Hyperinsulinemic Normoglycemia during Cardiac Surgery Reduces a Composite of 30-day Mortality and Serious In-hospital Complications

A Randomized Clinical Trial

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ABSTRACT

Background: Hyperinsulinemic normoglycemia augments myocardial glucose uptake and utilization. We tested the hypothesis that hyperinsulinemic normoglycemia reduces 30-day mortality and morbidity after cardiac surgery.

Methods: This dual-center, parallel-group, superiority trial randomized cardiac surgical patients between August 2007 and March 2015 at the Cleveland Clinic, Cleveland, Ohio, and Royal Victoria Hospital, Montreal, Canada, to intraoperative glycemic management with (1) hyperinsulinemic normoglycemia, a fixed high-dose insulin and concomitant variable glucose infusion titrated to glucose concentrations of 80 to 110 mg · dl^{-1}; or (2) standard glycemic management, low-dose insulin infusion targeting glucose greater than 150 mg · dl^{-1}. The primary outcome was a composite of 30-day mortality, mechanical circulatory support, infection, renal or neurologic morbidity. Interim analyses were planned at each 12.5% enrollment of a maximum 2,790 patients.

Results: At the third interim analysis (n = 1,439; hyperinsulinemic normoglycemia, 709, standard glycemic management, 730; 52% of planned maximum), the efficacy boundary was crossed and study stopped *per protocol*. Time-weighted average glucose concentration (means ± SDs) with hyperinsulinemic normoglycemia was 108 ± 20 *versus* 150 ± 33 mg · dl^{-1} with standard glycemic management, $P < 0.001$. At least one component of the composite outcome occurred in 49 (6.9%) patients receiving hyperinsulinemic normoglycemia *versus* 82 (11.2%) receiving standard glucose management ($P <$ efficacy boundary 0.0085); estimated relative risk (95% interim-adjusted CI) 0.62 (0.39 to 0.97), $P = 0.0043$. There was a treatment-by-site interaction ($P = 0.063$); relative risk for the composite outcome was 0.49 (0.26 to 0.91, $P = 0.0007$, n = 921) at Royal Victoria Hospital, but 0.96 (0.41 to 2.24, $P = 0.89$, n = 518) at the Cleveland Clinic. Severe hypoglycemia (less than 40 mg · dl^{-1}) occurred in 6 (0.9%) patients.

Conclusions: Intraoperative hyperinsulinemic normoglycemia reduced mortality and morbidity after cardiac surgery. Providing exogenous glucose while targeting normoglycemia may be preferable to simply normalizing glucose concentrations.
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HYPERGLYCEMIA is associated with mortality and morbidity in critically ill and cardiac surgical patients.[1–3] Consistent with these observations, intensive treatment of hyperglycemia aimed at normoglycemia reduced morbidity and mortality in a single-center randomized trial of critically ill surgical patients, most of whom had recent cardiac surgery.[4] Pediatric critically ill patients, most of whom had cardiac surgery and received intensive insulin therapy aimed at normoglycemia, similarly experienced reduced morbidity and mortality.[5] Other trials, however, found that treatment of hyperglycemia with conventional insulin infusions aimed at normoglycemia either provided no benefit[6,7] or increased mortality.[8,9] Complications resulted, at least in part, from hypoglycemia.[10]

Disparities in reported outcomes may be related to whether or not sufficient glucose was provided. Outcomes in normoglycemic patients were generally favorable in trials where glucose was supplemented, either intravenously or nutritionally.[4,5,11,12] In contrast, outcomes were unfavorable when normoglycemia was produced only by insulin

What We Already Know about This Topic

- Previous studies have demonstrated that hyperglycemia is associated with mortality and morbidity in critically ill and cardiac surgical patients.
- This study determined whether hyperinsulinemic normoglycemia reduces 30-day mortality and morbidity after cardiac surgery.

What This Article Tells Us That Is New

- Intraoperative hyperinsulinemic normoglycemia reduced mortality and morbidity after cardiac surgery. Providing exogenous glucose while targeting normoglycemia may be preferable to simply normalizing glucose concentrations.

The primary results of this investigation (the composite outcome of mortality and serious morbidity) have not been previously presented or published. Subinvestigations that were unrelated to the primary outcome have been presented at American Society of Anesthesiologists meetings in

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administration.[6–9] Provision of insulin and exogenous glucose while avoiding hyperglycemia promotes myocardial glucose uptake and utilization, augments myocardial efficiency, and increases cardiac output[13–18]—all of which may improve outcomes by increasing systemic perfusion and end-organ function. Cardiac surgical patients may especially benefit from normoglycemia with supplemental glucose because intraoperative myocardial ischemia and reperfusion injury are common.[12,19,20] An additional benefit of normoglycemia is a reduced risk of perioperative infection.[21–23]

Hyperinsulinemic normoglycemia is a well-established glycemic management technique in which exogenous glucose is combined with intensive insulin therapy to target normoglycemia.[24–26] Application of this technique in cardiac surgical patients aims to improve myocardial and end-organ function. Concurrent potassium supplementation is provided to avoid hypokalemia from insulin-induced cellular uptake of potassium.[27] The hyperglycemic normoglycemia technique thus bears a resemblance to glucose-insulin-potassium therapy,[12,28,29] except that normoglycemia is targeted. Normalization of glucose concentrations with the hyperinsulinemic normoglycemia technique may also reduce postoperative infections.

This investigation tested the hypothesis that intraoperative hyperinsulinemic normoglycemia improves a composite of 30-day postoperative mortality and serious cardiac, renal, neurologic, and infectious complications in patients recovering from cardiac surgery.

Materials and Methods

This dual-center, randomized, parallel-group, unblinded, superiority trial was approved by the Institutional Review Boards at the Cleveland Clinic, Cleveland, Ohio, and Royal Victoria Hospital, Montreal, Canada, and registered at ClinicalTrials.gov (NCT00524472) on August 31, 2007. Written, informed consent was obtained from each participant.

Adults between 18 and 90 yr old scheduled for elective coronary artery bypass grafting, valve repair or replacement, or a combination of these procedures with cardiopulmonary bypass between August 2007 and April 2015 were screened for inclusion by research personnel. Exclusion criteria included off-pump cardiac surgery, anticipated hypothermic circulatory arrest, elevated baseline cardiac troponin I (greater than 0.5 ng · l^{-1}, Montreal) or troponin T (greater than 0.1 ng · ml^{-1}, Cleveland), kidney disease requiring renal replacement therapy, or active infection requiring ongoing antibiotic therapy. Subinvestigations, unrelated to the primary outcome, have previously been published.[19,30–35]

Randomization and Masking

Study participants were randomly assigned (1:1) to hyperinsulinemic normoglycemia or standard glycemic management. Randomization was performed by the Plan procedure in SAS software, version 9.4 (SAS Institute Inc., USA), a web-based system, and was stratified by center (Cleveland *vs.* Montreal), cardiac surgical procedure (coronary artery bypass grafting, valve repair/replacement, or combined procedure) and history of diabetes (any diabetes [type 1/type 2/diet-controlled] *vs.* no diabetes). Block size within each stratum randomly ranged from 4 to 16 patients. Allocation was initially concealed in sealed, sequentially numbered envelopes, and later in a web-based system, both accessed shortly before induction of anesthesia.

It was not feasible to blind anesthesia and surgical personnel to the intraoperative glucose management strategy; however, primary outcomes and postoperative clinical and laboratory results were evaluated by research personnel blinded to group allocation.

Procedures

Anesthesia and Surgery. Standard anesthesia monitors were supplemented by central venous or pulmonary artery catheters and transesophageal echocardiography. Midazolam, etomidate, thiopental, propofol, sufentanil and/or fentanyl, volatile anesthetics, and a depolarizing or nondepolarizing muscle relaxant were given during induction and maintenance of anesthesia. Surgery was performed through a full midline sternotomy or minimally invasive upper hemisternotomy, and routine strategies for conduct of cardiopulmonary bypass were followed.

Intermittent antegrade and retrograde administration of Buckberg's cardioplegia mixed in 5% dextrose was used exclusively in Cleveland until December 2012; thereafter del Nido cardioplegia, a non–glucose-containing solution administered as a single anterograde infusion, was occasionally used for isolated valve repair/replacement without coronary artery bypass grafting.[36] In Montreal, intermittent anterograde and/or retrograde St. Thomas cardioplegia (Hospira Inc., USA), a non–glucose-containing solution, was administered. Intravenous vasoactive infusions and antibiotic medications were mixed in 5% dextrose in Cleveland and normal saline solution in Montreal.

October 2008 (Chowdary *et al.*, The influence of diabetes on intraoperative glucose control), in October 2008 (Said *et al.*, Comparison of within-patient glucose variability measures), and in October 2009 (Abd-Elsayed *et al.*, The effect of diabetes on intraoperative glycemic variability).

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During separation from cardiopulmonary bypass, epinephrine was infused for low cardiac index (less than 2.0 $l \cdot min^{-1} \cdot m^{-2}$) and/or norepinephrine or vasopressin were infused for low systemic vascular resistance (less than 700 dynes $\cdot s \cdot cm^{-5}$) to maintain mean arterial pressure greater than 80 mmHg and cardiac index greater than 2.0 $l \cdot min^{-1} \cdot m^{-2}$. Milrinone was infused when cardiac output was low and refractory to routine pharmacologic hemodynamic support. If a pulmonary artery catheter was not present, transesophageal echocardiography was used to assess myocardial contractility and determine whether inotropic *versus* vasopressor treatment was needed.

Glucose Management

Intraoperative glucose management with hyperinsulinemic normoglycemia involved a fixed-dose insulin infusion of 5 $mU \cdot kg^{-1} \cdot min^{-1}$ with a concomitant variable glucose (dextrose 20%) infusion supplemented with potassium (40 $mEq \cdot l^{-1}$) and phosphate (30 $mmol \cdot l^{-1}$) as previously described.[24] The glucose infusion was initiated at approximately 40 to 60 $ml \cdot hr^{-1}$ when serum glucose concentration was approximately 110 $mg \cdot dl^{-1}$ or less, and manually titrated to target glucose concentrations of 80 to 110 $mg \cdot dl^{-1}$ every 10 to 15 min throughout surgery. Additional boluses of insulin were given for blood glucose greater than 110 $mg \cdot dl^{-1}$. Arterial blood glucose concentrations were measured with an Accu-Check (Roche Diagnostics, Switzerland) glucose monitor. At sternal closure, the insulin infusion was reduced to 1 $mU \cdot kg^{-1} \cdot min^{-1}$ and converted to a standard low-dose insulin infusion upon intensive care unit admission. After intensive care unit arrival, the glucose infusion was decreased by 25 to 50% every 20 min when the blood glucose was greater than 110 $mg \cdot dl^{-1}$. When the infusion was at 20 $ml \cdot h^{-1}$ or less and blood glucose was greater than 110 $mg \cdot dl^{-1}$, the infusion was discontinued. Blood glucose concentrations were followed for 45 to 60 min after discontinuation of the dextrose infusion to ensure that hypoglycemia was avoided.

Standard glucose management involved a conventional low-dose insulin infusion titrated to blood glucose concentrations measured by arterial blood gas analysis every 30 to 90 min throughout surgery. This low-dose insulin infusion was initiated for blood glucose concentration greater than 120 $mg \cdot dl^{-1}$ before initiation of cardiopulmonary bypass or greater than 150 $mg \cdot dl^{-1}$ during or after cardiopulmonary bypass, at a rate based on patient weight and current glucose concentration. Subsequent adjustments were based on a sliding scale of current blood glucose concentration and the change from the previous measurement. Supplemental boluses of insulin were given with acute increases (greater than 30 $mg \cdot dl^{-1}$) in blood glucose. The insulin protocol for patients assigned to standard glucose management is listed in appendix 1.

Upon intensive care unit admission, both groups transitioned to the same standardized postoperative insulin treatment protocol in the intensive care unit. This involved measurement of blood glucose by arterial blood gas analysis approximately every 2 h with adjustment of insulin infusion to maintain serum glucose less than 150 $mg \cdot dl^{-1}$ on postoperative day one and less than 120 $mg \cdot dl^{-1}$ on day two and later. In 2009, after publication of the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial,[9] the postoperative glucose target increased to less than 180 $mg \cdot dl^{-1}$.

Severe and moderate hypoglycemia was defined as blood glucose less than 40 and 60 $mg \cdot dl^{-1}$, respectively. Hypoglycemia was treated by administration of 20% dextrose (25 to 100 ml). A summary of major protocol changes that occurred since initiation of this investigation is found in appendix 2.

Outcomes

The primary outcome was a collapsed composite (any *vs.* none) of the following major postoperative complications occurring within 30 days of surgery: (1) all-cause postoperative mortality; (2) failure to wean from cardiopulmonary bypass or postoperative low cardiac index (less than 1.8 $l \cdot min^{-1} \cdot m^{-2}$) requiring mechanical circulatory support with intra-aortic balloon counter-pulsation, ventricular assist device, and/or extracorporeal mechanical oxygenation; (3) serious postoperative infection including any of the following infectious complications: mediastinitis, sternal wound infection requiring surgical debridement, sepsis, or pneumonia requiring mechanical ventilatory support; (4) acute postoperative kidney injury requiring renal replacement therapy; and (5) new postoperative focal (aphasia, decrease in limb function, hemiparesis) or global (diffuse encephalopathy with greater than 24 h of severely altered mental status or failure to awaken postoperatively) neurologic deficit.

The secondary outcomes included postoperative atrial fibrillation, defined as the occurrence of new-onset postoperative atrial fibrillation after cardiac surgery, duration of hospitalization (days) and intensive care unit stay (days), and 1-yr all-cause mortality.

We also recorded a composite of minor postoperative complications within the first 30 days including mechanical ventilation greater than 72 h, low cardiac index (cardiac index less than 1.8 $l \cdot min^{-1} \cdot m^{-2}$ despite adequate fluid replacement (lack of hemodynamic response to repeated fluid administration of crystalloid or colloid intravascular solutions) and high-dose inotropic support for greater than 4 h), acute kidney injury (increase in creatinine greater than 100%), hospitalization greater than 30 days, and all-cause hospital readmission within 30 days. Detailed definitions of the primary and secondary outcomes are listed in appendix 3.

Statistical Analysis

Balance on baseline characteristics between randomized groups was assessed using the standardized difference

(difference in means or proportions divided by pooled SD). Imbalance was defined as a standardized difference greater than 0.2 in absolute value,[37] and such variables were adjusted for in all analyses.

We assessed the effect of hyperinsulinemic normoglycemia *versus* standard therapy on the primary outcome (any complication) using Cochran-Mantel-Haenszel chi-square analysis, adjusting for clinical site. Results were reported as the estimated relative risk and interim analysis adjusted 95% CI. We assessed the interaction between treatment effect and site using the Breslow-Day test for homogeneity of odds ratios. We also assessed the treatment-by-component (of the composite outcome) interaction overall and within site using multivariate (one record per component per subject) generalized estimating equation "distinct-effects" logistic models.[38] Groups were compared on binary secondary outcomes using the same methods as for the primary outcome. The treatment effect on time-to-event secondary outcomes (*i.e.*, duration of mechanical ventilation, and intensive care unit and hospital stay [time to discharge alive]) were assessed using Cox proportional hazards models adjusting for site. For patients who died during the index hospitalization (n = 22), the hospital stay was assigned to be the longest observed hospital stay plus 1 day, and censored at that time (*i.e.*, not discharged alive). "Time to discharge alive" was not used for intensive care unit length of stay because the exact date/time of death was not recorded (only whether in-hospital or not). Median (95% CI) survival time was estimated from Kaplan-Meier curves.

Intraoperative time-weighted mean glucose concentration was calculated across measurements for each patient using the trapezoidal method and equal to the area under the curve divided by the total glucose reading time.

The significance level for each hypothesis was 0.05, and all tests were two-sided. CIs were adjusted for the group sequential design (using confidence coefficient of 2.63) to maintain overall study α of 0.05 for combined sites and 0.025 (confidence coefficient of 2.86) within sites. Significance criterion for treatment-by-site interaction was set at 0.10 *a priori*. Bonferroni correction was performed while assessing each individual component of the composite primary outcome, with the significance criterion of 0.0017 (*i.e.*, 0.0085/5 components = 0.0017) with 99.83% CI, and 0.00084 (*i.e.*, 0.0042/5) with 99.92% CI within site. SAS software, version 9.4 or East 5.3 (Cytel Corp., USA) were used for all analyses.

Sample Size Calculations

A maximum of 2,790 patients was required to detect a 30% relative reduction in the composite of any major complications (*i.e.*, any *vs.* none) from an expected 15% incidence of complications in the standard group at the overall 0.05 significance level with 90% power. Interim analyses to assess efficacy and futility on the primary outcome of the occurrence of any major complication were planned at each 12.5% of the maximum planned enrollment in this group sequential design (n = 349, 697, 1,046, 1,394, 1,743, 2,091, and 2,440). Patient recruitment continued while the interim analyses were performed; thus, the timing of the interim analyses varied slightly from the original plan. We used the α (type I error) and β (type II error) spending approach of Hwang *et al.*[39] with parameters $\gamma = -2$ for efficacy and $\gamma = -3$ for futility.

Results

Patients were recruited from August 17, 2007, until March 30, 2015; 1,439 patients were randomly assigned to hyperinsulinemic normoglycemia (n = 709) and standard glycemic management (n = 730), with 518 in Cleveland and 921 in Montreal (fig. 1). The number of patients screened for this investigation was not available. At the third interim analysis with n = 1,439 (52% of maximum enrollment; patient recruitment continued during data analysis, thus the third interim analysis was later than initially planned), the treatment effect of hyperinsulinemic normoglycemia on the primary outcome crossed the predefined efficacy boundary for the combined sites, and the study was stopped as per the protocol. The *P* value boundaries for efficacy and futility were $P < 0.0085$ and $P \geq 0.803$, respectively.

Randomized groups were well-balanced (absolute standardized difference less than 0.20) on all preoperative patient demographics, clinical characteristics, preoperative echocardiographic measurements, and perioperative variables (table 1). Survival data at 1 yr were unavailable on 104 patients (hyperinsulinemic normoglycemia, n = 56; standard glycemic management, n = 48).

Insulin Administration and Treatment Effects

Overall mean ± SD time-weighted average glucose concentration was $108 \pm 20\,mg \cdot dl^{-1}$ with hyperinsulinemic normoglycemia *versus* $150 \pm 33\,mg \cdot dl^{-1}$ with standard glycemic management. The Cleveland site had higher time-weighted

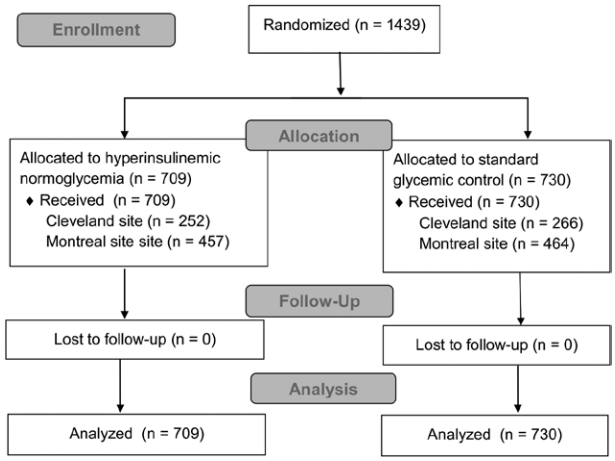

Fig. 1. Patient flow diagram.

Table 1. Baseline and Surgical Characteristics by Treatment and Site

Factor	Combined Sites			Cleveland Clinic			Royal Victoria Hospital		
	Hyperinsulinemic Normoglycemia (n = 709)	Standard Therapy (n = 730)	ASD	Hyperinsulinemic Normoglycemia (n = 252)	Standard Therapy (n = 266)	ASD	Hyperinsulinemic Normoglycemia (n = 457)	Standard Therapy (n = 464)	ASD
Demographics									
Age (yr)	66 ± 11‡	66 ± 11†	0.02	66 ± 13*	66 ± 12*	0.03	67 ± 11‡	66 ± 10†	0.05
Female	189 (27)†	184 (26)*	0.04	76 (30)*	72 (27)*	0.07	113 (26)†	112 (25)*	0.02
White race	596 (87)†	615 (86)*	0.01	245 (97)*	248 (93)*	0.19	351 (81)†	367 (82)*	0.04
Body mass index	28.5 ± 5.7†	28.3 ± 5.4*	0.03	29.6 ± 6.1*	28.9 ± 5.7*	0.11	27.9 ± 5.4†	28.0 ± 5.2*	0.01
Medical history									
Diabetes	226 (32)*	249 (34)*	0.05	69 (27)*	74 (28)*	0.01	157 (34)*	175 (38)*	0.07
COPD/asthma	107 (16)†	85 (12)*	0.10	41 (16)*	34 (13)*	0.10	66 (15)†	51 (11)*	0.11
Pulmonary Hypertension	101 (15)†	102 (14)*	0.01	57 (23)*	66 (25)*	0.05	44 (10)†	36 (8)*	0.07
Stroke	41 (6)†	32 (5)†	0.07	23 (9)*	19 (7)*	0.07	18 (4)†	13 (3)†	0.07
Hypertension	533 (77)†	561 (79)*	0.03	160 (63)*	171 (64)*	0.02	373 (86)†	390 (87)*	0.04
Heart failure	146 (21)†	137 (19)*	0.05	77 (31)*	73 (27)*	0.07	69 (16)†	64 (14)*	0.047
Myocardial infarction	193 (28)†	173 (24)*	0.09	59 (23)*	62 (23)*	0.002	134 (31)†	111 (25)*	0.13
Dialysis	4 (1)†	4 (1)*	0.003	2 (1)*	3 (1)*	0.03	2 (0)†	1 (0)*	0.04
Peripheral vascular disease	51 (7)†	42 (6)*	0.06	32 (13)*	28 (11)*	0.07	19 (4)†	14 (3)*	0.06
Smoking	197 (29)†	180 (25)*	0.05	109 (43)*	117 (44)*	0.01	88 (20)†	63 (14)*	0.16
ASA physical status			0.08			0.14			0.02
II	2 (0)†	0 (0)*		2 (1)*	0 (0)*		0 (0)*	0 (0)*	
III	334 (49)	349 (49)		46 (18)	48 (18)		288 (66)	301 (67)	
IV	348 (51)	363 (51)		201 (80)	215 (81)		147 (34)	148 (33)	
V	2 (0)	1 (0)		2 (1)	1 (0)		0 (0)	0 (0)	
Preoperative medications									
ACE inhibitor	266 (39)†	262 (37)†	0.03	96 (38)*	96 (36)*	0.04	170 (39)†	166 (38)†	0.03
Antiarrhythmic	56 (8)†	67 (10)†	0.05	34 (13)*	44 (17)*	0.09	22 (5)†	23 (5)†	0.01
ß-Blocker	434 (63)†	452 (64)*	0.01	116 (46)*	134 (50)*	0.09	318 (73)†	318 (71)*	0.03
Calcium blocker	128 (19)†	147 (21)†	0.05	32 (13)*	47 (18)*	0.14	96 (22)†	100 (23)†	0.01
Cox-2 inhibitor	13 (2)§	3 (0)§	0.14	6 (3)‡	1 (0)‡	0.19	7 (2)†	2 (0)†	0.12
Statin	475 (69)†	486 (69)†	0.004	130 (52)*	145 (55)*	0.06	345 (79)†	341 (78)†	0.04
Steroid	33 (5)†	23 (3)†	0.08	11 (4)*	16 (6)*	0.07	22 (5)†	7 (2)†	0.20
Diabetic medications	194 (30)§	193 (29)§	0.03	57 (28)‡	56 (26)‡	0.05	137 (31)†	137 (31)†	0.02
Sulfonylureas or meglitinides	52 (8)§	58 (9)§	0.02	21 (10)‡	18 (8)‡	0.071	31 (7)†	40 (9)†	0.07
Biguanides (metformin)	126 (20)§	124 (19)§	0.02	24 (12)‡	29 (13)‡	0.05	102 (23)†	95 (21)†	0.05
Thiazolidinediones	16 (3)§	11 (2)§	0.06	7 (3)‡	4 (2)‡	0.10	9 (2)†	7 (2)†	0.04
Insulin	70 (11)§	68 (10)§	0.02	24 (12)‡	26 (12)‡	0.005	46 (11)†	42 (9)†	0.04
Preoperative echocardiographic measurements									
Mitral regurgitation severity			0.17			0.25			0.29
0	97 (27)**	89 (24)‡		74 (37)‡	77 (36)‡	0.04	23 (14)#	12 (8)**	
+1	85 (23)	86 (23)		42 (21)	39 (18)	0.09	43 (27)	47 (31)	
+2	78 (22)	66 (18)		34 (17)	23 (11)	0.09	44 (28)	43 (28)	
+3	46 (13)	47 (13)		21 (10)	31 (14)		25 (16)	16 (11)	
+4	56 (15)	79 (22)		31 (15)	46 (21)		25 (16)	33 (22)	
Mitral stenosis	8 (2)**	6 (2)‡	0.04	6 (3)‡	5 (2)‡	0.04	2 (0)†	1 (0)**	0.05
Aortic regurgitation severity			0.18			0.17			0.36
0	187 (48)**	194 (51)‡		142 (57)*	164 (62)*		45 (33)††	30 (26)††	
+1	77 (20)	91 (24)		42 (17)	42 (16)		35 (25)	49 (42)	
+2	66 (17)	46 (12)		38 (15)	28 (11)		28 (20)	18 (16)	
+3	32 (8)	24 (6)		17 (7)	14 (5)		15 (11)	10 (9)	
+4	27 (7)	25 (7)		12 (5)	16 (6)		15 (11)	9 (8)	

(*Continued*)

Table 1. (Continued)

Factor	Combined Sites			Cleveland Clinic			Royal Victoria Hospital		
	Hyperinsulinemic Normoglycemia (n = 709)	Standard Therapy (n = 730)	ASD	Hyperinsulinemic Normoglycemia (n = 252)	Standard Therapy (n = 266)	ASD	Hyperinsulinemic Normoglycemia (n = 457)	Standard Therapy (n = 464)	ASD
Aortic stenosis	225 (47)†	201 (43)†	0.08	119 (47)*	111 (42)*	0.11	106 (47)†	90 (45)†	0.04
LV ejection fraction			0.13			0.07			0.20
LVEF > 60%	246 (37)‡	257 (37)‡		89 (39)†	91 (36)*		157 (36)†	166 (38)†	
LVEF 50–59%	236 (36)	238 (34)		91 (39)	106 (42)		145 (34)	132 (30)	
LVEF 45–49%	3 (0)	3 (0)		3 (1)	3 (1)		0 (0)	0 (0)	
LVEF 40–44%	54 (8)	65 (9)		10 (4)	13 (5)		44 (10)	52 (12)	
LVEF 35–39%	34 (5)	54 (8)		11 (5)	12 (5)		23 (5)	42 (10)	
LVEF < 35%	89 (13)	76 (11)		27 (12)	28 (11)		62 (14)	48 (11)	
Preoperative laboratory measurements									
BUN (mg · dl^{-1})	21 ± 17‖	21 ± 17‖	0.006	22 ± 11*	22 ± 10*	0.05	20 ± 20‖	21 ± 21‖	0.03
Creatinine (mg · dl^{-1})	1.09 ± 0.52†	1.10 ± 0.59†	0.007	1.18 ± 0.75*	1.14 ± 0.70*	0.05	1.04 ± 0.31†	1.07 ± 0.52†	0.06
Hematocrit (mg · dl^{-1})	40 ± 8†	40 ± 8†	0.03	40 ± 5*	41 ± 5*	0.09	40 ± 9†	40 ± 10†	0.007
Perioperative variables									
Cardiac surgical procedure			0.02			0.05			0.03
Coronary artery bypass grafting (no valve)	298 (42)	311 (43)		85 (34)	87 (33)		213 (47)	224 (48)	
Valve (no coronary artery bypass grafting)	272 (38)	281 (38)		97 (38)	109 (41)		175 (38)	172 (37)	
Coronary artery bypass grafting + valve	138 (19)	138 (19)		70 (28)	70 (26)		68 (15)	68 (15)	
Previous cardiac surgery	94 (14)†	84 (12)*	0.06	69 (27)	68 (26)	0.04	25 (6)†	16 (4)*	0.10
Surgical variables									
Duration of surgery (min)	260 [200, 341]#	273 [210, 351]#	0.08	376 [311, 444]‡	358 [305, 423]‡	0.1	215 [170, 250]‖	220 [180, 270]‖	0.14
Duration of cardio pulmonary bypass (min)	96 [77, 126]§	99 [77, 126]§	0.01	93 [77, 120]‡	94 [74, 116]‡	0.04	99 [77, 130]†	101 [79, 130]†	0.04
Duration of aortic cross-clamp (min)	77 [60, 104]§	79 [61, 103]§	0.02	71 [58, 93]‡	74 [57, 93]‡	0.001	82 [61, 108]†	84 [64, 107]†	0.03
Cardioplegia			0.07			0.12			0
St. Thomas	457 (64)	464 (64)		0 (0)	0 (0)		457 (100)	464 (100)	
Buckberg's	246 (35)	257 (35)		246 (98)	257 (97)		0 (0)	0 (0)	
Del Nido	5 (1)	9 (1)		5 (2)	9 (3)		0 (0)	0 (0)	
Microplegia	1 (0)	0 (0)		1 (0)	0 (0)		0 (0)	0 (0)	

Data are represented as N (%), mean ± SD, or median [25th, 75th percentiles]. ACE = angiotensin-converting enzyme; ASA = American Society of Anesthesiologists physical status classification system; ASD = absolute standardized difference (difference in means or proportions divided by SD; imbalance defined as absolute value of ASD > 0.20 [small effect size]); BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; LV = left ventricular; LVEF = left ventricular ejection fraction.

Ranges of missing data points: *1 to 19, †20 to 29, ‡35 to 51, §70 to 79, ‖150 to 162, #190 to 200, **231 to 299, and ††300 to 514.

average glucose concentration than Montreal overall, as well as within each treatment (all $P < 0.001$). In Cleveland, glucose concentration was 121 ± 19 mg · dl^{-1} with hyperinsulinemic normoglycemia and 171 ± 31 mg · dl^{-1} with standard glycemic management. At the Royal Victoria Hospital, patients in the hyperinsulinemic normoglycemia group had glucose concentrations of 101 ± 17 mg · dl^{-1} *versus* 136 ± 26 mg · dl^{-1} with standard glycemic management. Reduction in mean time-weighted average intraoperative glucose concentration was similar at each site, with the estimated ratio of means (hyperinsulinemic normoglycemia/standard; 95% CI) being 0.71 (0.69 to 0.73) in Cleveland *versus* 0.74 (0.72 to 0.76) in Montreal. The overall effect for combined sites was 0.73 (0.72 to 0.74; fig. 2).

Moderate hypoglycemia (glucose concentration less than 60 mg · dl^{-1}) occurred in 91 (13%) of the hyperinsulinemic normoglycemia group, and severe hypoglycemia (less than 40 mg · dl^{-1}) occurred in 6 (0.9%). The average duration of a hypoglycemic episode in the hyperinsulinemic normoglycemic group was 9 (range, 3 to 16) min. Only 1 patient in the conventional insulin infusion group had severe hypoglycemia, lasting 29 min.

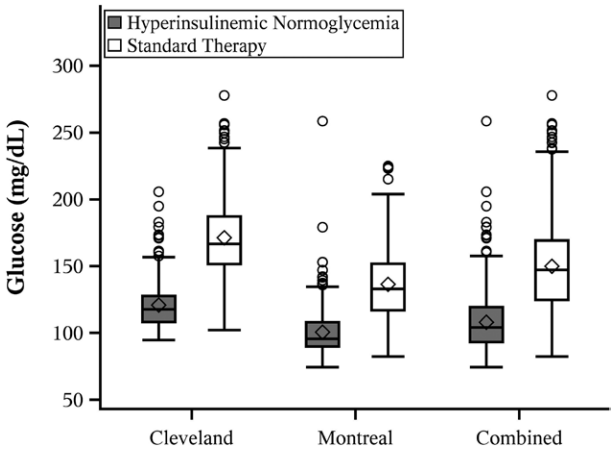

Fig. 2. *Box plots* comparing randomized groups on time-weighted intraoperative glucose concentrations overall (Combined) and within site. *Box* shows the interquartile range; *horizontal line* marks the median; *whiskers* extend to high and low values within 1.5 interquartile range of the box; *circles* are values beyond 1.5 interquartile range of the box; *diamond* shows the mean.

Primary Results

At least one component of the composite outcome occurred in 49 (6.9%) of patients receiving hyperinsulinemic normoglycemia *versus* 82 (11.2%) receiving standard glucose management (P < efficacy boundary of 0.0085) for an estimated relative risk (95% interim-adjusted CI) of 0.62 (0.39 to 0.97), P = 0.0043 (fig. 3A). However, there was a strong treatment-by-site interaction (P = 0.063, less than the *a priori* criterion of 0.10); the relative risk for the composite outcome was 0.49 (0.26 to 0.91, P = 0.0007, n = 921) at the Royal Victoria Hospital, Montreal, but 0.96 (0.41 to 2.24, P = 0.89, n = 518) at the Cleveland Clinic. Proportions and relative risks for the individual major complications in the combined sites are shown in figure 3A and by individual site in figure 3B. There was no evidence of treatment-by-component interaction overall (P = 0.84), for Cleveland (P = 0.96) or Montreal (P = 0.52), and thus inference within components was statistically unnecessary. Nevertheless, after adjusting for multiple comparisons across components, only serious infection morbidity in Montreal was significantly affected by intervention.

Secondary Results

Secondary outcomes for the combined sites are shown in table 2; no differences were found on any of the five outcomes. Secondary outcomes are shown by site in appendix 4; no differences were found in any secondary outcome within site. Although there was a significant treatment-by-site interaction for intensive care unit length of stay (P = 0.046), the treatment effect was not significant for either site; the hyperinsulinemic normoglycemia group was an estimated 1.24 (0.98 to 1.57) times more likely to be discharged earlier than in the standard group in Montreal (P = 0.0026, not significant after Bonferroni correction), and 0.99 (0.74 to 1.33) at the Cleveland Clinic (P = 0.89). Similarly, the treatment-by-site interaction was significant for hospital stay (P = 0.07), but the treatment effect was not significant at either site. There were no differences between groups on other secondary outcomes, including the composite of minor complications, postoperative atrial fibrillation, or 1-yr mortality (*i.e.*, all P > 0.0085, table 2).

Discussion

Hyperinsulinemic normoglycemia reduced the composite outcome of 30-day mortality and serious complications

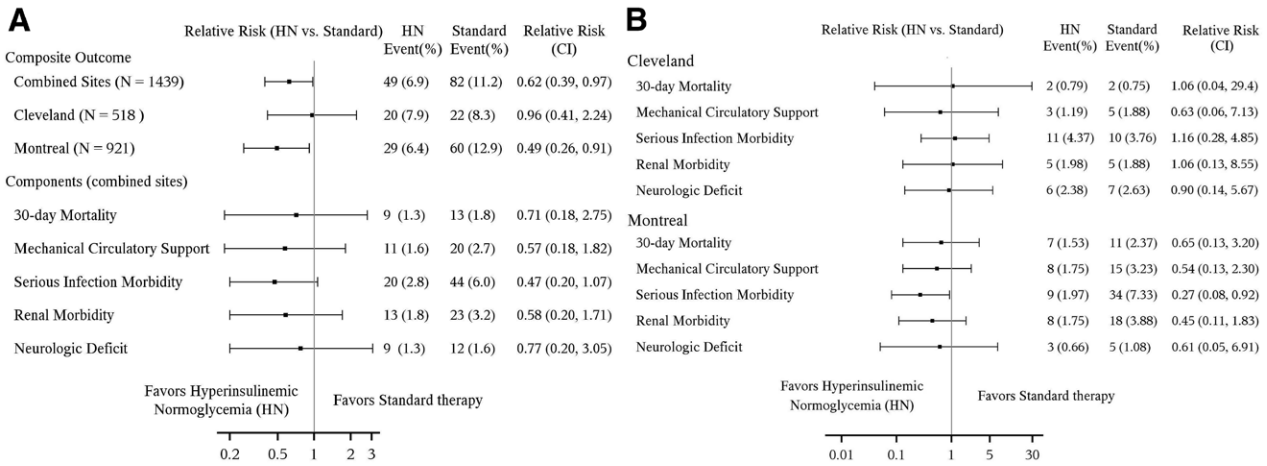

Fig. 3. Comparison of the hyperinsulinemic normoglycemia (HN) and standard therapy group on the composite outcome of any major morbidity/30-day mortality and individual components of the composite outcome at combined sites (*A*) and within individual sites (*B*). Interaction *P* value (treatment-by-site) = 0.063. CIs adjusted for group sequential design (using confidence coefficient of 2.633) to maintain overall study α of 0.05 for combined sites and confidence coefficient of 2.86 within sites. *P* values for combined sites: significant if $P < 0.0085$ for efficacy (with 99.15% CI); *P* values for each site: significant if $P < 0.0042$ for efficacy (with 99.58% CI); *P* values for each component: significant if $P < 0.0042/5 = 0.00084$ (with 99.92% CI) using Bonferroni correction.

Table 2. Comparison of the Hyperinsulinemic Normoglycemia *versus* Standard Therapy Groups on Secondary Outcomes

Outcomes	Hyperinsulinemic Normoglycemia (n = 709)		Standard Therapy (n = 730)		HR (99.83% CI)*	*P* Value*
	n	Median (95% CI)†	n	Median (95% CI)†		
Intensive care unit stay (hours)						0.046‖
	649	25 (24.9–26.3)	671	27 (25.2–27.3)	1.13 (0.95–1.35)	0.025
Hospital stay (days)‡						0.07‖
	686	8 (6, 12)	713	8 (6, 12)	1.05 (0.89–1.25)	0.35
	n	Event (%)	n	Event (%)	RR (99.83% CI)*	
Postoperative atrial fibrillation						0.51‖
	709	209 (29)	730	235 (32)	0.92 (0.75–1.13)	0.29
Any minor complication§						0.21‖
	709	194 (27)	730	227 (31)	0.89 (0.72–1.09)	0.13
1-yr mortality						0.13‖
	653	32 (5)	682	22 (3)	1.52 (0.74–3.11)	0.12

*CI and *P* values from Cox proportional hazards for intensive care unit stay and hospital stay, and Cochran-Mantel-Haenszel test for binary outcomes. CI adjusted for group sequential design using confidence coefficient of 2.633 for combined sites in order to maintain overall study α of 0.05. Significant if $P < 0.0085/6 = 0.0017$ using Bonferroni correction. †The estimated median survive time (95% CI) from Kaplan-Meier curve. ‡The observed longest hospital stay plus 1 day was assigned to patients who died during hospitalization (n = 22). §Minor complications include any one of the following: a prolonged requirement for mechanical ventilation (> 72 h), low cardiac index (cardiac index less than 1.8 l · min^{-1} · m^{-2} despite adequate fluid replacement and high-dose inotropic support for > 4 h), acute kidney injury (increase in creatinine > 100%), prolonged hospitalization (> 30 days), and all-cause hospital readmission within 30 days). ‖Treatment × site *P* value.

HR = hazard ratio; RR = relative risk.

by nearly 40% (CI, 3 to 61%) in patients having cardiac surgery across our two clinical sites. Our results are broadly consistent with previous work showing that normoglycemia reduces various complications when supplemental glucose is provided.[4,5,11,12]

The fixed high-dose insulin infusion technique contrasts with most previous trials in which only insulin, rather than insulin supplemented with glucose, was given to maintain normoglycemia. Insulin is cardioprotective independent of glucose concentrations.[40] Insulin administration during reperfusion reduces myocardial infarction *via* Akt and p70s6 kinase–dependent signaling pathways[28,40] and may improve myocardial metabolic and functional recovery after cardioplegic arrest.[41,42] Laboratory investigations similarly report myocardial benefit from provision of glucose and insulin.[43]

The protective effects of enhanced myocardial glucose uptake and utilization may be especially beneficial during cardiac surgery because it might counteract myocardial dysfunction consequent to cardioplegic arrest and ischemia and reperfusion injury. Previous studies that largely enrolled cardiac surgical patients (n = 1,548 and 700) similarly demonstrated benefit, although intensive insulin therapy targeting normoglycemia with supplemental glucose was initiated after surgery.[4,5] One other investigation (n = 371), however, examined the benefit of intraoperative glucose control during cardiac surgery and reported worse outcomes with intensive insulin therapy,[8] although a standard insulin infusion, rather than hyperinsulinemic normoglycemia, was evaluated.

Hyperinsulinemic normoglycemia resembles glucose-insulin-potassium therapy, which provided myocardial protection and improved left ventricular function in some,[14,28] but not all,[44] investigations. Both approaches are thought to provide cardioprotective benefits by increasing myocardial glucose uptake and improving coupling of glycolysis and glucose utilization.[43,45,46] However, hyperinsulinemic normoglycemia differs from glucose-insulin-potassium therapy in avoiding hyperglycemia, which is consistently associated with worse outcomes.[3,47] Variable degrees of hyperglycemia may explain why glucose-insulin-potassium demonstrated benefit in some investigations[12,28] but not in others.[29,48,49]

Aside from the overall significant benefit of hyperinsulinemic normoglycemia, the most striking aspect of our results is that the benefit was apparently restricted to one study site. We considered several potential explanations. Although glycemic management was standardized, cardioplegia at the Cleveland Clinic contained glucose, whereas it did not in Montreal; thus, both groups at the Cleveland Clinic received exogenous glucose during cardioplegic arrest. It is possible that routine provision of glucose-containing cardioplegia provided significant myocardial protection and reduced low cardiac output syndrome and mechanical circulatory support in all patients at the Cleveland Clinic, regardless of randomized group.

The need for mechanical circulatory support was low (less than 2%) among patients given glucose from either hyperinsulinemic normoglycemia or cardioplegia administration. Only the standard glycemic management group in Montreal did not receive exogenous glucose during cardioplegic arrest and also demonstrated the highest need for mechanical circulatory support. Consistent with this theory, a previously reported subinvestigation[50] from Montreal provided evidence of cardio-protection and improved myocardial function in patients who received hyperinsulinemic

normoglycemia, but not standard glucose management. In contrast, myocardial function at the Cleveland Clinic was not different between groups.[30]

Glucose concentrations for both randomized groups were higher in Cleveland than in Montreal, presumably because patients at the Cleveland Clinic were given cardioplegia with glucose and medications were mixed with glucose. Higher glucose concentrations at the Cleveland Clinic may explain the lack of difference between groups, whereas the effect was profound at the Royal Victoria Hospital.[51] Results for the primary outcome were clearly centered around the null hypothesis at the Cleveland Clinic, with a relative risk estimate of 0.96. However, Cleveland contributed only about a third of the patients; thus, the site-specific 95% CI for the primary outcome range from a 59% reduction to a 2.2-fold increase in the composite outcome, which does not allow a firm negative conclusion.

Hyperinsulinemic normoglycemia reduced serious postoperative infection only in Montreal. Others similarly reported a nearly 50% reduction in bloodstream and sternal wound infections in cardiac surgical and critically ill patients who received intensive insulin therapy.[4,22] Hyperglycemia impairs leukocyte function, increasing the risk of infection,[52,53] and our results are consistent with these observations. The Cleveland site, however, received no benefit from hyperinsulinemic normoglycemia. The incidence of postoperative infectious complications in the Cleveland control group was half of the incidence of infection in the Montreal control group. It is therefore possible that infection risk at the Cleveland Clinic was already low so that hyperinsulinemic normoglycemia provided little additional benefit.

Hypoglycemia, which has been closely linked to adverse outcomes in other investigations, rarely occurred in our study. We attribute the low incidence of hypoglycemia to the profound stress counterregulatory response and insulin-resistant state that ensues with cardiac surgery and during the conduct of cardiopulmonary bypass. But it is also due to frequent blood glucose measurements (generally every 10 to 15 min) and close titration of glucose by dedicated investigators.

We could not blind anesthesia or surgical personnel to intraoperative glycemic management; however, most outcomes occurred several hours to days postoperatively and were recorded by research personnel who were blinded to treatment assignment. Our investigation cannot determine whether the benefit of hyperinsulinemic normoglycemia was due to the administration of high-dose insulin with glucose supplementation *versus* benefits of normoglycemia; thus, the observed benefits may have resulted from more intensive glucose control, rather than the concomitant provision of supplemental glucose. The study stopped after slightly more than 50% of the planned patients were enrolled, but it was not "stopped early" for logistical or other nonstatistical reasons; enrollment was stopped *per protocol* by the Executive Committee because results at a planned interim analysis met *a priori* efficacy criteria. Our "group sequential" design protected the type I error at 5% and the type II error at 10% for the primary analyses. That said, as is true with any such design that crosses a boundary and thus (legitimately) stops enrollment before the maximum is reached, our CIs would have been somewhat narrower had we continued.

In summary, hyperinsulinemic normoglycemia in patients having cardiac surgery reduced a composite of postoperative morbidity and mortality. Because previous investigations targeting normoglycemia in the absence of exogenous glucose supply found no benefit, targeting normoglycemia while providing exogenous glucose may be preferable to simply normalizing blood glucose concentrations.

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Competing Interests

Dr. Duncan receives funding from Fresenius Kabi (Bad Homburg vor der Höhe, Germany) for research unrelated to the current investigation. Dr. Abd-Elsayed is a consultant for Medtronic (Minneapolis, Minnesota), Halyard (Atlanta, Georgia), Axsome (New York, New York), and SpineLoop (Newport Beach, California), and has shares in Ultimaxx Health (Frisco, Texas). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: duncana@ccf.org. Raw data will be available on a collaborative basis at: duncana@ccf.org.

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Appendix 1: Cleveland Clinic Operating Room Insulin Therapy Protocol

Blood glucose goal: 70 to 150 mg · dl^{-1}. Regular insulin 100 units/100 ml in 0.9% normal saline in a concentration of 1 unit · ml^{-1} will be used.

(1) Starting insulin: Start if pre-cardiopulmonary bypass blood glucose greater than 120, and if on pump or post pump blood glucose greater than 150.
- Bolus dose: 0.03 units · kg^{-1} (maximum bolus is 3 units)
- Initiate continuous infusion: initial rate 0.03 units · kg^{-1} · h^{-1} (maximum initial rate is 3 units · h^{-1})
- See table A1.1 (Insulin Infusion Adjustment) for adjustment of insulin rate.

(2) Blood glucose monitoring: Measure blood glucose between 30 to 60 min during surgery. (This recommendation was changed to 60 to 90 min in 2009).

(3) Hypoglycemia protocol:
- If blood glucose is less than or equal to 60 mg · dl^{-1}: stop insulin infusion, give 25 to 50 ml of 50% dextrose solution, obtain blood glucose level every 30 min until blood glucose is greater than 80 mg · dl^{-1} for three consecutive levels, and then check blood glucose every 30 to 60 min.
- If blood glucose is 60 to 70 mg · dl^{-1}, or 71 to 85 mg · dl^{-1} and decreasing: stop insulin infusion, obtain blood glucose level every 30 min until blood glucose is greater than 85 mg · dl^{-1} for three consecutive measurements, then check blood glucose every hour.

(4) Resuming insulin infusion:
- Restart at half the previous rate when blood glucose rises above 150 mg · dl^{-1}.

Table A1.1. Insulin Infusion Adjustment

Blood Glucose	If Blood Glucose Decreases ≥ 30 mg · dl^{-1} since Last Level	If Blood Glucose Is Stable (Change in Blood Glucose < 30 mg · dl^{-1}) since Last Level	If Blood Glucose Increases ≥ 30 mg · dl^{-1} since Last Level
≤ 60	Stop insulin infusion See Hypoglycemia Protocol	Stop insulin infusion See Hypoglycemia Protocol	–
61–70	Stop insulin infusion See Hypoglycemia Protocol	Stop insulin infusion See Hypoglycemia Protocol	–
71–85	Stop insulin infusion See Hypoglycemia Protocol	Stop insulin infusion	–
86–100	Decrease rate by 50%	Decrease rate by 50%	–
101–115	Decrease rate by 50%	Continue current rate	–
116–150	Decrease rate by 50%	Increase rate by 25%	Increase rate by 25%
151–200	Decrease rate by 25%	Increase rate by 25%	Bolus 2 units Increase rate by 25%
201–250	Continue current rate	Bolus 2 units Increase rate by 25%	Bolus 4 units Increase rate by 25%
251–300	Continue current rate	Bolus 4 units Increase rate by 50%	Bolus 6 units Increase rate by 50%
301–350	Continue current rate	Bolus 6 units Increase rate by 50%	Bolus 8 units Increase rate by 50%
351–400	Continue current rate	Bolus 8 units Increase rate by 50%	Bolus 10 units Increase rate by 50%
> 400	Notify staff anesthesiologist*	Notify staff anesthesiologist*	Notify staff anesthesiologist*

Do not adjust insulin rate every hour—only make adjustments to the insulin rate every 2 h. If insulin rate is ≥ 30 units · h^{-1},
*Notify staff anesthesiologist. Severe hyperglycemia will be treated per anesthesiologist's discretion.

Appendix 2: Hyperinsulinemic Normoglycemia *versus* Conventional Insulin Infusion for Intraoperative Glucose Management in Patients Having Cardiac Surgery: A Randomized Clinical Trial

Table A2.1. Summary of Major Protocol Changes from Original Protocol (July 23, 2006)

Date	Protocol Change	Rationale
07/23/2006	• Original protocol.	
11/19/2007	• Inclusion criteria were broadened. Initial inclusion criteria were changed from patients having mitral valve surgery with coronary artery bypass grafting to all cardiac surgeries requiring cardiopulmonary bypass.	An increase in patient enrollment was needed.
05/07/2008 (delirium) 07/17/2008 (echocardiographic and left atrial tissue analysis) 04/28/2008 and 05/07/2009 (new health survey)	Sub-investigation outcomes, which include postoperative delirium, echocardiographic measurement of left ventricular function, postoperative quality of life measured by a health survey, and analysis of left atrial tissue, were limited to a single center (Cleveland Clinic only) and are thus not reported in this manuscript.	These subinvestigations answered site-specific questions.
05/07/2008	Changed measurement of follow-up of endpoints, including all-cause mortality, from 15 to 30 days to 1 and 3 mo (30 and 90 days).	This change allowed better synchronization and efficiency of data collection with other timepoints. All 15-day outcomes continued to be captured at 30 days.
09/29/2008 (hospital readmission) 01/29/2009 (additional secondary outcomes)	We revised the secondary outcomes including a "composite of minor outcomes" that included prolonged intubation, low cardiac index, renal insufficiency, prolonged hospitalization, and hospital readmission.	This revised secondary outcome captured perioperative data that had a lesser, but still important, impact on postoperative course.
01/29/2009	The following exclusion criteria were added: • Active infection including patients with endocarditis or infected pacemaker leads. • Any infection requiring long-term antibiotics (> 14 days). • Kidney disease requiring renal replacement therapy.	To identify patients who required renal replacement therapy and serious infection, which are components of the primary composite outcome, we excluded patients who required renal replacement therapy or had severe infection at time of enrollment.
01/29/2009	The following primary outcomes were deleted: (1) Low cardiac index. (2) Perioperative myocardial infarction. (3) Prolonged intubation (> 72 h). (4) Anuria (urine output < 0.5 ml · kg^{-1} · $8h^{-1}$).	Changes to the primary outcome were made to improve measures of postoperative recovery. These outcomes were problematic because of the following: (1) Lack of standardized definition for perioperative myocardial infarction. (2) Inadequate documentation of low cardiac index and anuria. (3) Heterogeneity of patients who experience prolonged intubation.
01/29/2009	The following secondary outcomes were removed: dysrhythmias, hyperlactatemia, postoperative troponin I or T, inotropic support.	Secondary outcomes were revised to select more important clinical endpoints.
01/29/2009	The sample size was increased to 2,790 patients, and the number of interim analyses was changed from three to seven.	The sample size estimate was readjusted to power the study for a 30% reduction in risk of complications (previously a 60% reduction).

Appendix 3.

Table A3.1. Primary Outcome: Definitions of the Components of a Composite of Major Postoperative Complications Occurring Within 30 days after Surgery

Major Complications	Requirements for Acceptance
Death within 30 days	All-cause mortality identified during initial hospitalization or during 30 day follow-up.
Postoperative mechanical circulatory support	Failure to wean from cardiopulmonary bypass or postoperative low cardiac index (CI < 1.8 l · min^{-1} · m^{-2}) conditions requiring circulatory support with intra-aortic balloon pump, ventricular assist device, and/or extracorporeal mechanical oxygenation during or post-cardiopulmonary bypass or during postoperative course.
Serious infection morbidity	Postoperative course complicated by one of the following: (1) Sepsis with evidence of acute organ dysfunction. Sepsis is recognized as a clinical syndrome that may be defined by infection highly suspected (clinical syndrome pathognomonic for infection) or proven (by culture, stain, or polymerase chain reaction) and presence of two or more of the following systemic inflammatory response syndrome criteria: heart rate > 90 beats · min^{-1} (tachycardia); body temperature < 36°C or > 38°C (hypothermia or fever); respiratory rate > 20 breaths · min^{-1} or a P_{ACO_2} < 32 mmHg (tachypnea or hypocapnia due to hyperventilation); leukocyte count < 4,000 cells · mm^{-3} or > 12,000 cells · mm^{-3}, or greater than 10% band forms (immature white blood cells; leukopenia, leukocytosis, or bandemia). (2) Mediastinitis (sternal click, open sternal wound, drainage from mediastinal incision, with fever, and including positive cultures along with elevated leukocyte count and the institution of antimicrobial therapy and re-exploration with operative note diagnosing mediastinitis or sternectomy with muscle flap grafts to the affected area or diagnosis by physician of mediastinitis). (3) Sternal wound infection (sternal wound infection other than mediastinitis, documented with positive cultures, requiring surgical intervention). (4) Pneumonia (fever > 38°C, elevation in leukocyte count, increase in sputum production, infiltrate in chest x-ray film > 24 h, positive sputum culture) requiring mechanical ventilation.
Renal morbidity	Postoperative requirement for renal dialysis. Patients with preoperative requirement for dialysis are excluded.
Neurologic deficit	New postoperative focal (aphasia, decrease in limb function, or hemiparesis confirmed by clinical findings and/or computed tomographic scan) or global neurologic deficit (diffuse encephalopathy with greater than 24 h of severely altered mental status, and/or failure to awaken postoperatively).

Table A3.2. Secondary Outcomes

Secondary Outcomes	Requirements for Acceptance
Composite of minor outcomes	The occurrence of one of more of the minor complications listed in table A3.3 occurring within 30 days of surgery.
Postoperative atrial fibrillation	The occurrence of new-onset postoperative atrial fibrillation after cardiac surgery occurring within 30 days of surgery. Patients who had paroxysmal or persistent atrial fibrillation before surgery are excluded.
Duration of hospitalization	Days from day of surgery to hospital discharge.
Duration of intensive care unit stay	Days from day of surgery to discharge from intensive care unit.
All-cause mortality at 1 yr	All-cause mortality identified during 1-yr follow-up.

Table A3.3. Components of the Composite of the Minor Outcomes (a Secondary Outcome)

Minor Component	Definition
Prolonged intubation	Endotracheal intubation and mechanical ventilation required for > 72 h postoperatively, measured from arrival in intensive care unit after surgery until weaning from mechanical ventilation and endotracheal extubation. Additional periods of time when reintubation and mechanical ventilation are required are included.
Low cardiac index	Cardiac index < 1.8 l · min^{-1} · m^{-2} despite adequate fluid replacement and high-dose inotropic support for > 4 h.
Renal insufficiency	Postoperative increase in baseline creatinine > 100%. Baseline creatinine was defined as the preoperative measurement immediately before surgery.
Prolonged hospitalization	Hospitalization after surgery > 30 days.
Hospital readmission	Postoperative complications requiring readmission to a hospital for any reason identified during 30 day follow-up.

Appendix 4.

Table A4.1. Treatment Effect on Secondary Composite Outcome by Site

Site Complications	Hyperinsulinemic Normoglycemia	Standard Therapy	Relative Risk (99.92% CI)*	*P* Value‡
Cleveland Clinic, Cleveland, Ohio	n = 252	n = 266		
Postoperative atrial fibrillation	108 (43)	128 (48)	0.89 (0.64–1.23)	0.23
Duration of hospitalization (days)	7 [5, 12]	7 [5, 11]	0.93 (0.69–1.25)†	0.40
Intensive care unit stay (hours)	41 [27.8, 46.2]	32 [27.7, 5.2]	0.99 (0.74–1.33)†	0.89
1-yr all-cause mortality	18 (7)	8 (3)	2.38 (0.59–9.52)	0.031
Any minor complication§	115 (46)	123 (46)	0.99 (0.72–1.36)	0.89
Royal Victoria Hospital, Montreal, Canada	n = 457	n = 464		
Postoperative atrial fibrillation	101 (22)	107 (23)	0.96 (0.64–1.44)	0.73
Duration of hospitalization (days)	8 [7, 11]	9 [7, 13]	1.13 (0.90–1.42)†	0.066
Intensive care unit stay (hours)	24 [22.8, 24.5]	24 [23.6, 25.0]	1.24 (0.98–1.57)†	0.0026
1-yr all-cause mortality	14 (3)‖	14 (3)#	1.04 (0.30–3.59)	0.92
Any minor complication§	79 (17)	104 (22)	0.77 (0.49–1.21)	0.051

Data are presented as median [25th, 75th percentiles] for length of intensive care unit stay and hospital stay, event (%) for binary outcomes.

*CI adjusted for group sequential design using confidence coefficient of 2.633 for combined sites and 2.86 within sites in order to maintain overall study α of 0.05. †Hazard ratio (not Relative Risk). ‡Chi-square test for binary outcomes, and Cox proportional hazards model for length of intensive care unit stay and hospital stay. Bonferroni correction: significant if $P < 0.0042/5 = 0.00084$ within site. §Included mechanical ventilation greater than 72 h, low cardiac index, acute kidney injury, hospitalization greater than 30 days, all-cause hospital readmission within 30 days. ‖N = 401. #N = 416.