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Continuous Perioperative Insulin Infusion Decreases Major Cardiovascular Events in Patients Undergoing Vascular Surgery

A Prospective, Randomized Trial

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Background: **A growing body of evidence suggests that hyperglycemia is an independent predictor of increased cardiovascular risk. Aggressive glycemic control in the intensive care decreases mortality. The benefit of glycemic control in noncardiac surgery is unknown.**

Methods: **In a single-center, prospective, unblinded, active-control study, 236 patients were randomly assigned to continuous insulin infusion (target glucose 100–150 mg/dl) or to a standard intermittent insulin bolus (treat glucose > 150 mg/dl) in patients undergoing peripheral vascular bypass, abdominal aortic aneurysm repair, or below- or above-knee amputation. The treatments began at the start of surgery and continued for 48 h. The primary endpoint was a composite of all-cause death, myocardial infarction, and acute congestive heart failure. The secondary endpoints were blood glucose concentrations, rates of hypoglycemia (< 60 mg/dl) and hyperglycemia (> 150 mg/dl), graft failure or reintervention, wound infection, acute renal insufficiency, and duration of stay.**

Results: **The groups were well balanced for baseline characteristics, except for older age in the intervention group. There was a significant reduction in primary endpoint (3.5%) in the intervention group compared with the control group (12.3%) (relative risk, 0.29; 95% confidence interval, 0.10–0.83; *P* = 0.013). The secondary endpoints were similar. Hypoglycemia occurred in 8.8% of the intervention group compared with 4.1% of the control group (*P* = 0.14). Multivariate analysis demonstrated that continuous insulin infusion was a negative independent predictor (odds ratio, 0.28; 95% confidence interval, 0.09–0.87; *P* = 0.027), whereas previous coronary artery disease was a positive predictor of adverse events.**

Conclusion: **Continuous insulin infusion reduces perioperative myocardial infarction after vascular surgery.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

This article is accompanied by an Editorial View. Please see: Houle TT: Reporting the results of a study that did not go according to plan. ANESTHESIOLOGY 2009; 110:957–8.

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A GROWING body of evidence indicates that hyperglycemia is an independent predictor of increased cardiovascular risk and diabetes mellitus is a significant predictor of perioperative cardiovascular morbidity and mortality. Although the potential benefit of aggressive perioperative control of blood glucose concentrations in patients with or without diabetes has not been adequately evaluated, the results of several recent investigations suggest that mortality may be reduced by intensive glycemic control in cardiac surgical patients.[1–3] A multimodal approach using β blockade and statins has been shown to reduce the incidence of cardiac events in high-risk surgical patients with peripheral vascular disease[4]; however, the benefit of perioperative blood glucose control in this patient population has not previously been evaluated.

Intensive insulin therapy (*i.e.*, maintenance of blood glucose concentrations between 80 and 110 mg/dl with insulin) significantly decreased in-hospital deaths, from 10.9% to 7.2%, in critically ill surgical patients.[5] Continuous intravenous insulin infusion to maintain blood glucose concentrations less than 150 mg/dl has been shown to decrease deep sternal wound infections in cardiac surgical patients.[6,7] Most previous studies have focused on cardiac surgical patients and, in particular, on the postoperative period in the intensive care unit. Quattara *et al.*[3] and Gandhi *et al.*[8] each evaluated strategies of perioperative tight blood glucose control beginning in the operating room and continuing through the postoperative period with the former favoring this strategy. Gandhi *et al.* suggested that addition of intraoperative tight glycemic control to postoperative tight glycemic control might lead to possible deleterious effects in cardiac surgical patients. The role of blood glucose control to modulate outcome in vascular patients and in the nonintensive care setting is unknown.

In the current study, we tested the hypothesis that a strategy of tight perioperative blood glucose control using a continuous insulin infusion in patients undergo-

ing vascular surgery decreases major cardiovascular events (MACEs) when compared with conventional management.

Materials and Methods

Study Design

This was a single-center, prospective, randomized, nonblinded, active-control study comparing the efficacy and safety of perioperative tight blood glucose control (target glucose 100–150 mg/dl) in patients undergoing peripheral vascular bypass surgery, abdominal aortic aneurysm surgery, or below- or above-knee amputation. The institutional review board of Beth Israel Deaconess Medical Center in Boston, Massachusetts, approved the protocol, and informed consent was obtained from all participants.

All patients, both diabetic and nondiabetic, who (1) were aged 18 yr or older; (2) had an American Society of Anesthesiologists physical status of I–IV; (3) were undergoing peripheral vascular bypass surgery, abdominal aortic surgery, or major lower extremity amputation (above or below the knee); and (4) were expected to stay in the hospital for at least 48 h were included in the study. Patients with (1) brittle diabetes (as previously diagnosed by endocrinologist), (2) varicose vein ligation, (3) continuous insulin infusion pumps, (4) planned stent procedures for vascular disease, or (5) an American Society of Anesthesiologists physical status of V were excluded from the study.

Experimental Procedures

Patients were randomly assigned, using a 1:1 block randomization scheme, to either the experimental protocol using a continuous insulin infusion (CII) protocol (appendix 1) or to the control group using a standard intermittent sliding-scale insulin bolus (IIB) protocol (appendix 2). In the CII regimen, the target blood glucose concentration was 100–150 mg/dl. If blood glucose levels exceeded 150 mg/dl, a continuous insulin infusion was initiated. Adjustments to the insulin infusion were determined by both the current blood glucose concentrations and insulin infusion rates and as specified in appendix 1. Changes in the insulin infusion rate were made by the anesthesiologist in the operating room and by the patient's nurse in the postanesthetic care unit and vascular intensive care unit. This protocol had previously been evaluated and shown to achieve blood glucose concentrations within the target range in more than 70% of patients.[9] Blood glucose levels were measured in the CII group every hour until stable. Blood glucose was analyzed by arterial blood gas samples in the operating rooms and using a finger-stick capillary blood measured on a point-of-care glucometer on the vascular floors. When frequent changes in insulin dosage were no longer necessary and glucose was in the range of 100–150 mg/dl for three consecutive blood glucose measurements, blood glucose was measured every 2 h for three consecutive measurements in the target range, and every 4 h thereafter until 48 h after the start of surgery. Most of the target population resumed oral intake at 48 h, and they were started on their original antidiabetic regimen. If there was a change in the infusion rate, blood glucose measurements were performed hourly and the algorithm followed thereafter. It was possible using this protocol that a known diabetic patient might not receive intravenous insulin for a period exceeding 8 h. Therefore, to avoid the potential for ketoacidosis, all known diabetic patients received half of their standard baseline long-acting insulin regimen on the morning of surgery and at the time of transition. After 48 h of protocol-driven therapy, the patient's blood glucose management was assumed by the primary team and care was delivered as clinically indicated.

In the IIB group, the anesthesiologist (intraoperatively) or the registered nurse (postoperatively) managed perioperative blood glucose concentrations using only intermittent bolus therapy with intravenous regular insulin. Postoperatively, blood glucose concentrations were monitored every 4 h (until 48 h postoperatively), and blood glucose concentrations exceeding 150 mg/dl were treated with standardized intermittent intravenous regular insulin boluses (appendix 2). On the morning of surgery, diabetic patients received half of their baseline long-acting insulin, and their normal insulin regimen was resumed 48 h postoperatively.

Endpoint Definitions

The primary endpoint was defined as a composite rate of the following intraprocedural and postprocedural MACEs at hospital discharge:

1. All-cause death
2. Myocardial infarction (MI)
3. Acute congestive heart failure

All outcome data were defined per standard American College of Cardiology–American Heart Association definitions[10] on the basis of evaluation by an independent treating physician and were collected per vascular quality assurance database standards. Either one of the following criteria satisfied the diagnosis for an acute, evolving, or recent MI: (1) typical increase and gradual decrease (troponin) or (2) more rapid increase and decrease (creatine kinase MB) of biochemical markers of myocardial necrosis with at least one of the following: (a) ischemic symptoms, (b) development of pathologic Q waves on the electrocardiogram, (c) electrocardiographic changes indicative of ischemia (ST-segment elevation or depression), or (d) coronary artery intervention (*e.g.*, coronary angioplasty).[10] Signs of acute pulmonary edema on chest radiograph, in conjunction with the appro-

priate clinical symptoms/signs such as orthopnea and pulmonary rales, confirmed a diagnosis of acute congestive heart failure.

Secondary endpoints included the following efficacy and safety endpoints:

1. Blood glucose levels at 4-h intervals starting from 4 h after the procedure and ending at 48 h
2. Rate of hypoglycemia defined as glucose level less than 60 mg/dl (number of patients experienced at least one event) × 100%/(number of patients in the group)
3. Rate of glucose concentrations greater than 150 mg/dl
4. Graft failure or a need for reintervention (reoperation due to graft failure or lack of peripheral pulses in the postoperative period)
5. Surgical site infection
6. Acute renal insufficiency (a 25% change in creatinine from before surgery to after surgery)
7. Hospital duration of stay (from the date of surgery to discharge from the hospital)

Statistical Analysis

Based on our surgical database, perioperative rates of MACEs vary from 3% in patients undergoing below-knee amputation to 15% in patients undergoing open abdominal aneurysm repair. A conservative estimate of 5% rate of MACEs in patients undergoing vascular surgery was assumed for the current study. Assuming a 10% dropout rate, this study needed 993 patients in each group to show a 50% reduction in MACEs for 80% (1-β) power and a statistical significance of $P < 0.05$ (α) in patients receiving continuous intravenous insulin infusion compared with conventional therapy. An interim analysis was planned at 452 patients. However, because of slow recruitment (2 yr for the current study), increasing numbers of minimally invasive stent procedures being performed at our institution, and the planned hospital-wide implementation of a more aggressive perioperative glucose management strategy, the study was stopped after recruitment of 236 patients.

Continuous variables with normal distribution are presented as mean ± SD and compared by Student *t* test. Continuous variables with nonnormal distribution were assessed by the Kolmogorov–Smirnov test and are presented as median and interquartile range and compared with the Mann–Whitney test. Discrete variables were compared with the chi-square test or Fisher exact test when appropriate. Because of the unplanned issues with subject recruitment, no attempt was made to adjust the α levels for interim analyses.

Logistic regression was used to identify predictors of the primary composite endpoint. The variables age, sex, diabetes, indication for surgery, glucose control protocol, previous coronary artery disease, American Society of Anesthesiologists physical status, and blood glucose concentrations were considered in multivariable analyses as potential predictors. Forward stepwise regression

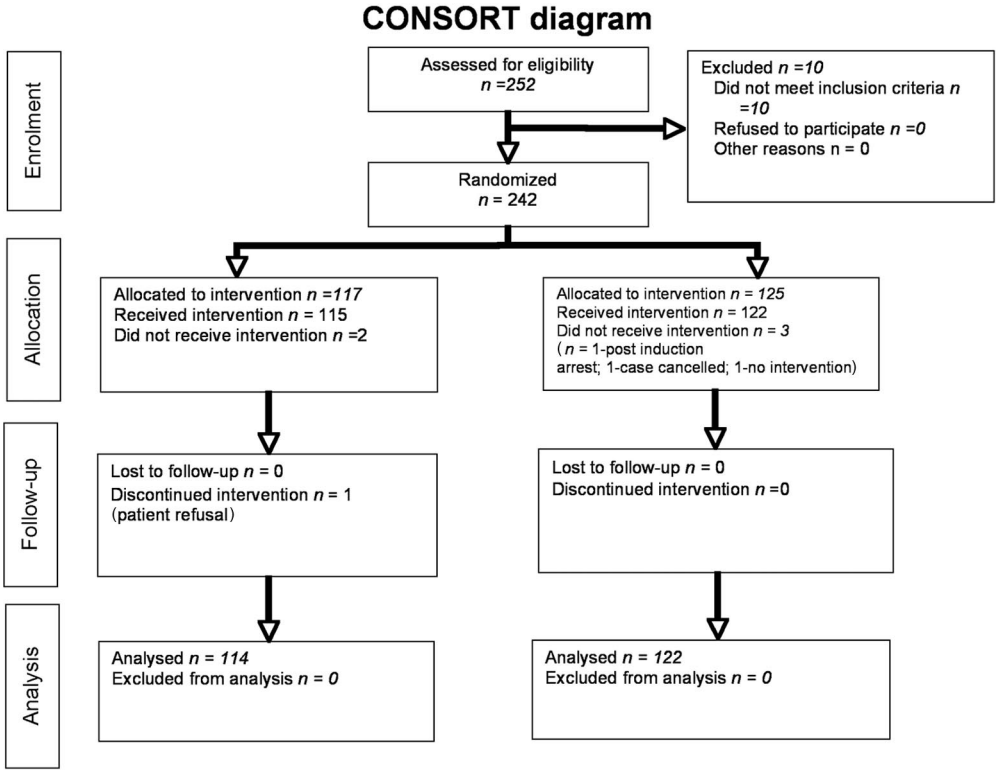

Fig. 1. Consolidated Standards of Reporting Trials study flowchart.

Table 1. Patient Characteristics

	IIB Group, n = 122	CII Group, n = 114	*P* Value
Age, yr	71 ± 11	67 ± 10	0.02
Male sex, n (%)	66 (54)	67 (59)	0.47
Height, cm	169 ± 11	169 ± 10	0.98
Weight, kg	81 ± 24	84 ± 23	0.34
BMI, kg/m^2	28 ± 8	30 ± 8.0	0.13
Preexisting conditions, n (%)			
Diabetes	64 (53)	62 (54)	0.80
Hypertension	95 (78)	92 (81)	0.59
CAD	71 (58)	58 (51)	0.26
CHF	11 (9)	13 (11)	0.54
CABG	36 (30)	24 (21)	0.14
CRF	15 (12)	15 (13)	0.84
Stroke	11 (9)	9 (8)	0.76
COPD	31 (25)	23 (20)	0.34
Statin, n (%)	70 (57)	76 (67)	0.14
Aspirin, n (%)	102 (84)	97 (85)	0.75
ACE inhibitor, n (%)	69 (57)	64 (56)	1.00
β Blocker, n (%)	98 (80)	83 (73)	0.17
Chronic hypoglycemic therapy,* n (%)			
Insulin	34 (53)	40 (65)	0.20
Metformin	12 (19)	9 (15)	0.63
Glyburide	19 (30)	23 (37)	0.45

* In patients with diabetes.

ACE = angiotensin-converting enzyme; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; CII = continuous insulin infusion; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; IIB = intermittent insulin bolus.

with stay criterion of 0.10 was used to determine potential significant predictors. All reported *P* values are two-sided, and $P < 0.05$ was considered significant.

Results

Two hundred thirty-six patients were randomly assigned to the CII group (114 subjects) or to the IIB (control) group (122 subjects) (fig. 1). The clinical characteristics of the patient populations are shown in table 1. The treatment groups were well balanced for baseline characteristics, except that mean age was lower in the CII group. Fifty-seven to 66% of patients came with preoperative statin therapy as mentioned in table 1. Once the patients began oral intake, statin therapy was started in all the patients as a routine. Seventy-two to 80% of patients were already on a preoperative β blocker, and this was comparable between the two groups. Intraoperative and postoperative metoprolol was given to all the patients as a routine. Per oral metoprolol was continued for a month if patients were not on preoperative β blockade. Lower extremity bypass surgery was performed in 173 patients (73.3%), abdominal aorta aneurysm repair was performed in 58 patients (24.6%), and major amputation was performed in 5 patients (2.1%) (table 2). Six patients were excluded from the study because of protocol violations (case cancellations, 2; patient withdrawal, 1; postinduction arrest, 1; and other reasons, 2). There were no deaths in either group during the hospital stay.

Table 2. Surgical Characteristics

	IIB Group, n = 122	CII Group, n = 114	*P* Value
ASA physical status, n (%)			0.16
II	4 (3.3)	10 (8.5)	
III	103 (84.4)	94 (83)	
IV	15 (12.3)	10 (8.5)	
Revised Cardiac Risk Index score, n (%)			0.39
2	34 (28)	36 (31)	
3	50 (41)	37 (33)	
4	38 (31)	41 (36)	
Type of surgery, n (%)			0.44
Abdominal aortic aneurysm	34 (28)	24 (21)	
Lower extremity bypass	86 (71)	87 (76)	
Amputation	2 (1)	3 (3)	
Duration of surgery, min	199 ± 78	199 ± 77	0.95

ASA = American Society of Anesthesiologists; CII = continuous insulin infusion; IIB = intermittent insulin bolus.

Comparison of blood glucose concentrations over the first 48 h between groups is shown in figure 2. Blood glucose concentrations were similar at baseline in both groups. In contrast, blood glucose levels were significantly lower in the CII group between 12 and 24 h after surgical start compared with the IIB group. Patients with diabetes were more likely to develop hyperglycemia than were patients without diabetes in the CII group, although this effect was not observed in the IIB group. In the CII group, 68.3% of patients with diabetes had glucose levels above 150 mg/dl at least once, as compared with 30.6% in patients without diabetes ($P < 0.001$). In contrast, rates of hyperglycemia were similar among diabetic (66.1%) and nondiabetic (49.0%) patients in the IIB group ($P = 0.07$). The incidence of hypoglycemia in patients with or without diabetes was 12.9% *versus* 3.8% ($P = 0.052$) in the CII group and 3.1% *versus* 5.2% ($P = 0.74$) in the CII group, respectively. The incidence of hypoglycemia was similar between the two groups (8.8% in the CII group compared with 4.1% in the IIB group; $P = 0.18$). There were no adverse neurologic sequelae in patients with hypoglycemia

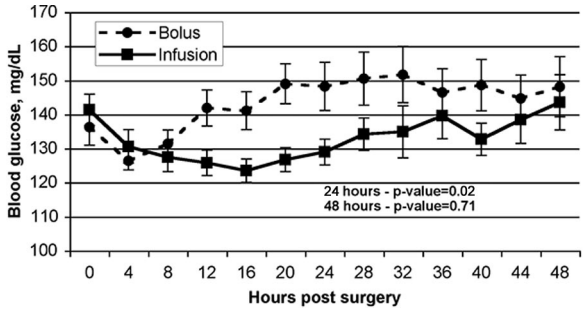

Fig. 2. Blood glucose concentrations at 12, 16, 20, 24, 28, 32, and 40 h from the surgical start in the continuous insulin infusion (CII) group compared with the intermittent insulin bolus (IIB) group. *P* value at 24 h was 0.02 and at 48 h was 0.71.

Table 3. Clinical Outcomes

	IIB Group, n = 122	CII Group, n = 114	Relative Risk for Continuous Infusion (95% CI)	*P* Value
Composite (MI and CHF), n (%)	15 (12.3)	4 (3.5)	0.29 (0.10–0.83)	0.013*
MI, n (%)	7 (5.7)	0 (0)	—	0.015*
CHF decompensation, n (%)	9 (7.4)	4 (3.5)	0.48 (0.15–1.50)	0.19
Wound infection, n (%)	29 (23.8)	35 (30.7)	1.29 (0.85–1.97)	0.23
Graft failure or need for reintervention, n (%)	18 (14.8)	14 (12.3)	0.83 (0.43–1.59)	0.58
Creatinine increase > 25% above baseline, n (%)	22 (18.2)	23 (20.5)	0.89 (0.52–1.50)	0.65
Hypoglycemia (level < 60 mg/dl) recorded at least once, n (%)	5 (4.1)	10 (8.8)	2.14 (0.75–6.07)	0.14
Glucose level > 150 mg/dl, No. of events (IQR)	1.0 (0.0–3.0)	1.0 (0.0–2.0)	—	0.11
Total No. of events	235	167		
Hospital duration of stay, median (IQR), days	7.0 (5.0–9.0)	6.0 (4.0–8.0)	—	0.06

* $P < 0.05$ is significant.

CHF = congestive heart failure; CI = confidence interval; CII = continuous insulin infusion; IIB = intermittent insulin bolus; IQR = interquartile range; MI = myocardial infarction.

in either group. No patient in either group sustained severe hypoglycemia (< 40 mg/dl).

Table 3 depicts clinical outcomes in the two treatment groups. There was a significantly lower risk of MACEs in patients treated with continuous intravenous insulin (3.5%) compared with those receiving bolus insulin (12.3%) ($P = 0.013$; relative risk of MACEs, 0.29; 95% confidence interval, 0.10–0.83). Diabetes alone did not increase overall cardiovascular event rate in this high-risk population of vascular surgery patients (7.9% diabetics *vs.* 8.2% nondiabetics; $P = 0.95$). In diabetics, the MACE rate was 3.2% in the CII group compared with 12.5% in the IIB group ($P = 0.10$). In nondiabetics, the MACE rate was 3.8% in the CII group compared with 12.1% in the IIB group ($P = 0.12$). Patients with known coronary artery disease demonstrated increased rates of composite MI and congestive heart failure compared with those without previous heart disease (12.4% *vs.* 2.8%; $P = 0.007$). There were no cases of perioperative MI in patients without underlying coronary artery disease, whereas 5.4% of patients with coronary artery disease sustained an MI ($P = 0.017$). Patients with perioperative MI or congestive heart failure exacerbation had a longer hospital stay compared with patients who did not sustain adverse cardiac events (median of 9 *vs.* 7 days; $P = 0.01$).

Multivariate analysis (logistic regression) demonstrated that continuous insulin infusion (odds ratio, 0.28; 95% confidence interval, 0.09–0.87; $P = 0.027$) was a negative independent predictor, whereas previous coronary artery disease (odds ratio, 4.65; 95% confidence interval, 1.31–16.56; $P = 0.018$) was a positive predictor of MACEs after vascular surgery.

Discussion

The current results provide the first evidence to demonstrate that perioperative continuous infusion of insulin, targeting a blood glucose concentration of 100–150 mg/dl, decreases major cardiovascular events in a population of patients undergoing vascular surgery. Previous studies of intensive insulin therapy in critically ill patients have yielded mixed results.[5,11–14] Our study differs from these previous studies in a number of important respects. First, we began insulin therapy in the operating room and continued the protocol throughout the first 48 h postoperatively. Second, our patient population was medically complicated, but with the exception of the abdominal aortic aneurysm surgery patients did not require admission to an intensive care unit. Third, the goals of therapy were different in this investigation compared with many other previous studies. In the continuous insulin group, blood glucose concentrations were targeted to between 100 and 150 mg/dl. Some have advocated that a more conservative approach to blood glucose management, such as this, may be warranted in view of conflicting evidence regarding the safety and efficacy of intensive insulin therapy (blood glucose concentrations targeted between 80 and 110 mg/dl) in critically ill patients.[15] Finally, the primary endpoint of our study was not mortality alone, because perioperative death is a rare occurrence in this patient population. We focused this investigation on the efficacy of continuous insulin infusion, compared with conventional therapy with intermittent bolus insulin, to decrease MACEs in vascular surgery patients.

The results confirm and extend previous findings indicating that there is a direct relation between fasting blood glucose levels and the risk of sustaining a cardiovascular event in patients with or without diabetes.[16] Recently, a J-shaped relation between average glucose and mortality was described in patients with acute MI.[17] Mortality rates increased with each 10-mg/dl increase in mean glucose ≥ 120 mg/dl and with incremental decreases ≤ 70 mg/dl. The moderate glycemic target (100–150 mg/dl) chosen in our study avoided severe hypoglycemia (< 40 mg/dl) and provided beneficial cardioprotective effects. Clinical observations are also sup-

ported by the experimental data relating to hyperglycemia and cardiovascular risk that indicate a direct relation between the severity of hyperglycemia and the extent of MI.[18] In animal models, myocardial infarct size was linearly related to blood glucose concentration, and this relation was similar whether hyperglycemia was produced by chemical induction of diabetes or by acute infusion of intravenous dextrose.[18] Interestingly, cardioprotective signaling with ischemic or anesthetic preconditioning was abolished by hyperglycemia or diabetes in a dose-dependent fashion.[19]

Variability of blood glucose concentrations may also play a role in producing adverse outcomes after surgery. Egi *et al.*[20] demonstrated that decreased variability of blood glucose concentrations may provide a cardioprotective effect. In fact, blood glucose variability was a stronger predictor of vascular intensive care unit mortality than absolute blood glucose values. Hirsh and Brownlee[21] recently stressed the importance of variability of glucose concentrations and a potential role for fluctuations in glucose as a mechanism responsible for increased oxidative stress.[22] Interestingly, cell damage seems to be most prominent when glucose concentrations increase rapidly from a normal level.[23]

Continuous intravenous administration of insulin is likely to be associated with less variability of blood glucose concentrations compared with either bolus subcutaneous or bolus intravenous insulin administration. Less variability of blood glucose concentrations might account for the observation that the SD of glucose concentrations was less in the continuous infusion group, compared with the bolus insulin group, from 8 h postoperatively until 24 h. In contrast, greater variability might be expected to occur early after initiation of insulin therapy, because of rapidly decreasing blood glucose concentrations and possibly because of varying degrees of surgical stress. Twenty-four hours after the start of surgery, there was an apparent increase in variability of blood glucose concentration in both groups. By design, blood glucose measurements were performed with less frequency in both groups at times remote from the surgery, and this might also account for increased SD of blood glucose concentration after 24 h.

Subgroup analysis did not demonstrate a difference in outcome between patients with and without diabetes, although this trial was not adequately powered to specifically address this hypothesis. Some evidence suggests that nondiabetic patients may sustain a greater benefit from control of blood glucose concentrations as compared with diabetic patients. For example, Egi *et al.*[20] reported that in contrast to patients with acute hyperglycemia without diabetes, patients with diabetes did not demonstrate an association between increasing levels of glucose or glucose variability and intensive care unit or hospital mortality. The mechanism for this differential effect of blood glucose variability in patients with and without diabetes is unclear and warrants further investigation.

It has been suggested that hypoglycemia may limit the beneficial effects of tight blood glucose control in critically ill patients.[24] Our results indicate that moderate blood glucose control was associated with cardioprotective effects, and with a low rate of hypoglycemic events and no immediate or long-term sequelae related to hypoglycemia. Other studies, such as those by Van den Berghe *et al.*,[5,12] targeted a blood glucose concentration of 80–110 mg/dl, with a mean value of 100 mg/dl. The incidence of severe hypoglycemia (< 40 mg/dl) was close to 18% in the medical population[12] and 5.1% in the surgical population.[5] The incidence of hypoglycemia reported by Van den Berghe *et al.*[5] in surgical patients was similar to that observed in the current investigation (4.1%). Other trials using a moderate target for blood glucose control (130 mg/dl) similarly demonstrate a low risk for severe hypoglycemia (0.34% of patients studied).[25]

There are a number of limitations to our study. There were no patient deaths within 30 days of surgery in either group, and the current trial was not adequately powered to detect differences in overall mortality between groups. Such a trial would require approximately 5,000–6,000 patients[26] to address a mortality benefit of moderate blood glucose control. The α levels for significance were not adjusted for the interim analyses because of the unplanned issues with subject recruitment. There were no differences in the incidence of postoperative infections between groups. It is possible that a more aggressive approach to blood glucose management may be required to reduce the incidence of surgical site infections.[27] In their *post hoc* analysis of Leuven trial patients, Van den Berghe *et al.*[28] suggested that the benefits of blood glucose control to decrease morbidity such as acute renal failure, bacteremia, and infection might require a target blood glucose concentration of 110 mg/dl. In our study, a moderate degree of blood glucose control was achieved in the intervention group, and this might explain the lack of protection against renal failure and other morbidity; however, this hypothesis remains to be further tested. Crossover between the two groups and the use of long-acting baseline insulin (used to avoid ketoacidosis) in both the groups could have limited the effect size seen in the trial. Although the study was not blinded, an accurate assessment of postoperative outcomes was made with operationalized definitions and a trained research assistant using the ongoing New England Quality assurance database methods. We did not calculate health care utilization costs in our study.[28] It has been suggested that intensive glucose control has the potential for producing substantial cost savings, particularly in patients requiring intensive care.

In conclusion, the results demonstrate that continuous infusion of insulin in hyperglycemic patients, with or without diabetes, substantially decreases MACEs com-

pared with patients receiving intermittent bolus insulin. This beneficial effect was observed concomitantly with a low risk of hypoglycemia.

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Appendix 1: Continuous Insulin Infusion Group

Start insulin infusion when blood glucose concentration is greater than 150 mg/dl.

All diabetics will receive half of their baseline long-acting insulin regimen. No oral hypoglycemic drugs will be given throughout the study period. All patients will have hourly blood glucose checks.

Drug: regular insulin only
Route: by intravenous route only

Blood Glucose, mg/dl	Regular Insulin, Bolus	Regular Insulin, Infusion
151–200	No bolus	2 units/h intravenously
201–250	3 units intravenously	2 units/h intravenously
251–300	6 units intravenously	3 units/h intravenously
301–350	9 units intravenously	3 units/h intravenously
> 350	10 units intravenously	4 units/h intravenously

If restarting insulin infusion drip for a blood glucose of 151–200 mg/dl, start at 1 unit/h.

Monitoring:

1. Check glucose every hour until stable.
2. A stable blood glucose is when three consecutive values are in desired range (100–150 mg/dl).
3. If blood glucose is stable, checks can be reduced to every 2 h × 4, then every 4 h.
4. Restart blood glucose checks every hour if there is any change in the insulin infusion rate or if the insulin drip is restarted.
5. If glucose is changing rapidly (even if in the desired range) or if in a critical range (< 65 or > 360 mg/dl), every-30-min blood glucose checks may be needed. Insulin infusion adjustments based on current blood glucose and current insulin infusion rates:

Current Blood Glucose, mg/dl	Current Insulin Infusion Rates	
	1–3 units/h	> 3 units/h
< 65	Discontinue infusion; 50 ml dextrose, 50%, IVP; recheck blood glucose in 30 min; inform physician; if blood glucose > 65 mg/dl, check blood glucose every hour; restart insulin infusion if blood glucose > 150 mg/dl	
65–100	Discontinue infusion; recheck blood glucose in 1 h; if blood glucose > 100 mg/dl, go to appropriate box below	
101–125	Decrease by 2 units/h from previous insulin infusion rates	Decrease rate to 50% from previous insulin infusion rates
126–150	Decrease by 1 unit/h from previous insulin infusion rates	Decrease by 2 units/h from previous insulin infusion rates

If the patient has a history of diabetes or is currently on steroids, when the blood glucose is in the range of 101–150 mg/dl, maintain the same insulin infusion rate.

IVP = intravenous push.

Current Blood Glucose, mg/dl	Current Insulin Infusion Rates		
	1–5 units/h	6–10 units/h	11–15 units/h
151–200	No intravenous bolus ↑ by 1 unit/h	No intravenous bolus ↑ 2 units/h	No intravenous bolus ↑ 2 units/h
201–250	3 units intravenous bolus ↑ by 1 unit/h	5 units intravenous bolus ↑ 2 units/h	5 units intravenous bolus ↑ 2 units/h
251–300	8 units intravenous bolus ↑ by 1 unit/h	8 units intravenous bolus ↑ 2 units/h	8 units intravenous bolus ↑ 2 units/h
301–350	10 units intravenous bolus ↑ by 1 unit/h	10 units intravenous bolus ↑ 2 units/h	10 units intravenous bolus ↑ 2 units/h
> 350	10 units intravenous bolus ↑ by 2 units/h	10 units intravenous bolus ↑ 3 units/h	10 units intravenous bolus ↑ 3 units/h

If the infusion rates go more than 16 units/h and subsequent blood glucose checks reveal a blood glucose greater than 250 mg/dl, recheck insulin infusion drips, intravenous site, and carrier flows and call house officer for new orders.

Appendix 2: Intermittent Insulin Bolus Group

All diabetics will receive half of their long-acting insulin on the morning of surgery. Oral hypoglycemic drugs will be withheld. The long-acting insulin will be reinitiated during the transition period at 48 h. Regular insulin will be used intravenously in the operating rooms at the discretion of treating anesthesiologist, as is the standard of care, and in the postoperative period will be initiated for blood glucose greater than 150 mg/dl. All patients will receive 4 hourly blood glucose checks.

Sliding scale nomogram:

Glucose, mg/dl	Coverage
< 60	Call physician
60–150	None
151–200	2 units
201–250	4 units
251–300	6 units
301–350	8 units
351–400	12 units