Intensive versus conventional insulin therapy: A randomized controlled trial in medical and surgical critically ill patients*

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Objective: **The role of intensive insulin therapy in medical surgical intensive care patients remains unclear. The objective of this study was to examine the effect of intensive insulin therapy on mortality in medical surgical intensive care unit patients.**

Design: **Randomized controlled trial.**

Settings: **Tertiary care intensive care unit.**

Patients: **Medical surgical intensive care unit patients with admission blood glucose of >6.1 mmol/L or 110 mg/dL.**

Intervention: **A total of 523 patients were randomly assigned to receive intensive insulin therapy (target blood glucose 4.4–6.1 mmol/L or 80–110 mg/dL) or conventional insulin therapy (target blood glucose 10–11.1 mmol/L or 180–200 mg/dL).**

Measurements and Main Outcomes: **The primary end point was intensive care unit mortality. Secondary end points included hospital mortality, intensive care unit and hospital length of stay, mechanical ventilation duration, the need for renal replacement therapy and packed red blood cells transfusion, and the rates of intensive care unit acquired infections as well as the rate of hypoglycemia (defined as blood glucose ≤2.2 mmol/L or 40 mg/dL). There was no significant difference in intensive care unit mortality between the intensive insulin therapy and conventional insulin therapy groups (13.5% vs. 17.1%, $p = 0.30$). After adjustment for baseline characteristics, intensive insulin therapy was not associated with mortality difference (adjusted hazard ratio 1.09, 95% confidence interval 0.70–1.72). Hypoglycemia occurred more frequently with intensive insulin therapy (28.6% vs. 3.1% of patients; $p < 0.0001$ or 6.8/100 treatment days vs. 0.4/100 treatment days; $p < 0.0001$). There was no difference between the intensive insulin therapy and conventional insulin therapy in any of the other secondary end points.**

Conclusions: **Intensive insulin therapy was not associated with improved survival among medical surgical intensive care unit patients and was associated with increased occurrence of hypoglycemia. Based on these results, we do not advocate universal application of intensive insulin therapy in intensive care unit patients.**

Trial Registration: **Current Controlled Trials registry (ISRCTN07413772) http://www.controlled-trials.com/ISRCTN07413772/07413772;2005. (Crit Care Med 2008; 36:3190–3197)**

KEY WORDS: critical care; insulin; mortality; controlled clinical trial; hypoglycemia; nosocomial infection; intensive care

In 2001, Van den Berghe et al. (1) reported that intensive insulin therapy (IIT) in surgical intensive care unit (ICU) patients was associated with reduction in mortality and morbidity. The study, which was stopped early at interim analysis, ignited great interest leading to calls to adopt this therapy as a standard of care for ICU patients (2–4). Caution was raised after a multicenter study of IIT in patients with severe sepsis (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis–VISEP Trial) was stopped because of significant increase in hypoglycemia without improved survival (5). Furthermore, Van den Berghe et al. (6) reported the results on a similar study in medical ICU patients and found no overall mortality reduction with IIT. However, they found that patients with ICU stay of ≥3

***See also p. 3271.**

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Contributions: The PI (YMA) had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. YMA, OCD, AAS, ZAM, MOD were responsible for the conception and design. YMA, OCD, SHH, SJS, HRG, AHR, SHK, RJB, MHS took part in the acquisition of data. YMA, OCD, HMT, AAS, AHR were responsible for analysis and interpretation of data. YMA, OCD, HMT, AAS, SJS, HRG, AHR, SHK were responsible for drafting the manuscript. YMA, OCD, AAS, ZAM, SHH, MOD, RJB, MHS were in charge for the critical revision of the manuscript for important intellectual content. YMA, OCD, HMT were responsible for statistical analysis. YMA, AAS, ZAM, SHK took part in obtaining funding. YMA, AAS, SHH, SJS, SHK, RJB were responsible for administrative, technical, or material support. YMA, OCD, SJS, HRG, SHK, RJB were in charge for the general supervision. All authors have seen and approved of the final text.

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Supplementary Tables 1–3 and Figures 1 and 2 can be viewed online at http://www.ccmjournal.org.

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days had reduced mortality with IIT (6). Because of concerns about trials stopped early for benefit (7), it was suggested that the potential benefits of IIT shown in surgical patients had been inflated (8), thereby causing a premature rush to adopt the therapy (2). It was also suggested that the second trial in medical patients ran a similar risk by overemphasizing *post hoc* results and secondary end points (8). The uncertainty about the impact of IIT on the outcome of critically ill patients, the methodologic concerns in the existing studies (8) in addition to the potential risk of hypoglycemia (9) calls for the need for further studies to confirm the efficacy and safety of this therapeutic modality (10).

The purpose of our study was to examine whether IIT is beneficial in reducing mortality in medical (nonoperative) and surgical (postoperative) ICU patients.

METHODS

Setting. King Abdulaziz Medical City is a tertiary care teaching medical center in Riyadh, Saudi Arabia. The study was conducted in the 21-bed ICU which admits medical, surgical, and trauma patients and is run as a closed unit by onsite coverage 24-hr/7 days of critical care board-certified intensivists. This type of coverage in our ICU has been described elsewhere and has been demonstrated to be associated with consistency of care at all times (11). Our nurse:patient ratio is approximately 1:1.2.

Study Design. The study was conducted as a randomized controlled clinical trial. Patients were eligible for the study if they were ≥18 yrs and had serum glucose level as measured by the laboratory of >6.1 mmol/L (110 mg/dL) during the first 24 hrs of ICU admission. Exclusion criteria included: type I diabetes, diabetic ketoacidosis, documented hypoglycemia on ICU admission or in the same hospitalization, brain death, do-not-resuscitate status, terminal illness defined as expected survival of <4 weeks as judged by the treating physician, postcardiac arrest, seizures within past 6 months, pregnancy, liver transplantation, burn victims, readmission to ICU within the same hospitalization, expected ICU length of stay (LOS) of <24 hrs, inability to obtain consent within the randomization window of 24 hrs of ICU admission, and enrollment in a competing trial. Consecutive patients were checked for eligibility by one of the investigators who was not involved in the allocation process. Informed consent was obtained for eligible patients from the next of kin if the patient could not give consent. Enrolled patients were then referred to the nurse coordinator who performed the randomization to IIT or conventional insulin therapy (CIT) based on computer-generated random permuted blocks of 20 patients each. Stratified randomization was performed for postoperative and nonoperative patients. The study was approved by the Institutional Review Board and was registered at Current Controlled Trials registry (ISRCTN07413772) (12). The trial was conducted between January 2004 and March 2006.

Insulin Protocols. IIT and CIT protocols were designed by a multidisciplinary team that included intensivists, an endocrinologist, a clinical pharmacist, and nurses. The protocols included several safe-guards to reduce the prevalence of hypoglycemia including, reducing or holding insulin infusion, and/or adding intravenous dextrose when glucose levels dropped abruptly, or during discontinuation or intolerance of enteral feeding (see insulin protocol in the supplementary material). Before launching the study, all ICU physicians and nurses attended training sessions, which included mock scenarios about protocols implementation with special emphasis on prevention of hypoglycemia. Follow-up training sessions were conducted periodically to provide feedback. A study committee met frequently at the initial stages of the study and on bimonthly basis thereafter to ensure the correct implementation of the protocols.

In both groups, insulin (250 units of Humulin R, Eli Lilly and Company, Indianapolis, IN) mixed in 250 mL of 0.9% normal saline was infused using a volumetric infusion pump (Baxter Healthcare, Deerfield, IL). Insulin protocols were implemented by the bedside nurses. In the IIT group, insulin infusion was adjusted to maintain a blood glucose level of 4.4 to 6.1 mmol/L (80–110 mg/dL). If the blood glucose levels fell below 4.4 mmol/L (80 mg/dL), insulin infusion was reduced or stopped. In the CIT, insulin infusion was adjusted to maintain a blood glucose level of 10.0–11.1 mmol/L (180–200 mg/dL). If the

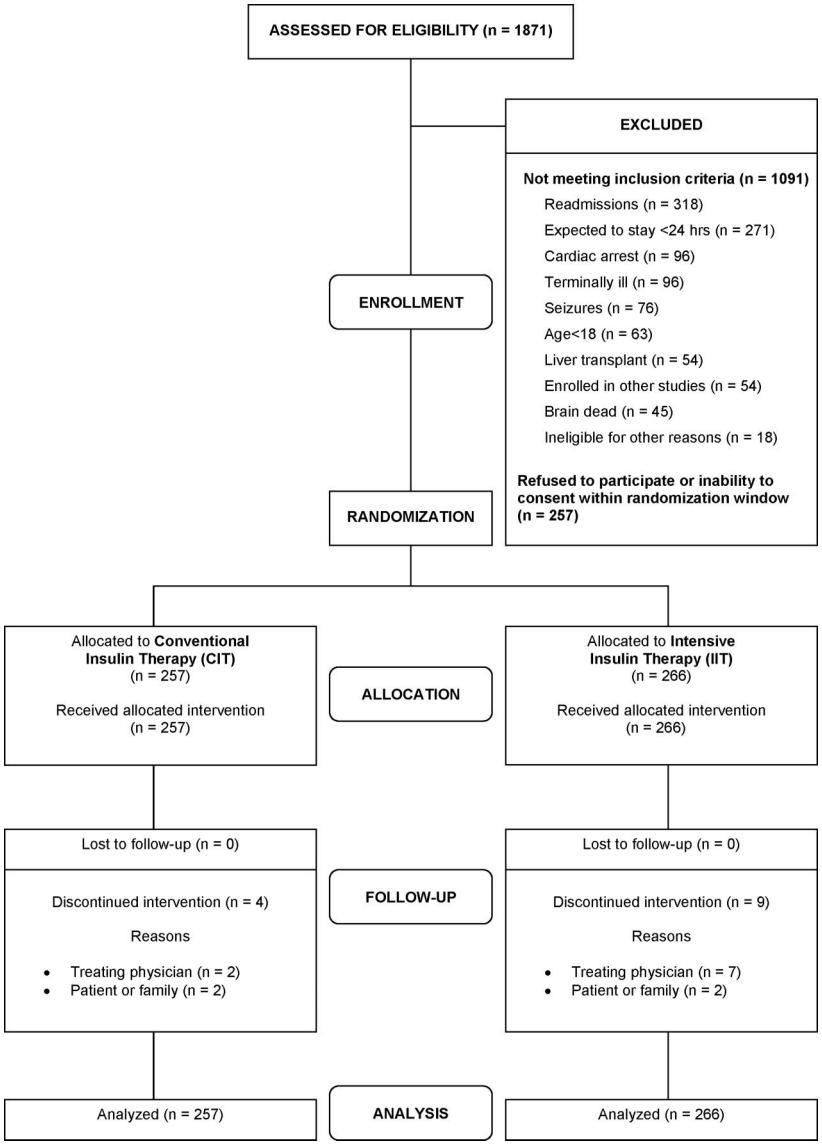

Figure 1. Flowchart of study subjects. All randomized patients were included in the analysis as per intention-to-treat principle.

blood glucose level fell below 10.0 mmol/L (180 mg/dL), insulin was reduced or stopped. Blood glucose was checked hourly using arterial or capillary whole blood samples using a glucose analyzer (Accu-CheckInform meter, Roche, Mannheim, Germany). Frequency of blood glucose monitoring increased to every 20 mins when blood glucose levels decreased to ≤3.2 mmol/L (58 mg/dL) and reduced to every 2–4 hrs when measurements were stable (see protocols in the supplementary material).

Nutrition was prescribed by the treating intensivists after a previously published protocol from our ICU (13), early in the ICU course with enteral feeding being the standard route. Caloric requirement was estimated by a dietitian using the Harris-Benedict equations and adjusting for stress factors (14). Protein requirement was calculated as 0.8–1.5 g/kg based on the patient condition and underlying diseases (14).

Data Collection. Data were collected by the study coordinator using preestablished definitions.

At baseline the following data were recorded: patient's demographics, weight, height, body mass index (BMI), Acute Physiology and Chronic Health Evaluation (APACHE) II score (15), Sequential Organ Failure Assessment (SOFA) score (16), admission category (postoperative vs. nonoperative), history of diabetes, inclusion blood glucose, ICU admission diagnosis and the presence of chronic illnesses using APACHE II definitions (15), vasopressor therapy (defined as the use of any vasopressor infusion except dopamine <5 μg/kg/min), mechanical ventilation, serum creatinine, platelet count, bilirubin, international normalization ratio, partial pressure of oxygen to fraction of inspired oxygen ratio (Pao_2:FIO_2 ratio), and Glasgow Coma Scale (GCS) score. For the latter, we used the worst GCS value for nonsedated patients and the presedation score for patients under sedation as described in the literature (17). We documented the daily average of all blood glucose measurements and daily insulin doses until ICU discharge, death or the declaration of do-not-resuscitate status. We calculated daily total caloric and protein intake for the first 7 days of the study. For caloric intake, we calculated separately calories from enteral and total parentral nutrition and from intravenous dextrose and propofol.

The primary end point was ICU mortality. Secondary end points included causes of death, hospital mortality, ICU LOS, hospital LOS, mechanical ventilation duration (in calendar days), number of hypoglycemic episodes (defined as glucose ≤2.2 mmol/L or 40 mg/dL), and the need for renal replacement therapy or packed red blood cell transfusion. To adjust the number of hypoglycemic episodes to the duration of treatment, we calculated the rate of hypoglycemic episodes per 100 days as the total number of hypoglycemic episodes divided by total ICU LOS for the group (intention to treat duration) multiplied by 100. We also documented the occurrence of ICU-acquired infections defined as those occurring after 48 hrs of ICU admission and until 48 hrs after ICU discharge. Sepsis, severe sepsis, and septic shock were defined according to the 2001 International Sepsis Definitions Conference (18) and types of nosocomial infections were defined according to the National Nosocomial Infections Surveillance System (19).

Statistical Analysis. In the study by Van den Berghe et al. on surgical patients, ICU mortality was reduced from 8% to 4.6% for all patients and from 20.2% to 10.6% in those who stayed >5 days. When compared with the patients in the study by Van den Berghe et al., our patients had higher severity of illness and were more likely to stay >5 days. Using calculations from our ICU database, we estimated ICU mortality of patients meeting the inclusion criteria to be 16%. Based on the study by Van den Berghe et al., we anticipated 50% relative risk reduction or 8% absolute risk reduction. As such, we needed 258 patients in each group to demonstrate a reduction in mortality from 16% to 8% using a two-sided type I error of 5% and power of 80%.

No interim analysis was planned nor was a stopping rule set. The analysis was designed on intention-to-treat principle. Data were entered to a Microsoft Access program and database management and statistical analyses were performed by the Statistical Analysis Software (SAS, Release 8, SAS Institute, Cary, NC, 1999).

Baseline characteristics and outcome variables were compared using *t* test, chi-square, and proportional tests, as appropriate. Adjusted intervention effects were calculated with well-known and clinically relevant baseline characteristics in a time-to-death multivariate stepwise Cox regression model. These factors were checked for the absence of colinearity by calculating variance inflation factors. Missing information was replaced by median values. The results were expressed as adjusted hazard ratios (AHR) and 95% confidence intervals (CI). Additionally, we carried out stratified analyses by selected factors to detect any modification of the association between the intervention and ICU mortality based on any of these risk factors. For stratification, we categorized continuous variables into two groups based on median values. For outcomes presented as rates, such as hypoglycemia, we used Z-approximation to compare IIT with CIT. Statistical significance was defined as p value ≤0.05.

RESULTS

Characteristics of Patients. During the study period, a total of 1871 patients were screened, of whom 523 were enrolled (Fig. 1). Table 1 summarizes the baseline characteristics of the study par-

Table 1. Baseline characteristics of patients who received the intensive insulin therapy and the conventional insulin therapy

	Intensive Insulin Therapy (n = 266)	Conventional Insulin Therapy (n = 257)	*p*
Age, mean ± SD (yrs)	50.6 ± 22.6	54.3 ± 20.5	0.05
Female gender, n (%)	66 (24.8)	66 (25.7)	0.82
BMI, mean ± SD	26.8 ± 6.9	27.9 ± 8.1	0.10
ICU admission category, n (%)			
Postoperative	43 (16.2)	45 (17.5)	0.68
Nonoperative	223 (83.8)	212 (82.5)	
APACHE II, mean ± SD	22.5 ± 7.9	23.1 ± 8.4	0.41
SOFA, mean ± SD	8.7 ± 3.5	8.8 ± 3.5	0.59
History of diabetes, n (%)	85 (32.0)	123 (47.9)	0.0002
Inclusion blood glucose, mean ± SD (mmol/L)[a]	10.8 ± 4.2	11.7 ± 4.5	0.01
Time to randomization, mean ± SD (hrs)	10.1 ± 7.4	8.9 ± 7.6	0.10
Mechanically ventilated, n (%)	228 (85.7)	217 (84.4)	0.68
Vasopressors, n (%)	173 (65)	168 (65.4)	0.90
Sepsis, n (%)	55 (20.7)	67 (26.1)	0.14
Traumatic brain injury, n (%)	55 (20.7)	39 (15.2)	0.10
Creatinine, mean ± SD (μmol/L)[a]	149 ± 144	164 ± 147	0.24
Platelet count, mean ± SD ($\times 10^9$/L)[a]	194 ± 119	207 ± 121	0.20
Bilirubin, mean ± SD, μmol/L	32.7 ± 65.7	29.2 ± 44.3	0.50
INR, mean ± SD	1.6 ± 1.0	1.5 ± 0.8	0.47
Pao_2:FIO_2 ratio, mean ± SD	228 ± 127	216 ± 113	0.28
GCS, mean ± SD	9.2 ± 4.3	9.5 ± 4.2	0.40

BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; INR, international normalized ratio; Pao_2:FIO_2 ratio, the ratio of partial pressure of oxygen to the fraction of inspired oxygen; GCS, Glasgow Coma Scale; ICU, intensive care unit.

[a]To convert to conventional units in mg/dL, divide by 0.0555 for glucose, 88.4 for creatinine, and 17.1 for bilirubin.

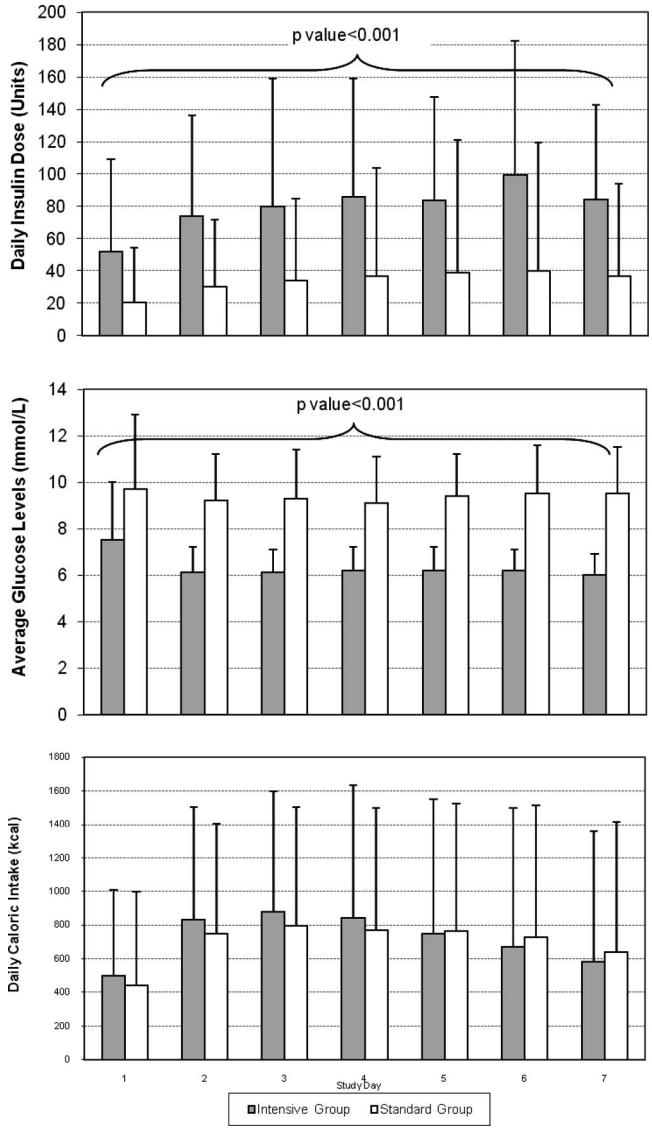

Figure 2. Daily insulin doses, average glucose levels and daily caloric intake from study day 1 to 7 expressed as means and standard deviations. The figure shows that the intensive insulin therapy group had higher insulin doses, lower glucose levels, and similar caloric intake compared with the conventional insulin therapy group.

Table 2. Insulin, glucose, and caloric intake data in patients who received the intensive insulin therapy and conventional insulin therapy

	Intensive Insulin Therapy (n = 266)	Conventional Insulin Therapy (n = 257)	*p*
Received insulin, n (%)	262 (98.5)	193 (75.1)	<0.0001
Average insulin daily dose, mean ± SD, units[a]	71.2 ± 50.2	31.4 ± 42.4	<0.0001
Average glucose levels, mean ± SD (mmol/L)[a,b]	6.4 ± 1.0	9.5 ± 1.9	<0.0001
Average daily caloric intake, mean ± SD (kcal)[c]	916 ± 500	830 ± 509	0.05
Enteral intake, mean ± SD (kcal)[c]	706 ± 557	673 ± 547	0.50
Dextrose intake, mean ± SD (kcal)[c]	159 ± 167	117 ± 128	0.002
Propofol intake, mean ± SD (kcal)[c]	20 ± 50	24 ± 70	0.53
TPN intake, mean ± SD (kcal)[c]	29.9 ± 176.8	15.5 ± 107	0.27
Average daily protein intake, mean ± SD (gram)[c]	29.5 ± 23.2	27.6 ± 23.2	0.35

TPN, total parental nutrition.

[a]Calculated for entire ICU stay; [b]To convert to conventional units in mg/dL, divide by 0.0555 for glucose; [c]Calculated for study day 1 to 7.

ticipants. There was high male:female ratio, primarily because of trauma admissions. Patients in the IIT (n = 266) and the CIT group (n = 257) were similar in most baseline characteristics. However, patients in the IIT group were slightly younger (50.6 ± 22.6 vs. 54.3 ± 20.5), less likely to have diabetes (32.0% vs. 47.9%), and had slightly lower inclusion blood glucose (10.8 ± 4.2 vs. 11.7 ± 4.5 mmol/L).

Intervention. Figure 2 shows the daily doses of insulin, average blood glucose, and caloric intake in both groups. Average daily insulin dose throughout the study period was 71.2 ± 50.2 units in the IIT group and 31.4 ± 42.4 in the CIT group ($p < 0.0001$) with corresponding average glucose levels of 6.4 ± 1.0 mmol/L vs. 9.5 ± 1.9 ($p < 0.0001$). Enteral caloric intake was similar in the two groups. However, caloric intake from intravenous dextrose was higher in the IIT group compared with the CIT group (159 ± 167 vs. 117 ± 128 kcal, $p = 0.002$) leading to higher total caloric intake (916 ± 500 vs. 830 ± 509 kcal, $p = 0.05$). Caloric intake from other sources as well as protein intake was similar (Table 2).

Mortality. There was no significant difference in ICU mortality between the IIT and CIT groups (13.5% vs. 17.1%, $p = 0.3$). After adjustment for baseline characteristics, IIT therapy was also not associated with mortality difference (AHR 1.09, 95% CI 0.70–1.72, $p = 0.70$). Figure 3 shows the Kaplan-Meier survival curves for IIT vs. CIT where no difference is observed (p value 0.65 by Log-rank test).

Table 3 summarizes mortality analyses stratified by baseline characteristics. Two subgroups, (BMI ≤ 26.2 and APACHE II ≤ 22) had lower mortality with IIT compared with CIT (AHR 0.50, 95% CI 0.25–0.99, $p = 0.05$ and 0.22, 95% CI 0.07–0.71, $p = 0.01$, respectively). In one subgroup (GCS ≤ 9), IIT was associated with increased ICU mortality (AHR 1.92, 95% CI 1.04–3.55, $p = 0.04$).

Hypoglycemia and Mortality. IIT was associated with significant increase in hypoglycemia incidence (Table 4). At least one hypoglycemia episode occurred in 28.6% of patients in IIT and 3.1% in CIT group ($p < 0.0001$). When adjusted to the intended duration of therapy, the hypoglycemia rate was 6.8/100 treatment days in IIT vs. 0.4/100 treatment days in CIT group ($p < 0.0001$). Patients with hypoglycemia had higher ICU mortality than those who did not (20/84, 23.8% vs. 60/439, 13.7%, $p = 0.02$). Mortality of pa-

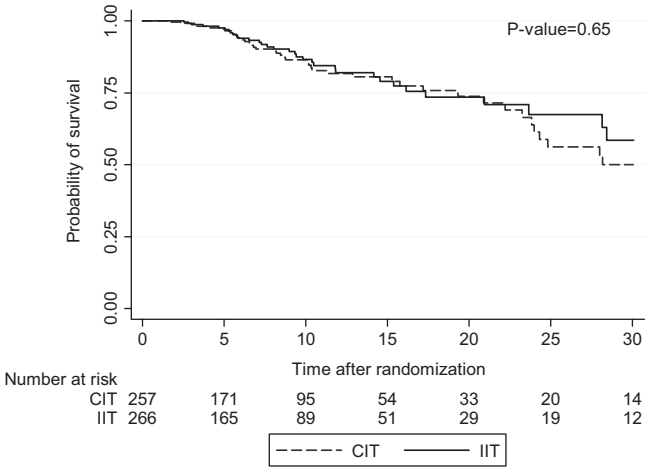

Figure 3. Kaplan-Meier survival curves for intensive insulin therapy (*IIT*) and conventional insulin therapy (*CIT*). No difference in mortality is observed.

tients who developed hypoglycemia was 19/76 (25.0%) in the IIT group compared with 1/8 (12.5%) in the CIT group.

Secondary End Points. There was no difference in causes of death between the two groups (Table 4). Furthermore, there was no difference in hospital mortality, ICU or hospital LOS, mechanical ventilation duration, the need for renal replacement therapy or packed red blood cell transfusion between IIT and CIT groups. Similarly, there was no difference in the rates of ICU-acquired urinary tract infection, catheter-related infection, ventilator-associated pneumonia, tarcheobronchitis or in the overall rate of ICU acquired infections. Nevertheless, there was a trend towards lower episodes of severe sepsis and septic shock in the IIT compared with CIT (20.7% vs. 27.2%, $p = 0.08$).

In the two subgroups in which IIT was associated with reduction in ICU mortality (patients with BMI $\leq$ 26.2 and APACHE II $\leq$ 22) and in the subgroup in which IIT was associated with increased ICU mortality (GCS $\leq$ 9), we found no consistent changes in the secondary end points (causes of death, hospital mortality, ICU LOS, hospital LOS, mechanical ventilation duration, the rate of ICU acquired sepsis, renal replacement therapy, or packed red blood cell transfusion) (Supplemental Tables 1–3).

DISCUSSION

In our study, we found that IIT in general medical surgical ICU patients was not associated with reduction in ICU mortality or any change in the secondary end points. Subgroup analyses showed that IIT was associated with reduction in ICU mortality in patients with BMI $\leq$ 26.2 or APACHE II $\leq$ 22 and increased ICU mortality in patients with GCS $\leq$ 9. However, this did not correspond with consistent changes in secondary end points. IIT was associated with a significant increase in hypoglycemia.

Tight glucose control in critically ill patients became a major therapeutic target after the 2001 study by Van den Berghe et al. indicated a mortality reduction with IIT among patients in a surgical ICU (1). Several concerns were raised about this study because of the relatively high mortality in the control group in relation to the severity of illness, the administration of 200–300 g of intravenous glucose in the first 24 hrs, the routine early use of total parenteral nutrition, and the narrow population predominantly made up of cardiac surgery patients (20, 21). In addition, it has been suggested that the results of randomized controlled trials stopped early for benefit should be viewed with skepticism, because they often show implausibly large treatment effects, particularly when the number of events is small (7). Therefore, it was suggested that the positive impact of IIT in surgical patients might have been exaggerated (8).

Despite these concerns, intensive control of blood glucose became widely accepted and, to some extent, became a benchmark for the quality of ICU care (2). However, the wide generalizability of these results has been questioned. Egi et al. (21) conducted a decision analysis and found that the number needed to treat varied considerably from 35 to as high as 125. These numbers were significantly higher than the number needed to treat to save one life from the original study (29 for all patients and 10 for patients staying $>$ 5 days in the ICU) (21).

Van den Berghe et al. (24) conducted another study to examine the effect of IIT in medical patients. In their study, which included 1200 patients, the intention-to-treat analysis revealed no difference in mortality between the IIT and CIT groups. However, subgroup analyses showed that among the 767 patients who actually remained in the medical ICU for at least 3 days, there was a reduction in mortality. The study was critiqued for several reasons. First, the investigators emphasized the results of *post hoc* and subgroup analyses over the results of the intention-to-treat analysis. In addition, there is no easy way to predict the duration of a patient's stay in the ICU; therefore, it remains unclear which patients should receive IIT as they enter the ICU. Additionally, the mortality of 53% among control patients in the conventional-treatment group seems to be high for the apparent severity of illness (20). Notably, among patients whose stay in the ICU was shorter (i.e., those who were predicted to need but did not actually require 3 days of intensive care), there was an increase in mortality among those receiving IIT (56 deaths out of 209 patients), as compared with those in the CIT group (42 deaths out of 224 patients, $p = 0.046$).

A multicenter study of IIT in patients with severe sepsis (VISEP Trial) intended to randomize 600 patients with severe sepsis and septic shock to IIT vs. CIT was stopped early because of the observed high risk of hypoglycemia with no survival benefit (5). Another recent randomized controlled trial showed that intensive intraoperative IIT during cardiac surgery was not associated with reduction in perioperative morbidity and mortality (22).

Our insulin protocols had the same glucose level targets as both Van den Berghe et al. trials and achieved comparable glucose control leading to similar separation in the glucose levels. Mean glucose levels in our IIT and CIT groups were 6.4 $\pm$ 1.0 vs. 9.5 $\pm$ 1.9 mmol/L, in the trial on surgical patients were 5.7 $\pm$ 1.1 vs. 8.5 $\pm$ 1.8 mmol/L, and in the trial on medical patients were 6.2 $\pm$ 1.6 vs. 8.5 $\pm$ 1.7 mmol/L.

The results of our study are in concordance with Van den Berghe et al. trial in medical patients and with VISEP trial, both demonstrating no survival benefit with IIT. The apparent discrepancy with

Table 3. Intensive care unit (ICU) mortality in the intensive insulin therapy group compared to the conventional insulin therapy group adjusted using multivariate stepwise Cox proportional hazards regression analysis

	Intensive Insulin Therapy (n = 266)	Conventional Insulin Therapy (n = 257)	Adjusted Hazard Ratio[a]	95% Confidence Interval	*p*
ICU mortality, n (%)	36(13.5)	44 (17.1)	1.09[b]	(0.70–1.72)	0.70
Stratified by					
Age					
≤58	12/144 (8.3%)	17/119 (14.3%)	0.86	(0.40–1.88)	0.71
>58	24/122 (19.7%)	27/138 (19.6%)	1.27	(0.72–2.26)	0.41
Gender					
Male	23/200 (11.5%)	31/191 (16.2%)	0.79	(0.45–1.40)	0.42
Female	13/66 (19.7%)	13/66 (19.7%)	1.73	(0.75–3.96)	0.20
BMI					
≤26.2	17/142 (12.0%)	24/123 (19.5%)	0.50	(0.25–0.99)	0.05
>26.2	19/124 (15.3%)	20/134 (14.9%)	1.46	(0.74–2.87)	0.28
Admission category					
Postoperative	3/43 (7.0%)	5/45 (11.1%)	1.07	(0.67–1.72)	0.78
Nonoperative	33/223 (14.8%)	39/212 (18.4%)	0.50	(0.09–2.91)	0.44
APACHE II					
≤22	6/140 (4.3%)	14/131 (10.7%)	0.22	(0.07–0.71)	0.01
>22	30/126 (23.8%)	30/126 (23.8%)	1.54	(0.90–2.64)	0.11
SOFA					
≤9	14/161 (8.7%)	16/144 (11.1%)	0.81	(0.37–1.79)	0.61
>9	22/105 (21.0%)	28/113 (24.8%)	1.01	(0.56–1.80)	0.98
History of diabetes					
Yes	11/85 (12.9%)	25/123 (20.3%)	0.68	(0.33–1.43)	0.31
No	25/181 (13.8%)	19/134 (14.2%)	1.51	(0.82–2.79)	0.19
Inclusion blood glucose[c]					
≤10 mmol/L	13/148 (8.8%)	16/117 (13.7%)	0.60	(0.27–1.31)	0.20
>10 mmol/L	23/118 (19.5%)	28/140 (20.0%)	0.93	(0.53–1.64)	0.80
Time to randomization					
≤9	21/132 (15.9%)	21/144 (14.6%)	1.34	(0.73–2.48)	0.35
>9	15/134 (11.2%)	23/113 (20.4%)	0.85	(0.42–1.70)	0.64
Vasopressor therapy					
Yes	29/173 (16.8%)	30/168 (17.9%)	1.10	(0.64–1.87)	0.74
No	7/93 (7.5%)	14/89 (15.7%)	0.79	(0.30–2.11)	0.64
Sepsis					
Yes	18/55 (32.7%)	15/67 (22.4%)	1.57	(0.75–3.28)	0.24
No	18/211 (8.5%)	29/190 (15.3%)	0.88	(0.47–1.63)	0.68
Traumatic brain injury					
Yes	2/55 (3.6%)	1/39 (2.6%)	1.58	(0.14–17.40)	0.71
No	34/211 (16.1%)	43/218 (19.7%)	1.13	(0.71–1.80)	0.61
Creatinine[c]					
≤100 μmol/L	13/144 (9.0%)	11/119 (9.2%)	1.14	(0.48–2.71)	0.76
>100 μmol/L	23/122 (18.9%)	33/138 (23.9%)	1.13	(0.64–1.99)	0.68
Platelets					
≤181	23/141(16.3%)	29/122 (23.8%)	0.89	(0.50–1.56)	0.67
>181	13/125 (10.4%)	15/135 (11.1%)	1.02	(0.48–2.16)	0.97
Bilirubin[c]					
≤16 μmol/L	15/133 (11.3%)	20/145 (13.8%)	1.14	(0.57–2.27)	0.72
>16 μmol/L	21/133 (15.8%)	24/112 (21.4%)	1.10	(0.59–2.05)	0.77
INR					
≤1.2	13/131 (9.9%)	16/132 (12.1%)	1.36	(0.63–2.93)	0.43
>1.2	23/135 (17.0%)	28/125 (22.4%)	1.03	(0.57–1.87)	0.92
Pa_{O_2}:F_{IO_2}					
≤194	24/129 (18.6%)	27/133 (20.3%)	1.23	(0.68–2.22)	0.50
>194	12/137 (8.8%)	17/124 (13.7%)	0.91	(0.36–2.30)	0.84
GCS					
≤9	23/149 (15.4%)	25/143 (17.5%)	1.92	(1.04–3.55)	0.04
>9	13/117 (11.1%)	19/114 (16.7%)	0.60	(0.28–1.29)	0.19
Caloric intake					
≤875 kcal/day	15/132 (11.4%)	22/127(17.3%)	0.59	(0.29–1.21)	0.15
>875 kcal/day	21/134 (15.7%)	22/130 (16.9%)	1.54	(0.79–2.98)	0.20
Length of stay					
≤5 days	6/102 (5.9%)	6/86 (7.0%)	0.18	(0.03–1.24)	0.08
>5 days	30/164 (18.3%)	38/171 (22.2%)	1.02	(0.62–1.67)	0.94
Mechanical ventilation					
Yes	33/228 (14.5%)	38/217 (17.5%)	1.33	(0.82–2.16)	0.25
No	3/38 (7.9%)	6/40 (15.0%)	0.30	(0.06–1.52)	0.15

BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; INR, international normalized ratio; Pa_{O_2}:F_{IO_2} ratio, the ratio of partial pressure of oxygen to the fraction of inspired oxygen; GCS, Glasgow Coma Scale.

[a]Variables entered initially in the stepwise regression model included: age, gender, body mass index (BMI), admission category (nonoperative vs. postoperative), APACHE II, SOFA, history of diabetes, inclusion blood glucose, time to randomization, vasopressor use, mechanical ventilation, sepsis, traumatic brain injury, creatinine, chronic respiratory disease, chronic cardiac disease, chronic renal disease, chronic liver disease, immunosuppression, Pa_{O_2}:F_{IO_2} ratio, platelet count, bilirubin, GCS, and INR; [b]The variables retained in the final model: chronic liver disease, traumatic brain injury, APACHE II, and INR; [c]To convert to conventional units in mg/dL, divide by 0.0555 for glucose, 88.4 for creatinine, and 17.1 for bilirubin.

Table 4. Secondary end points in the intensive insulin therapy and conventional insulin therapy groups

	Intensive Insulin Therapy (n = 266)	Conventional Insulin Therapy (n = 257)	*p*
Causes of death			
Multiorgan failure, n (%)	27 (10.2)	29 (11.3)	0.68
Brain death, n (%)	6 (2.3)	8 (3.1)	0.54
Other causes, n (%)	3 (1.1)	7 (2.7)	0.22
Hospital mortality, n (%)	72 (27.1)	83 (32.3)	0.19
ICU LOS, mean ± SD (days)	9.6 ± 8.5	10.8 ± 11.3	0.18
Hospital LOS, mean ± SD (days)	54.1 ± 84.1	57.5 ± 77.1	0.63
Hypoglycemia			
Patients, n (%)	76 (28.6%)	8 (3.1%)	<0.0001
Rate of hypoglycemias/100 treatment days	6.8	0.4	<0.0001
ICU-acquired infections			
Urinary tract infection/1000 Foley catheter days	6	6	0.98
Catheter-related infection/1000 central line days	4	4	0.81
Ventilator-associated pneumonia/1000 ventilator days	25	23	0.61
Tracheobronchitis/1000 ventilator days	11	14	0.39
Any ICU-acquired infections/1000 ICU days	56	59	0.69
ICU acquired sepsis			
All sepsis episodes, n (%)	98 (36.9)	105 (40.9)	0.35
Severe sepsis/septic shock, n (%)	55 (20.7)	70 (27.2)	0.08
Mechanical ventilation duration, mean ± SD (days)	8.3 ± 7.9	9.7 ± 11.0	0.11
PRBC transfusion, mean ± SD, units	1.5 ± 3.2	1.8 ± 3.5	0.30
New renal replacement therapy, n (%)	31 (11.7)	31 (12.1)	0.89

ICU, intensive care unit; LOS, length of stay; PRBC, packed red blood cell.

results of the study on surgical patients can be related to several factors. First, as indicated before, the positive effects of IIT in the trial on surgical patients might have been related to methodologic reasons and not a reflection of true effect. Second, differences in patient population might be associated with different responses to IIT. The majority of patients in Van den Berge et al. surgical study were recovering from cardiac surgery; a group that has been shown to have reduction in mortality with IIT (23). In our study, we found no differences in the effect of IIT in postoperative (surgical) patients and nonoperative (medical) patients suggesting that admission category is not *per se* a modifier of IIT effect. Third, severity of illness might be a modifier of the IIT effect. Positive effect of IIT was noted in Van den Berghe et al. trial on surgical patients who had relatively low APACHE II scores (median of 9) but not in the trial on medical patients who had higher APACHE II scores (mean of 23). In our study, we found reduction in ICU mortality in patients with APACHE II of ≤ 22, but not in those with higher APACHE II. However, this was not associated with change in any of the secondary end points including hospital mortality, suggesting that this finding might be related to multiple testing. Finally, Van den Berghe et al. found in their combined analyses of the medical and surgical cohorts that the subgroup with a previous diagnosis of diabetes did not benefit from IIT (24). One may question whether the absence of benefit of IIT in our study was related to the larger proportion of diabetic patients compared with those of Van den Berghe et al. (40% vs. 15%). However, stratified analyses did not show benefit of IIT in either diabetics or nondiabetics.

One finding of concern is the apparent increase in ICU mortality in the subgroup of patients with GCS ≤ 9 (AHR 1.92, 95% CI 1.04–3.55, $p = 0.04$). It is important to keep this finding in the context of being a result of *post hoc* subgroup analyses and that there were no corresponding changes in the secondary end points. It is possible that this finding is related to multiple testing. However, we cannot exclude potential harmful effect of IIT in this subgroup. Hyperglycemia has been shown to be detrimental to patients with neurologic dysfunction (25, 26), but whether intensive control of blood glucose in such patients is beneficial is yet to be clarified. In a *post hoc* analysis of 63 neurologic patients, Van den Berghe et al. found that IIT reduced ventilation dependency, intracranial pressure, seizures, and diabetes insipidus, but did not affect mortality (27). It is important to note that the sample size of our subgroup is significantly larger (n = 292). Therefore, it may be prudent to call for caution in using IIT in this group of patients until there is further conclusive evidence.

Reported incidence of hypoglycemia with IIT varied considerably. In a study by Van den Berghe et al. on surgical patients, hypoglycemia occurred in 5% of IIT patients vs. 1% of CIT patients. In the trial on medical patients, the rates of hypoglycemia were 19% in IIT patients vs. 3% in CIT patients. In the VISEP study, the rates were 17.0% in IIT vs. 4.1% in CIT (5). In our study, the rate of hypoglycemia was 28.6% of IIT patients vs. 3.1% in the CIT patients. These differences might be related, in part, to how rates were reported as percentage of patients without considering the duration of treatment. For example, the low rates in the first trial were also associated with short ICU stay (median 3 days). This contrasts with LOS in our study (10 days). When adjusted to the intention-to-treat duration, the rates were 6.8/100 treatment days vs. 0.4/100 treatment days.

Patients in the IIT group received slightly higher caloric intake from intravenous dextrose, most likely because of present or feared hypoglycemia. Caloric intake from enteral feeding or other sources was not different. To evaluate for the potential impact of intravenous dextrose on outcome, we conducted stratified analysis according to caloric intake (Table 3) and found no significant impact of IIT on mortality in patients grouped by caloric intake. Nevertheless, this unusual pattern of increased intravenous dextrose administration in our patients further questions the intensive insulin intervention.

Our results should be viewed in light of the study's strengths and limitations. Strengths of our study include the randomized controlled trial design and the intention-to-treat analysis. In addition, the protocols were designed to include several safeguards against hypoglycemia and followed by mandatory in-services to all medical and nursing ICU staff in addition to bedside training. We believe the performance was the best that could be achieved in real-life ICU. Other aspects of ICU care were homogeneous as our unit is run as a closed model, has a high nursing staffing ratio, and run 24 hrs a day/7 days a week by on-site critical care board certified intensivists. On the other hand, our study has several limitations. These include the unblinded design due to the nature of the intervention. It was a mono-center trial, but so was the case for

the existing studies supporting IIT. Our study did not have the power to detect small differences in mortality; however, our sample size had adequate power to detect 8% absolute risk reduction. Furthermore, our sample size and power calculation are comparable with other published studies (5). Another limitation was the difference in the baseline characteristics (namely age, inclusion blood glucose, and history of diabetes). More diabetic patients were in the CIT group, which might explain slightly older age and higher inclusion blood glucose. However, we adjusted for these differences using two methods: stratification and multivariate analyses. In both methods, we found that these variables did not modify the effect of IIT; therefore, these imbalances did not influence the final outcomes.

The lack of mortality benefit demonstrated in our study in addition to the increase in occurrence of hypoglycemia calls for caution in using IIT indiscriminately in medical-surgical ICU patients. Final results from two other larger multicenter trials, the NICE-SUGAR study and GLUControl (28), are awaited. These trials will further add to our knowledge about glycemic control in critically ill patients.

CONCLUSIONS

IIT was not associated with improved survival among medical surgical patients, but was associated with an increase in the occurrence of hypoglycemia. Based on these results, we do not advocate universal application of IIT in ICU patients.

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Supplementary Table 1. Secondary end points in intensive insulin therapy and conventional insulin therapy in the subgroup of body mass index ≤ 26.2

	Intensive Insulin Therapy (n = 142)	Conventional Insulin Therapy (n = 123)	*p*
Cause of death			
Multi-organ failure, n (%)	13 (9.2)	14 (11.4)	0.60
Brain death, n (%)	1 (0.7)	4 (3.3)	0.19
Other causes, n (%)	3 (2.1)	6 (4.9)	0.31
Hospital mortality, n (%)	38 (26.8)	46 (37.4)	0.06
ICU LOS, mean ± SD, days	9.8 ± 9.0	9.7 ± 7.8	0.90
Hospital LOS, mean ± SD, days	48.7 ± 62.8	50.4 ± 65.6	0.83
ICU acquired sepsis			
All sepsis episodes, n (%)	53 (37.3)	45 (36.6)	0.90
Severe sepsis/septic shock, n (%)	25 (17.6)	29 (23.6)	0.23
Mechanical ventilation duration, mean ± SD, days	8.3 ± 8.3	9.2 ± 7.9	0.38
PRBC transfusion, mean ± SD, units	1.6 ± 4.4	1.8 ± 3.4	0.76
New renal replacement therapy, n (%)	14 (9.9)	15 (12.2)	0.54

ICU, intensive care unit; LOS, length of stay; PRBC, packed red blood cell.

Supplementary Table 2. Secondary end points in intensive insulin therapy and conventional insulin therapy in the subgroup of Acute Physiology and Chronic Health Evaluation ≤ 22

	Intensive Insulin Therapy (n = 140)	Conventional Insulin Therapy (n = 131)	*p*
Cause of death			
Multi-organ failure, n (%)	4 (2.9)	6 (4.6)	0.53
Brain death, n (%)	2 (1.4)	4 (3.1)	0.43
Other causes, n (%)	0 (0)	4 (3.1)	0.03
Hospital mortality, n (%)	14 (10.0)	21 (16.0)	0.14
ICU LOS, mean ± SD, days	8.9 ± 7.7	9.1 ± 9.7	0.81
Hospital LOS, mean ± SD, days	51.5 ± 76.2	51.7 ± 78.9	0.98
ICU acquired sepsis			
All sepsis episodes, n (%)	51 (36.4)	49 (37.4)	0.87
Severe sepsis/septic shock, n (%)	25 (17.9)	27 (20.6)	0.57
Mechanical ventilation duration, mean ± SD, days	7.3 ± 6.9	8.0 ± 9.9	0.53
PRBC transfusion, mean ± SD, units	1.2 ± 4.2	1.3 ± 3.3	0.82
New renal replacement therapy, n (%)	8 (5.7)	7 (5.3)	0.89

ICU, intensive care unit; LOS, length of stay; PRBC, packed red blood cell.

Supplementary Table 3. Secondary end points in intensive insulin therapy and conventional insulin therapy in the subgroup of Glasgow Coma Scale ≤ 9

	Intensive Insulin Therapy (n = 149)	Conventional Insulin Therapy (n = 143)	*p*
Cause of death			
Multi-organ failure, n (%)	15 (10.1)	13 (9.1)	0.78
Brain death, n (%)	5 (3.4)	8 (5.6)	0.35
Other causes, n (%)	3 (2.0)	4 (2.8)	0.72
Hospital mortality, n (%)	43 (28.9)	51 (35.7)	0.21
ICU LOS, mean ± SD, days	9.9 ± 7.5	12.3 ± 9.4	0.02
Hospital LOS, mean ± SD, days	57.0 ± 77.1	66.5 ± 83.0	0.30
ICU acquired sepsis			
All sepsis episodes, n (%)	67 (45.0)	72 (50.4)	0.36
Severe sepsis/septic shock, n (%)	32 (21.5)	47 (32.9)	0.03
Mechanical ventilation duration, mean ± SD, days	9.3 ± 7.2	11.7 ± 9.5	0.01
PRBC transfusion, mean ± SD, units	1.1 ± 1.9	1.6 ± 3.1	0.09
New renal replacement therapy, n (%)	13 (8.7)	17 (11.9)	0.37

ICU, intensive care unit; LOS, length of stay; PRBC, packed red blood cell.

King Fahad National Guard Hospital
National Guard – Health Affairs
King Abdulaziz Medical City

Intensive Care Department

Regular Insulin Intravenous Infusion Scale
INTENSIVE GROUP

Blood Glucose Goal	4.4 – 6.1 mmol/L
Insulin start if BG	>6.1 mmol/L

0.5 μ/h if BG	6.2 – 8.0 mmol/L
1 μ/h if BG	8.1 – 10.0 mmol/L
2 μ/h if BG	10.1 – 12.0 mmol/L
3 μ/h if BG	>12.0 mmol/L

* No change if BG	4.4 – 6.1 mmol/L
* ↑ **Insulin by:**	
0.5 μ/h if BG	6.2 – 8 mmol/L
1 μ/h if BG	8.1 – 10 mmol/L
2 μ/h if BG	>10 mmol/L
* ↓ **Insulin by:**	
1 μ/h if BG	3.9 – 4.3 mmol/L
2 μ/h if BG	3.3 – 3.8 mmol/L

Stop insulin, give 25 ml of D50%, notify MD and check blood glucose after 20 minutes and 40 minutes. After 2 hours, if BG >6.1, restart at ½ previous rate and recheck BG in 1 hour.	2.2 – 3.2 mmol/L
*** Stop insulin, give 50 ml of D50%, notify MD and check blood glucose after 20 minutes and 40 minutes. After 2 hours, if BG >6.1, restart at ½ previous rate and recheck BG in 1 hour.**	<2.2 mmol/L
*** If BG decreased by 50% or more or by 4mmol or more within 2 hours ↓ insulin dose by 50% and notify MD**	↓ 50%

* Blood glucose should be measured immediately in any sedated patient with unexplained tachycardia, tachypnea, or hypotension.
* Check blood glucose every hour after doing any change in insulin infusion or nutrition (Enteral/Parenteral).
* Check blood glucose every 2 hours if blood glucose has been at goal (4.4-6.1) x 4 hours and the patient is at a steady state regarding feeding.
* Check blood glucose every 4 hours if the patient did not require insulin for 4 hours.
* In case of holding enteral feeding (vomiting or for procedures), ↓ insulin drip by 50% and start the patient on D10W at 50 ml/hr unless otherwise specified by the physician.
* Notify Physician:
  1. For blood glucose > 20mmol/L
  2. For hypoglycemia which has not resolved within 20minutes of administering 50ml of D50W and discontinuing insulin drip.

PHYSICIAN'S SIGNATURE **DATE / TIME**

Supplemental Figure 1. Intensive insulin therapy protocol. *BG,* blood glucose; *MD,* physician.

King Fahad National Guard Hospital
National Guard – Health Affairs
King Abdulaziz Medical City

Intensive Care Department

Regular Insulin Intravenous Infusion Scale
CONVENTIONAL GROUP

Blood Glucose Goal	10.0 – 11.1 mmol/L
Insulin start if BG	>11.2 mmol/L

Starting Insulin Dose @ (Only at the first time of starting insulin)	
1 μ/h if BG	11.2 – 14.0 mmol/L
2 μ/h if BG	14.1 – 16.0 mmol/L
3 μ/h if BG	16.1 – 18.0 mmol/L
4 μ/h if BG	>18.0 mmol/L

Dose adjustment after initial start:	
* No change if BG	10.0 – 11.1 mmol/L
* **↑ Insulin by:**	
0.5 μ/h if BG	11.2 – 12.0 mmol/L
1 μ/h if BG	12.1 – 15.0 mmol/L
2 μ/h if BG	>15.1 mmol/L
* **↓ Insulin by:**	
1 μ/h if BG	8.0 – 9.9 mmol/L
2 μ/h if BG	6.0 – 7.9 mmol/L

* Stop insulin if BG	3.3 – 5.9 mmol/L
Stop insulin, give 25 ml of D50%, notify MD & check blood glucose in 20 minutes and 40 minutes. After 2 hours, if BG > 11.2, restart at ½ previous rate, recheck BG in 1 hour.	2.2 – 3.2 mmol/L
Stop insulin, give 50 ml of D50%, notify MD & check blood glucose in 20 minutes and 40 minutes. After 2 hours, if BG > 11.2, restart at ½ previous rate, recheck BG in 1 hour.	<2.2 mmol/L
* If BG decreased by 50% or more or by 4mmoL or more within 2 hours ↓ insulin dose by 50% and notify MD	↓ 50%

* Blood glucose should be measured immediately in any sedated patient with unexplained tachycardia, tachypnea, hypotension, sweating or seizures.
* Check blood glucose every hour after doing any change in insulin infusion or nutrition (Enteral/Parenteral).
* Check blood glucose every 2 hours if blood glucose has been at goal (10-11.1) x 4 hours and the patient at a steady state in terms of his enteral feeding.
* Check blood glucose every 4 hours if the patient did not require insulin for 4 hours.
* In case of holding enteral feeding (vomiting or for procedures), ↓ insulin drip by 50% and start the patient on D10W at 50 ml/hr unless otherwise specified by the physician.
* Notify Physician:
  1. For blood glucose > 20mmol/L
  2. For hypoglycemia which has not resolved within 20minutes of administering 50ml of D50W and discontinuing insulin drip.

PHYSICIAN'S SIGNATURE **DATE / TIME**

Supplemental Figure 2. Conventional insulin protocol. *BG,* blood glucose; *MD,* physician.