (%)‡	0 (0)	7 (4)	0.015
ICU hypoglycemia (glucose level <3.3 mmol/L [<60 mg/dL]), n (%)‡	8 (4)	14 (8)	0.192
ICU hyperglycemia (glucose level >13.9 mmol/L [>250 mg/dL]), n (%)‡	0 (0)	11 (6)	0.001
Mean length of stay in hospital (SD), d	8 (4)	8 (5)	0.66
Median length of stay in hospital (interquartile range), d	6 (5–8)	6 (5–8)	
Mean length of stay in ICU (SD), d	2 (2)	2 (3)	0.37
Median length of stay in ICU (interquartile range), d	1 (1–2)	1 (1–2)	

* Variables are compared across treatment groups using chi-square or Fisher exact test for dichotomous variables and *t*-test or Wilcoxon rank-sum test for continuous variables. The 8 patients (3 in the intensive treatment group and 5 in the conventional treatment group) who were randomly assigned but were lost to follow-up are not included in the analyses. ICU = intensive care unit.
 † P values are unadjusted.
 ‡ Refers to number of patients who had ≥ 1 episode.

Figure 2. Mean intraoperative glucose concentration (top) and mean postoperative glucose concentration (bottom).



CPB = cardiopulmonary bypass; ICU = intensive care unit. To convert glucose values to mmol/L, multiply by 0.055.

patients (44%) in the intensive treatment group had an event, and 86 of 186 patients (46%) in the conventional treatment group had an event (risk ratio, 1.0 [CI, 0.8 to 1.2]; $P = 0.71$) (Table 4). We obtained similar findings from a multiple logistic regression analysis adjusted for age, sex, diabetes mellitus, type of surgery, body mass index, and smoking status (odds ratio, 0.9 [CI, 0.6 to 1.4]; $P = 0.68$). We also did not detect benefit of intensive insulin therapy for the individual components of the composite end point (Table 4). In fact, deaths (4 of 185 patients [2%] vs. 0 of 186 [0%] patients), strokes (8 of 185 patients [4%] vs. 1 of 186 patients [0.5%]), and heart block requiring pacemaker (5 of 185 patients [3%] vs. 1 of 186 patients [0.5%]) increased in the intensive treatment group (Tables 4, 5, and 6). The predominant outcomes were atrial arrhythmias and prolonged pulmonary ventilation. The groups did not differ in the mean length of stay in the ICU (2 days [SD, 2] vs. 2 days [SD, 3]) or in the mean length of hospital stay (8 days [SD, 4] vs. 8 days [SD, 5]) (Table 3).

When we analyzed patients with diabetes separately as a group, we found that their outcomes did not improve with intensive intraoperative insulin therapy (Appendix

Tables 5 and 6, available at www.annals.org). Using a multivariable model, we did not find diabetes to be significantly associated with the composite outcome (odds ratio, 1.3 [CI, 0.7 to 2.3]; $P = 0.36$). The length of stay in the ICU and hospital also did not differ in the 2 groups when analyzed by diabetes status (Appendix Tables 7 and 8, available at www.annals.org).

DISCUSSION

To our knowledge, this is the first randomized, controlled trial to assess the effect of strict intraoperative glycemic control during cardiac surgery on clinically significant outcomes when added to rigorous postoperative glycemic control. When intensive intravenous intraoperative insulin therapy was administered in a controlled setting by using standardized protocols, it maintained glucose concentrations close to normal during surgery without appreciably increasing the risk for hypoglycemia. In contrast to previous observational studies that showed that intraoperative hyperglycemia strongly predicted adverse postoperative outcomes after adjustment for the effects of postoperative glucose levels, our study showed that lowering glucose concentrations to near normal levels intraoperatively by intravenous insulin infusion did not reduce short-term death, morbidity, or length of stay in the ICU or hospital. On the other hand, increased incidence of death and stroke in the intensive treatment group raises concern about routine implementation of this intervention.

Besides the few observational studies that have concluded that intraoperative hyperglycemia may lead to worse outcomes (8–10), previous interventional studies have been limited by their study design to assess the independent effect of strict glucose control during cardiac surgery (5, 6). Lazar and colleagues (5) prospectively allocated 141 patients with diabetes who were undergoing CABG to receive glucose–insulin–potassium infusion (glucose concentration goal, 6.9 [125 mg/dL] to 11.1 mmol/L [200 mg/dL]) or standard therapy (glucose <13.9 mmol/L [250 mg/dL]). The researchers initiated glucose–insulin–potassium infusion just before anesthetic induction and for 12 hours after surgery. Patients who received glucose–insulin–potassium infusion had a substantially lower incidence of atrial fibrillation than patients who received standard therapy (17% vs. 42%; $P = 0.0017$) and a shorter postoperative length of hospital stay (6.5 vs. 9.2 days; $P = 0.003$). Patients who received glucose–insulin–potassium infusion also had a survival advantage and had decreased episodes of recurrent ischemia and wound infections over the subsequent 2 years (5). We should point out that the study enrolled only patients with known diabetes, and clinically significant hyperglycemia occurred in the control group after 12 hours in the ICU (mean glucose concentration, 14.81 mmol/L [SD, 0.35] [266.8 mg/dL {SD, 6.3}] vs. 7.45 mmol/L [SD, 0.21] [134.3 mg/dL {SD, 3.7}]) in the glucose–insulin–potassium infusion group). Similarly, in

Table 4. Comparison of Primary and Secondary Outcomes*

Outcome	Intensive Treatment Group (n = 185), n (%)	Conventional Treatment Group (n = 186), n (%)	Relative Risk or Odds Ratio (95% CI)†	P Value‡
Any events§	82 (44)	86 (46)	1.0 (0.8 to 1.2)	0.71
In hospital	78 (42)	82 (44)		
Postdischarge (up to 30 days after surgery)	8 (4)	9 (5)		
Death	4 (2)	0 (0)	∞ (0.9 to ∞)	0.061
In hospital	4 (2)	0 (0)		
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)		
Stroke	8 (4)	1 (1)	8.0 (1.0 to 63.7)	0.020
In hospital	7 (4)	1 (1)		
Postdischarge (up to 30 days after surgery)	1 (1)	0 (0)		
Deep sternal infection	6 (3)	7 (4)	0.9 (0.3 to 2.5)	0.79
In hospital	3 (2)	1 (1)		
Postdischarge (up to 30 days after surgery)	3 (2)	6 (3)		
Cardiac arrest	1 (1)	0 (0)	∞ (0.1 to ∞)	0.50
In hospital	1 (1)	0 (0)		
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)		
Heart block requiring pacemaker	5 (3)	1 (1)	5.0 (0.6 to 42.6)	0.121
In hospital	5 (3)	1 (1)		
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)		
New-onset atrial fibrillation	54 (29)	59 (32)	0.9 (0.7 to 1.3)	0.60
In hospital	50 (27)	57 (31)		
Postdischarge (up to 30 days after surgery)	4 (2)	2 (1)		
Acute renal failure	6 (3)	4 (2)	1.5 (0.4 to 5.3)	0.54
In hospital	6 (3)	3 (2)		
Postdischarge (up to 30 days after surgery)	0 (0)	1 (1)		
Prolonged (>24 h) intubation	36 (19)	38 (20)	1.0 (0.6 to 1.4)	0.82
In hospital	36 (19)	38 (20)		
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)		

* Variables are compared across treatment groups by using chi-square or Fisher exact test. The 8 patients (3 in the intensive treatment group and 5 in the conventional treatment group) who were randomly assigned but were lost to follow-up are not included in the analyses.

† Relative risk estimates and corresponding 95% CIs are provided for dichotomous outcomes that occurred in ≥6 patients, with ≥1 event occurring in each treatment group. In cases with <6 events or 0 events in either group, the values presented correspond to the odds ratio with exact 95% CI.

‡ P values are unadjusted.

§ Numbers for “any event” correspond to the number of patients who experienced ≥1 individual event.

an observational study (6), insulin infusion that was initiated in patients in the operating room before sternotomy and continued until the third postoperative day resulted in improved glucose control and a 57% mortality rate decrease compared with historical control groups treated with subcutaneous insulin. Treatment regimens differed in the last 2 studies, and the effects of intraoperative versus postoperative glycemic control cannot be determined.

Strict glucose control is difficult to achieve during cardiac procedures requiring cardiopulmonary bypass because of the stress of surgery, including anesthesia, cardioplegia, and inotropic support (19–21). Optimal glucose control is unlikely when glucose concentrations are measured only episodically (2). In addition, administration of large amounts of insulin during surgery has been associated with an increased risk for postoperative hypoglycemia (19).

Table 5. Details of Study Patients Who Died*

Age, y	Sex	Treatment Group	DM	CABG	Cause of Death	In-Hospital Death
69	Male	Intensive	Yes	Yes	Right ventricular tamponade	Yes
57	Male	Intensive	Yes	No	Sepsis	Yes
59	Male	Intensive	No	No	Stroke	Yes
82	Female	Intensive	No	No	Multiorgan failure	Yes

* CABG = coronary artery bypass grafting; DM = diabetes mellitus.

Table 6. Details of Study Patients Who Had a Stroke*

Age, y	Sex	Treatment Group	DM	CABG	Aspirin Use	In-Hospital Stroke
82	Male	Intensive	Yes	Yes	No	No
67	Male	Intensive	No	Yes	Yes	Yes
81	Female	Conventional	No	No	Yes	Yes
59	Male	Intensive	No	No	No	Yes
69	Male	Intensive	No	No	Yes	Yes
78	Male	Intensive	No	No	No	Yes
80	Female	Intensive	Yes	Yes	Yes	Yes
78	Male	Intensive	No	Yes	No	Yes
75	Male	Intensive	No	No	Yes	Yes

* CABG = coronary artery bypass grafting; DM = diabetes mellitus.

However, in our study, glucose concentrations were maintained close to normal during surgery without increasing the risk for hypoglycemia by using a carefully monitored intravenous insulin infusion protocol. Although glucose concentrations in the intensive treatment group at the end of surgery were approximately 2.4 mmol/L (43 mg/dL) lower than those in the conventional treatment group, postoperative complications did not differ. Of interest, Van den Berghe and colleagues (3) reported that a 2.8-mmol/L (50-mg/dL) decrease in glucose concentration achieved as part of a randomized, controlled trial in an ICU setting resulted in a 34% relative reduction in death (3). Taken together, these data suggest that the benefit of rigorous glycemic control during surgery is minimal, perhaps because the time of exposure to hyperglycemia during surgery (hours) is brief. In the surgical ICU study (3), benefit was observed only after 5 days.

Although glycemic control differed between groups in our study, glucose concentrations were not completely normalized in the intensive treatment group. In addition, 15% of patients in the conventional treatment group were given insulin during surgery. Therefore, the difference in intraoperative glucose concentrations may not have been adequate to detect a true beneficial effect of intensive intraoperative insulin therapy. We doubt that this was the case because in our retrospective study (8), which was also performed at St. Marys Hospital, for every 1.1-mmol/L (20-mg/dL) increase in mean intraoperative glucose, there was a 34% increase in the likelihood of patients experiencing a worse outcome. The mean intraoperative glucose concentration in that study was 7.4 mmol/L (SD, 1.7) (133 mg/dL [SD, 31]), which is almost identical to that observed in the conventional treatment group in our present study (7.1 mmol/L [SD, 1.4] [128 mg/dL {SD, 25}]). Furthermore, death, stroke, and heart block requiring pacemaker occurred more in the intensive treatment group than in the conventional treatment group. Thus, although our present study may have missed a beneficial effect of improved glycemic control that would have become more evident if intraoperative glucose concentrations were completely normalized, the relationship between intraoperative glucose concentrations and postoperative complications

was more likely due to the fact that hyperglycemia was a marker of greater underlying illness, stress, or both that predisposed patients to a subsequent adverse event.

The incidence of hypoglycemia in our trial was low. Although there is no consensus on the definition of hypoglycemia, we conservatively defined hypoglycemia as a glucose level less than 3.3 mmol/L (<60 mg/dL). Van den Berghe and colleagues (3) defined it as a glucose level less than 2.2 mmol/L (<40 mg/dL). Physiologic changes, with increased levels of counterregulatory hormones, occur at a glucose level of approximately 3.6 mmol/L (65 mg/dL), adrenergic symptoms at approximately 3.1 mmol/L (55 mg/dL), and cognitive dysfunction at approximately 2.5 mmol/L (45 mg/dL) (22). In addition, identification of the symptoms of hypoglycemia is challenging during surgery under general anesthesia or in critically ill patients who are often sedated and are receiving mechanical ventilation. Although not systematically studied in our study, substantial additional resources were required to successfully achieve desired glycemic control in the operating room and ICU, including repeated in-service training sessions for staff, more frequent glucose monitoring (every 30 minutes in the operating room), dedicated laboratory personnel, and safety measures in the protocol that required strict adherence by staff with increased workload. Although a more aggressive insulin infusion protocol may have further lowered intraoperative glucose concentrations, it also may have resulted in a greater frequency of hypoglycemia.

Our study had several limitations. It was not feasible to design a protocol that enabled blinding of the intensive insulin treatment. We do not believe that this influenced outcomes because study personnel used objective definitions to assess outcomes, and individuals involved in the care of patients were unaware of study hypotheses. We chose a composite outcome as the primary study end point because it was not feasible to power the study to detect differences in individual components, such as death, because the rare occurrence would mandate a very large sample size. In addition, we believe that the components of the composite outcomes are clinically meaningful; of more importance, researchers have previously reported that they are related to the degree of glycemic control. As we anti-

pated, the most frequent, although not necessarily the most important, composite outcomes (atrial arrhythmias and prolonged pulmonary ventilation) dominated event rates. The incidence of the more important and serious adverse events, such as death, stroke, and heart block requiring pacemaker, were infrequent but were unexpectedly more common in the intensive treatment group. However, the absolute number of these adverse events was small. Thus, it is difficult to speculate on the clinical implications of this unexpected observation, which needs to be assessed in larger studies. One must keep in mind the challenge of reporting and interpreting results of a composite outcome (23, 24). Because there were few diabetic patients in the study, we could not examine whether outcomes differed by diabetes status. Difference in mean intraoperative glucose concentrations might have been greater if the study had included more patients with diabetes or only patients with diabetes, which could have led to different results. However, we did not see a trend in outcomes suggesting benefit of intensive intraoperative insulin therapy in subgroup analyses of patients with diabetes. Also, the reported number of patients with known diabetes may be an underestimate because patients with type 2 diabetes frequently do not know that they have the disease. We ascertained outcomes of interest that occurred between hospital discharge and 30 days after surgery with follow-up telephone calls. Postdischarge outcomes occurred in only 5% of patients in the conventional treatment group and 4% of patients in the intensive treatment group. We could confirm these data objectively by review of medical records only if patients returned to our institution for care. Thus, we could not ascertain 30-day patient reported outcomes as reliably as events that occurred during the hospital stay. Also, because our study was conducted at a single tertiary care center, we do not know whether potential risks or benefits would differ in other institutions.

In conclusion, our study demonstrates that glucose concentrations can be maintained close to normal during cardiac surgery when insulin is infused intravenously as part of an intensive insulin treatment protocol. Compared with initiation of insulin when glucose concentration remains persistently greater than 11.1 mmol/L (>200 mg/dL), intensive intraoperative insulin therapy did not reduce death or morbidity when added to strict postoperative glucose control. Substantial additional resources were required. We cannot exclude the possibility of harm to patients, given the increased rate of death and stroke in the intensive treatment group.

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Appendix Table 1. Insulin Infusion Protocol*

Column 1†		Column 2‡		Column 3§	
Serum Glucose Level, mg/dL	Insulin Infusion Rate, U/h	Serum Glucose Level, mg/dL	Insulin Infusion Rate, U/h	Serum Glucose Level, mg/dL	Insulin Infusion Rate, U/h
>400	18	>400	25	>400	30
351–400	16	351–400	22	351–400	27
301–350	14	301–350	20	301–350	24
251–300	12	251–300	18	251–300	21
201–250	10	201–250	15	201–250	18
176–200	8	176–200	12	176–200	15
151–175	6	151–175	9	151–175	12
121–150	4	121–150	7	121–150	9
101–120	2	101–120	4	101–120	6
80–100	1	80–100	2	80–100	3
<80	Off	<80	Off	<80	Off

* When glucose level is <80 mg/dL, stop insulin infusion and initiate 50 mL/h of 10% dextrose infusion. Check glucose every 30 minutes until glucose level is ≥80 mg/dL. Discontinue 10% dextrose infusion. Resume insulin infusion, always in column 1. If glucose level is <60 mg/dL, initiate treatment of hypoglycemia protocol. Restart insulin infusion in column 1 when glucose level ≥80 mg/dL. To convert glucose values to mmol/L, multiply by 0.055.

† Start in this column; restart in this column when insulin infusion has to be discontinued for glucose level <80 mg/dL.

‡ Patient has not reached glucose level range of 80–100 mg/dL within 2 h of using column 1 and glucose level has decreased by <50 mg/dL over preceding 1 h.

§ Patient has not reached glucose level range of 80–100 mg/dL within 2 h of using column 2 and glucose level has decreased by <50 mg/dL over preceding 1 h.

Appendix Table 2. Preoperative and Operative Characteristics of All Randomly Assigned Study Patients*

Characteristic	Intensive Treatment Group (n = 199)	Conventional Treatment Group (n = 201)
Mean age at surgery (SD), y	62 (15)	63 (16)
Male, n (%)	140 (70)	133 (66)
White, n (%)	190 (95)	193 (96)
Mean body mass index (SD), kg/m ²	29 (6)	29 (6)
Diabetes, n (%)	38 (19)	40 (20)
Diabetes treatment, n (%)		
Insulin only	8 (20)	10 (24)
Oral diabetes medications only	21 (53)	13 (32)
Insulin and oral diabetes medications	6 (15)	8 (20)
Mean hemoglobin A _{1c} level, %†	7 (2)	7 (2)
Smoking history, n (%)		
Current	14 (7)	22 (11)
Past	94 (47)	90 (45)
Never	87 (44)	86 (43)
Not known	4 (2)	3 (1)
Chronic renal failure, n (%)	2 (1)	3 (2)
History of myocardial infarction, n (%)	21 (11)	31 (16)
Stroke or transient ischemic attack, n (%)	22 (11)	13 (7)
Angiotensin-converting enzyme inhibitor use, n (%)	68 (35)	74 (37)
β-Blocker use, n (%)	102 (52)	110 (55)
Antiarrhythmic use, n (%)	18 (9)	21 (11)
Aspirin use, n (%)	92 (47)	120 (60)
ASA classification, n (%)‡		
2	3 (2)	2 (1)
3	171 (88)	176 (88)
4	20 (10)	21 (11)
Type of surgery, n (%)		
CABG with or without other procedures	88 (44)	95 (47)
No CABG	111 (56)	106 (53)

* ASA = American Society of Anesthesiologists; CABG = coronary artery bypass grafting.

† Only in patients with diabetes.

‡ We were unable to ascertain ASA class for 7 patients.

Appendix Table 3. Glycemic Control in Patients with Diabetes*

Variable	Intensive Treatment Group	Conventional Treatment Group	Mean Difference (95% CI)	P Value†
Intraoperative				
Baseline glucose level				
Patients, n‡	37	36		
Mean level (SD)				
mmol/L	7.7 (1.7)	7.8 (3)	-0.1 (-1.2 to 1)	0.83
mg/dL	139 (31)	141 (53)	-2 (-22 to 18)	
Post-CPB glucose level				
Patients, n‡	37	35		
Mean level (SD)				
mmol/L	7.3 (1.6)	9.4 (2.7)	-2.1 (-3.1 to -1)	<0.001
mg/dL	132 (29)	169 (49)	-37 (-56 to -18)	
Mean total amount of insulin, U	26 (19)	4 (8)	22 (15 to 29)	<0.001
Intensive care unit				
Baseline glucose level				
Patients, n‡	37	36		
Mean level (SD)				
mmol/L	7.2 (1.6)	10 (2.8)	-2.8 (-3.8 to -1.7)	<0.001
mg/dL	130 (29)	180 (50)	-50 (-69 to -30)	
24-h glucose level				
Patients, n‡	28	28		
Mean level (SD)				
mmol/L	5.9 (1)	5.8 (1.4)	0.1 (-0.6 to 0.7)	0.84
mg/dL	106 (18)	105 (25)	1 (-10 to 13)	
Mean total amount of insulin (SD), U	99 (42)	82 (46)	17 (-4 to 38)	0.104

* Variables are compared across treatment groups using *t*-test or Wilcoxon rank-sum test. CPB = cardiopulmonary bypass.

† P values are unadjusted.

‡ Number of patients with data available.

Appendix Table 4. Glycemic Control in Patients without Diabetes*

Variable	Intensive Treatment Group	Conventional Treatment Group	Mean Difference (95% CI)	P Value†
Intraoperative				
Baseline glucose level				
Patients, n‡	148	150		
Mean level (SD)				
mmol/L	5.8 (0.7)	5.8 (0.9)	0 (-0.2 to 0.2)	0.83
mg/dL	105 (13)	104 (16)	1 (-3 to 4)	
Post-CPB glucose level				
Patients, n‡	147	149		
Mean level (SD)				
mmol/L	6.7 (1.3)	7.9 (1.6)	-1.2 (-1.6 to -0.9)	<0.001
mg/dL	120 (23)	143 (29)	-23 (-29 to -17)	
Mean total amount of insulin, U	18 (16)	1 (3)	17 (14 to 19)	<0.001
Intensive care unit				
Baseline glucose level				
Patients, n‡	148	150		
Mean level (SD)				
mmol/L	6.1 (1.5)	8.4 (2.1)	-2.3 (-2.7 to -1.9)	<0.001
mg/dL	110 (27)	151 (38)	-41 (-49 to -34)	
24-h glucose level				
Patients, n‡	98	101		
Mean level (SD)				
mmol/L	5.7 (0.9)	5.8 (1.2)	-0.1 (-0.4 to 0.2)	0.59
mg/dL	102 (17)	104 (22)	-2 (-7 to 4)	
Mean total amount of insulin (SD), U	65 (38)	70 (34)	-5 (-14 to 3)	0.196

* Variables are compared across treatment groups using *t*-test or Wilcoxon rank-sum test. CPB = cardiopulmonary bypass.

† P values are unadjusted.

‡ Number of patients with data available.

Appendix Table 5. Comparison of Primary and Secondary Outcomes for Patients with Diabetes*

Outcome	Intensive Treatment Group (n = 37), n (%)	Conventional Treatment Group (n = 36), n (%)	P Value†
Any event‡	19 (51)	22 (61)	0.40
In hospital	19 (51)	21 (58)	
Postdischarge (up to 30 days after surgery)	2 (5)	2 (6)	
Death	2 (5)	0 (0)	0.49
In hospital	2 (5)	0 (0)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
Stroke	2 (5)	0 (0)	0.49
In hospital	1 (3)	0 (0)	
Postdischarge (up to 30 days after surgery)	1 (3)	0 (0)	
Deep sternal infection	3 (8)	1 (3)	0.61
In hospital	2 (5)	1 (3)	
Postdischarge (up to 30 days after surgery)	1 (3)	0 (0)	
Cardiac arrest	0 (0)	0 (0)	1.00
In hospital	0 (0)	0 (0)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
Heart block requiring pacemaker	2 (5)	0 (0)	0.49
In hospital	2 (5)	0 (0)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
New-onset atrial fibrillation	13 (35)	16 (44)	0.42
In hospital	13 (35)	15 (42)	
Postdischarge (up to 30 days after surgery)	0 (0)	1 (3)	
Acute renal failure	3 (8)	2 (6)	1.00
In hospital	3 (8)	1 (3)	
Postdischarge (up to 30 days after surgery)	0 (0)	1 (3)	
Prolonged (>24 h) intubation	7 (19)	9 (25)	0.53
In hospital	7 (19)	9 (25)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	

* Variables are compared across treatment groups by using chi-square or Fisher exact test.

† P values are unadjusted.

‡ Numbers for “any event” correspond to the number of patients who experienced ≥1 individual event.

Appendix Table 6. Comparison of Primary and Secondary Outcomes for Patients without Diabetes*

Outcome	Intensive Treatment Group (n = 148), n (%)	Conventional Treatment Group (n = 150), n (%)	P Value†
Any event‡	63 (43)	64 (43)	0.99
In hospital	59 (40)	61 (41)	
Postdischarge (up to 30 days after surgery)	6 (4)	7 (5)	
Death	2 (1)	0 (0)	0.25
In hospital	2 (1)	0 (0)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
Stroke	6 (4)	1 (1)	0.066
In hospital	6 (4)	1 (1)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
Deep sternal infection	3 (2)	6 (4)	0.50
In hospital	1 (1)	0 (0)	
Postdischarge (up to 30 days after surgery)	2 (1)	6 (4)	
Cardiac arrest	1 (1)	0 (0)	0.50
In hospital	1 (1)	0 (0)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
Heart block requiring pacemaker	3 (2)	1 (1)	0.37
In hospital	3 (2)	1 (1)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
New-onset atrial fibrillation	41 (28)	43 (29)	0.85
In hospital	37 (25)	42 (28)	
Postdischarge (up to 30 days after surgery)	4 (3)	1 (1)	
Acute renal failure	3 (2)	2 (1)	0.68
In hospital	3 (2)	2 (1)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
Prolonged (>24 h) intubation	29 (20)	29 (19)	0.95
In hospital	29 (20)	29 (19)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	

* Variables are compared across treatment groups by using chi-square or Fisher exact test.

† P values are unadjusted.

‡ Numbers for “any event” correspond to the number of patients who experienced ≥1 individual event.

Appendix Table 7. Comparison of Glycemic Control and Length of Stay for Patients with Diabetes*

Outcome	Intensive Treatment Group (n = 37)	Conventional Treatment Group (n = 36)	P Value†
Intraoperative hypoglycemia (glucose level <3.3 mmol/L [<60 mg/dL]), n (%)‡	0 (0)	1 (3)	0.49
Intraoperative hyperglycemia (glucose level >13.9 mmol/L [>250 mg/dL]), n (%)‡	0 (0)	5 (14)	0.025
ICU hypoglycemia (glucose <3.3 mmol/L [<60 mg/dL]), n (%)‡	1 (3)	5 (14)	0.214
ICU hyperglycemia (glucose level >13.9 mmol/L [>250 mg/dL]), n (%)‡	0 (0)	6 (17)	0.011
Mean length of stay in hospital (SD), d	8 (6)	8 (3)	0.63
Median length of stay in hospital (interquartile range), d	7 (5–10)	7 (6–9)	
Mean length of stay in ICU (SD), d	2 (2)	2 (2)	0.95
Median length of stay in ICU (interquartile range), d	1 (1–3)	2 (1–3)	

* Variables are compared across treatment groups using chi-square or Fisher exact test for dichotomous variables and *t*-test or Wilcoxon rank-sum test for continuous variables. ICU = intensive care unit.

† P values are unadjusted.

‡ Refers to number of patients who had ≥1 episode.

Appendix Table 8. Comparison of Glycemic Control and Length of Stay for Patients without Diabetes*

Outcome	Intensive Treatment Group (n = 148)	Conventional Treatment Group (n = 150)	P Value†
Intraoperative hypoglycemia (glucose level <3.3 mmol/L [<60 mg/dL]), n (%)‡	1 (1)	0 (0)	0.50
Intraoperative hyperglycemia (glucose level >13.9 mmol/L [>250 mg/dL]), n (%)‡	0 (0)	2 (1)	0.50
ICU hypoglycemia (glucose level <3.3 mmol/L [<60 mg/dL]), n (%)‡	7 (5)	9 (6)	0.63
ICU hyperglycemia (glucose level >13.9 mmol/L [>250 mg/dL]), n (%)‡	0 (0)	5 (3)	0.060
Mean length of stay in hospital (SD), d	7 (4)	8 (6)	0.49
Median length of stay in hospital (interquartile range), d	6 (5–9)	6 (5–8)	
Mean length of stay in ICU (SD), d	2 (2)	2 (3)	0.35
Median length of stay in ICU (interquartile range), d	1 (1–2)	1 (1–2)	

* Variables are compared across treatment groups using chi-square or Fisher exact test for dichotomous variables and *t*-test or Wilcoxon rank-sum test for continuous variables. ICU = intensive care unit.

† *P* values are unadjusted.

‡ Refers to number of patients who had ≥ 1 episode.