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Intensive Insulin Therapy in the Medical ICU

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ABSTRACT

BACKGROUND

Intensive insulin therapy reduces morbidity and mortality in patients in surgical intensive care units (ICUs), but its role in patients in medical ICUs is unknown.

METHODS

In a prospective, randomized, controlled study of adult patients admitted to our medical ICU, we studied patients who were considered to need intensive care for at least three days. On admission, patients were randomly assigned to strict normalization of blood glucose levels (80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]) with the use of insulin infusion or to conventional therapy (insulin administered when the blood glucose level exceeded 215 mg per deciliter [12 mmol per liter], with the infusion tapered when the level fell below 180 mg per deciliter [10 mmol per liter]). There was a history of diabetes in 16.9 percent of the patients.

RESULTS

In the intention-to-treat analysis of 1200 patients, intensive insulin therapy reduced blood glucose levels but did not significantly reduce in-hospital mortality (40.0 percent in the conventional-treatment group vs. 37.3 percent in the intensive-treatment group, $P=0.33$). However, morbidity was significantly reduced by the prevention of newly acquired kidney injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital. Although length of stay in the ICU could not be predicted on admission, among 433 patients who stayed in the ICU for less than three days, mortality was greater among those receiving intensive insulin therapy. In contrast, among 767 patients who stayed in the ICU for three or more days, in-hospital mortality in the 386 who received intensive insulin therapy was reduced from 52.5 to 43.0 percent ($P=0.009$) and morbidity was also reduced.

CONCLUSIONS

Intensive insulin therapy significantly reduced morbidity but not mortality among all patients in the medical ICU. Although the risk of subsequent death and disease was reduced in patients treated for three or more days, these patients could not be identified before therapy. Further studies are needed to confirm these preliminary data. (ClinicalTrials.gov number, NCT00115479.)

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HYPERGLYCEMIA AND INSULIN RESISTANCE are common in severe illness and are associated with adverse outcomes.¹⁻⁴ In a previous randomized, controlled study conducted in a surgical intensive care unit (ICU), strict control of blood glucose levels with insulin reduced morbidity and mortality,^{5,6} significantly reducing in-hospital mortality from 11 to 7 percent in the entire study population. In a subgroup of patients who stayed in the ICU for three or more days, however, the benefit was much more pronounced, reducing mortality from 21 to 14 percent among patients treated for at least three days and from 26 to 17 percent among those treated for at least five days. Complications, such as severe infections and organ failure, were reduced. Several potential mechanisms may explain these benefits — prevention of immune dysfunction,⁷ reduction of systemic inflammation,⁸ and protection of the endothelium^{9,10} and of mitochondrial ultrastructure and function.¹¹

It remains unclear whether intensive insulin therapy also improves the prognosis of patients in a medical ICU, who often are more severely ill than are patients in a surgical ICU and have a higher risk of death.^{4,12,13} The study in a surgical ICU,⁵ two studies of patients with diabetes with acute myocardial infarction,^{14,15} and observations in patients with diabetes undergoing coronary-bypass surgery¹⁶ suggested that insulin-titrated blood glucose control should be continued for at least a few days to achieve a detectable outcome benefit. We therefore conducted a randomized, controlled study of patients in a medical ICU, targeting those requiring intensive care for at least a third day.

METHODS

Adult patients admitted to the medical ICU who were assumed to require at least a third day of intensive care were eligible for inclusion. We excluded surgical ICU patients and medical patients able to receive oral nutrition, because such patients usually need less than three days of intensive care, and patients with do-not-resuscitate orders on admission (Fig. 1). Written informed consent was obtained from the closest family member, because patients were unable to give consent. The protocol and consent forms were approved by the institutional review board of the university. The study was carried out between March 2002 and May 2005.

STUDY DESIGN

On admission to the ICU, patients were randomly assigned to receive either intensive insulin treatment (intensive-treatment group) or conventional insulin treatment (conventional-treatment group). Treatment assignment was performed with the use of sealed envelopes, stratified according to diagnostic category (Table 1), and balanced with the use of permuted blocks of 10. In the conventional-treatment group, continuous insulin infusion (50 IU of Actrapid HM [Novo Nordisk]) in 50 ml of 0.9 percent sodium chloride) with the use of a pump (Perfusor-FM pump, B. Braun), was started only when the blood glucose level exceeded 215 mg per deciliter (12 mmol per liter) and was adjusted to maintain a blood glucose level of between 180 and 200 mg per deciliter (10 and 11 mmol per liter). When the blood glucose level fell below 180 mg per deciliter, the insulin infusion was tapered and eventually stopped.

In the intensive-treatment group, insulin infusion was started when the blood glucose level exceeded 110 mg per deciliter (6.1 mmol per liter) and was adjusted to maintain normoglycemia (80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]). The maximal continuous intravenous insulin infusion was arbitrarily set at 50 IU per hour. At the patient's discharge from intensive care, a conventional approach was adopted (maintenance of blood glucose at 200 mg per deciliter or less).

The dose of insulin was adjusted according to whole-blood glucose levels, measured at one-to-four-hour intervals in arterial blood or, when an arterial catheter was not available, in capillary blood, with the use of a point-of-care glucometer (HemoCue B-glucose analyzer, HemoCue). Adjustments were made by the nurses in the ICU; the usual number of nurses (2.5 full-time-equivalent nurses per bed in the ICU) was not changed for the study. The nurses used titration guidelines that were adapted from the study in the surgical ICU.⁵

When patients were hemodynamically stable, enteral feeding was started according to routine guidelines. The guidelines aimed at a total of 22 to 30 kcal per kilogram of body weight per 24 hours with balanced composition (0.08 to 0.25 g of nitrogen per kilogram of body weight per 24 hours and 20 to 40 percent of nonprotein kilocalories as lipids).¹⁷ Enteral feeding was attempted as early as possible.

DATA COLLECTION

At baseline, data on demographic and clinical characteristics of the patients were obtained, including information necessary to determine the severity of illness and the use of intensive care resources (Table 1). These data were scored according to the Acute Physiology and Chronic Health Evaluation (APACHE II)¹⁸ system and simplified Therapeutic Intervention Scoring System-28 (TISS-28),^{19,20} with higher values indicating more severe illness and more therapeutic interventions, respectively.

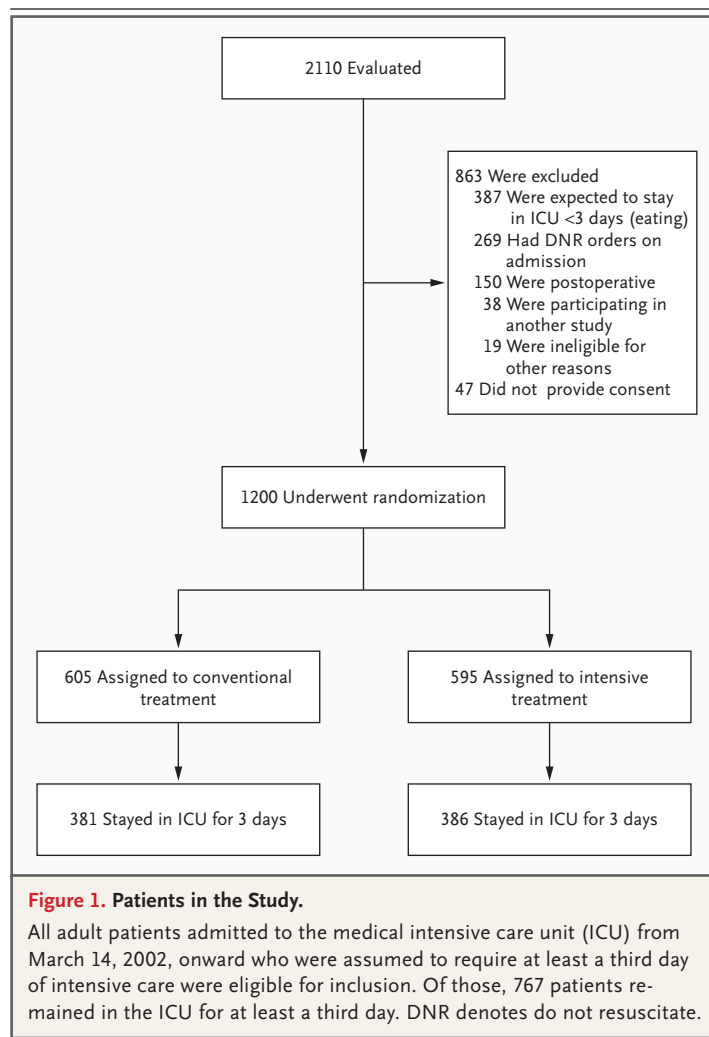
Blood was systematically sampled and blood glucose levels were measured on admission and subsequently every four hours in all patients. More frequent blood glucose measurements were performed whenever the attending nurse considered them necessary and whenever there had been a steep rise or fall in the blood glucose level on the previous reading. Blood glucose levels that were measured on admission and daily in the morning during the study, and hypoglycemic events (defined as blood glucose levels of ≤ 40 mg per deciliter [2.2 mmol per liter]) were analyzed.

According to clinical guidelines, blood cultures were obtained whenever the central body temperature exceeded 38.5°C or when other clinical signs of sepsis were present.^{21,22} Results were interpreted by an investigator blinded to the treatment assignment. An episode of bacteremia was defined by the first positive culture in a series. To identify bacteremia with coagulase-negative staphylococci, identical strains (compared by antibiogram) in two or more positive blood cultures were required.^{21,22} A distinction was made between primary and secondary bacteremia, depending on whether or not a focus could be identified.

The clinical cause of a death in the ICU was determined by a senior physician blinded to the treatment assignments. The causes of deaths occurring after discharge from the ICU could not be identified.

OUTCOME MEASURES

The primary outcome measure was death from any cause in the hospital. Secondary, predefined outcome measures were mortality in the ICU, 90-day mortality, days to weaning from mechanical ventilation, days in the ICU and in the hospital, the initiation of dialysis, new kidney injury during intensive care (defined as either a level of serum



creatinine twice that present on admission to the ICU²³ or a peak level of serum creatinine of >2.5 mg per deciliter [220 μ mol per liter]), days of inotropic or vasopressor support, presence or absence of hyperinflammation (defined as a C-reactive protein level of >150 mg per deciliter), presence or absence of bacteremia, prolonged (i.e., more than 10 days) use of antibiotics, and the presence or absence of hyperbilirubinemia (defined as a bilirubin level of >3 mg per deciliter [51 μ mol per liter]). Use of intensive care resources was assessed on the basis of cumulative TISS-28 scores (the sum of daily scores), indicating the total number of interventions per patient.¹⁹ We performed a predefined subgroup analysis for patients staying in the ICU for at least a third day. A post hoc exploratory mortality analysis was performed censoring

Table 1. Baseline Characteristics of the Patients.*

| Variable | Intention-to-Treat Group | | | Group in ICU for ≥ 3 Days | | |
|--|--------------------------------|-----------------------------|---------|--------------------------------|-----------------------------|----------|
| | Conventional Treatment (N=605) | Intensive Treatment (N=595) | P Value | Conventional Treatment (N=381) | Intensive Treatment (N=386) | P Value† |
| Male sex — no. (%) | 382 (63.1) | 356 (60) | 0.24 | 243 (64) | 224 (58) | 0.10 |
| Age — yr | 64 \pm 16 | 63 \pm 16 | 0.61 | 64 \pm 16 | 62 \pm 16 | 0.20 |
| BMI | 24.8 \pm 5.1 | 25.1 \pm 5.5 | 0.29 | 24.6 \pm 5.1 | 25.4 \pm 5.9 | 0.06 |
| Diagnostic category — no. (% of patients in the category) | | | 0.99 | | | 0.70 |
| Respiratory | 261 (51.0) | 251 (49.0) | | 172 (47.9) | 187 (52.1) | |
| Gastrointestinal or liver | 152 (49.7) | 154 (50.3) | | 89 (55.6) | 71 (44.4) | |
| Hematologic or oncologic | 51 (52.6) | 46 (47.4) | | 37 (48.7) | 39 (51.3) | |
| Other sepsis | 45 (50.0) | 45 (50.0) | | 30 (46.9) | 34 (53.1) | |
| Cardiovascular | 24 (48.0) | 26 (52.0) | | 15 (45.5) | 18 (54.5) | |
| Neurologic | 31 (50.8) | 30 (49.2) | | 14 (50.0) | 14 (50.0) | |
| Renal | 20 (45.5) | 24 (54.5) | | 11 (45.8) | 13 (54.2) | |
| Metabolic | 11 (55.0) | 9 (45.0) | | 10 (66.7) | 5 (33.3) | |
| Other | 10 (50.0) | 10 (50.0) | | 3 (37.5) | 5 (62.5) | |
| History of cancer — no. (%) | 128 (21.2) | 134 (22.5) | 0.57 | 90 (23.6) | 98 (25.4) | 0.57 |
| Dialysis-dependent kidney failure before acute event — no. (%) | 37 (6.1) | 37 (6.2) | 0.94 | 29 (7.6) | 31 (8.0) | 0.83 |
| Kidney failure on admission to ICU — no. (%)‡ | 120 (19.8) | 119 (20.0) | 0.94 | 92 (24.1) | 82 (21.2) | 0.34 |
| History of diabetes — no. (%) | 97 (16.0) | 106 (17.8) | 0.41 | 58 (15.2) | 59 (15.3) | 0.98 |
| Treated with insulin | 51 (8.4) | 65 (10.9) | | 27 (7.0) | 41 (10.6) | |
| Treated with oral antidiabetic agent, diet, or both | 46 (7.6) | 41 (6.9) | | 31 (8.1) | 18 (4.7) | |
| Baseline APACHE II score§ | | | | | | |
| Mean | 23 \pm 9 | 23 \pm 10 | 0.50 | 24 \pm 9 | 24 \pm 10 | 0.95 |
| >40 — no. (%) | 18 (3.0) | 26 (4.4) | 0.19 | 11 (2.9) | 18 (4.7) | 0.19 |

patients for whom intensive care was limited or who were withdrawn from intensive care by a senior attending physician within 72 hours after admission for reasons of futility.

To minimize the possibility of bias in assessing the ICU stay caused by delays in the transfer of patients to a regular ward because of the unavailability of beds, patients were considered to be ready for discharge when they no longer needed vital-organ support and were receiving at least two thirds of their caloric intake by the normal enteral route or when they were sent to a ward. Physicians on the general wards to which patients

were transferred from intensive care had no access to the results of blood glucose testing and were unaware of the study treatment assignment.

STATISTICAL ANALYSIS

On the basis of data from our previous study,⁵ we hypothesized an absolute reduction in the risk of death of 7 percent after at least three days of intensive insulin therapy. Testing this hypothesis required a sample of 1200 patients for a two-sided alpha level of less than 0.05 and a beta level of 0.2 in the targeted group of patients staying in the ICU for three or more days.

Table 1. (Continued.)

| Variable | Intention-to-Treat Group | | | Group in ICU for ≥ 3 Days | | |
|--|--------------------------------|-----------------------------|---------|--------------------------------|-----------------------------|----------|
| | Conventional Treatment (N=605) | Intensive Treatment (N=595) | P Value | Conventional Treatment (N=381) | Intensive Treatment (N=386) | P Value† |
| Baseline TISS-28 score¶ | | | | | | |
| Mean score | 29 \pm 7 | 29 \pm 7 | 0.45 | 30 \pm 7 | 31 \pm 7 | 0.46 |
| Score >33 — no. (%) | 125 (20.6) | 158 (26.6) | 0.02 | 96 (25.2) | 129 (33.4) | 0.01 |
| Blood glucose on admission — mg/dl | 162 \pm 70 | 162 \pm 71 | 0.98 | 164 \pm 68 | 163 \pm 67 | 0.87 |
| Glycosylated hemoglobin on admission — % | 6.2 \pm 0.9 | 6.3 \pm 0.9 | 0.12 | 6.2 \pm 0.9 | 6.3 \pm 0.9 | 0.21 |
| Plasma creatinine on admission — mg/dl | | | | | | |
| Median | 1.2 | 1.2 | 0.25 | 1.4 | 1.3 | 0.06 |
| Interquartile range | 0.9–2.1 | 0.8–2.1 | | 0.9–2.4 | 0.8–2.1 | |
| Plasma urea on admission — mg/dl | | | | | | |
| Median | 67 | 65 | 0.26 | 71 | 69 | 0.16 |
| Interquartile range | 40–110 | 36–104 | | 45–115 | 37–106 | |
| Plasma ALT on admission — IU/liter | | | | | | |
| Median | 29 | 30 | 0.50 | 33 | 31 | 0.55 |
| Interquartile range | 15–64 | 16–63 | | 17–77 | 17–63 | |
| Plasma CRP on admission — mg/liter | | | | | | |
| Median | 124 | 108 | 0.27 | 146 | 132 | 0.31 |
| Interquartile range | 39–226 | 36–218 | | 55–236 | 48–229 | |

* Plus-minus values are means \pm SD. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for urea to millimoles per liter, multiply by 0.357. ICU denotes intensive care unit, BMI body-mass index (the weight in kilograms divided by the square of the height in meters), APACHE II Acute Physiology and Chronic Health Evaluation, TISS-28 Therapeutic Intervention Scoring System, ALT alanine aminotransferase, and CRP C-reactive protein.

† P values for the comparison between the conventional-treatment group and the intensive-treatment group were calculated by Student's t-test, the Mann-Whitney U test, or the chi-square test, as appropriate.

‡ Established kidney failure on admission was defined as dependence on dialysis or a serum creatinine level >2.5 mg per deciliter. To convert values for creatinine to micromoles per liter, multiply by 88.4.

§ Higher APACHE II scores indicate more severe illness, with a score greater than 40 representing the 90th percentile, indicating the most severe illness.

¶ According to the TISS-28, each therapeutic intervention is assigned a number of points, with higher scores indicating a greater number of therapeutic interventions. The sum of the points is calculated daily for each patient. A score greater than 33 is at the upper limit of the interquartile range.

|| Glycosylated hemoglobin was measured by immunoturbidimetric assay (Dimension, Dade Behring) (normal range, 4 to 6 percent).

The baseline and outcome variables were compared with the use of Student's t-test, the chi-square test, and the Mann-Whitney U test, as appropriate. The effect of the intervention on time to death in the hospital was assessed with the use of Kaplan-Meier estimates and proportional-hazards regression analysis. Patients discharged alive from the hospital were considered survivors. The hazard ratios for death, calculated by proportional-hazards regression analysis, were corrected

for all well-known, clinically relevant baseline risk factors. The effect on time to weaning from mechanical ventilation and time to discharge from the ICU and from the hospital was assessed by cumulative hazard estimates and proportional-hazards regression analysis, with censoring for early deaths.

The data are presented as means \pm SD or medians (with interquartile ranges), unless otherwise indicated. Separate analyses were performed for

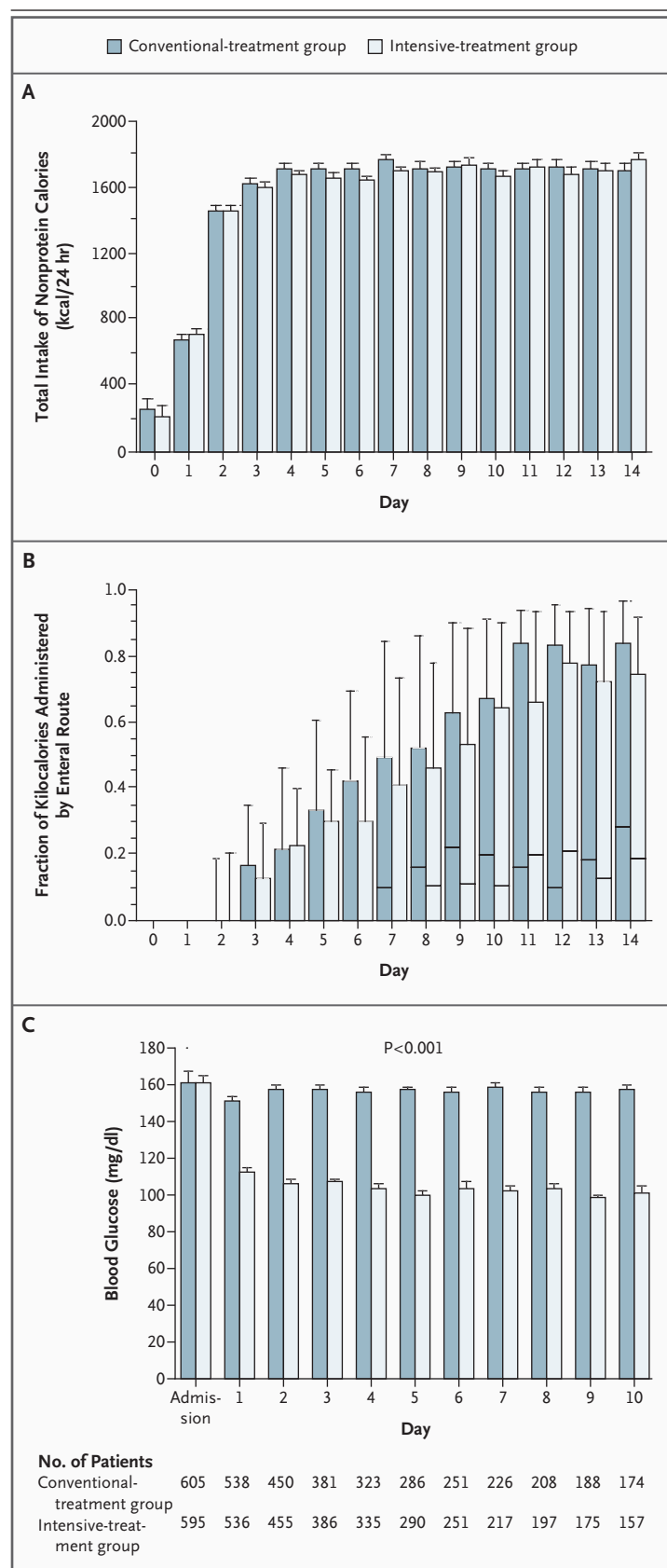


Figure 2. Nutrition Administered to All 1200 Patients during the First 14 Days of Intensive Care and Daily Morning Blood Glucose Levels during the First 10 Days of Intensive Care.

In Panel A, feeding at 0 represents the administration of nutrition to patients admitted to the intensive care unit (ICU) after midnight between admission and 7 a.m., and 1 represents feeding on the first day after admission, from 7 a.m. on. Nutrition in the two groups was similar. Total kilocalories are given as means \pm SE. In Panel B, in the box plot the fraction of nutrition administered by the enteral route is expressed as medians (indicated by horizontal lines within the bars) and interquartile ranges (with the 90th percentile indicated by the I bar). In Panel C, among patients staying in the ICU for three or more days, intensive insulin treatment was continued until discharge from the ICU (mean, 12.5 days, with a range up to 65 days). $P < 0.001$ for the comparison between the two groups. To convert values for glucose to millimoles per liter, multiply by 0.05551.

the intention-to-treat group and for the group staying in the ICU for three or more days. For comparison with the results of our previous study in the surgical ICU,⁵ the effects on patients in the ICU for at least a fifth day were also documented. P values were not adjusted for multiple comparisons. The study sponsors were not involved in the design of the study, the collection, analysis, or interpretation of the data, or the preparation of the manuscript.

RESULTS

NUTRITION AND BLOOD GLUCOSE CONTROL

Table 1 gives the baseline characteristics on admission of all 1200 patients enrolled in the study, including the 767 patients who stayed in the ICU for at least a third day. Nutritional intake and blood glucose levels are shown in Figure 2 (for insulin doses, see Table A in the Supplementary Appendix, available with the full text of this article at www.nejm.org). Hypoglycemia occurred more often in the intensive-treatment group than the conventional-treatment group. Most patients who had hypoglycemia had only one episode. The severity of hypoglycemia was similar in the two groups (Table A in the Supplementary Appendix). No hemodynamic deterioration, convulsions, or other events were noted in association with any hypoglycemic event. Mortality among patients in the ICU who had hypoglycemia was 66.7 percent in the conventional-treatment group, as compared with 46.4 percent in the intensive-treatment group

($P=0.1$); the in-hospital mortality was 73.3 percent and 61.9 percent, respectively ($P=0.4$). Two patients in the conventional-treatment group and three in the intensive-treatment group died within 24 hours after having a hypoglycemic event. Independent risk factors for hypoglycemia, aside from intensive insulin therapy (odds ratio, 7.50; 95 percent confidence interval, 4.50 to 12.50; $P<0.001$), were a stay in the ICU for three or more days (odds ratio, 3.33; 95 percent confidence interval, 1.95 to 5.70; $P<0.001$), renal failure requiring dialysis (odds ratio, 1.94; 95 percent confidence interval, 1.19 to 2.84; $P=0.006$), and liver failure as defined by alanine aminotransferase levels above 250 U per liter (odds ratio, 1.62; 95 percent confidence interval, 1.01 to 2.60; $P=0.04$).

MORBIDITY

Intention-to-Treat Population

In the intention-to-treat population, there was no significant difference between the two treatment groups in the use of medications other than insulin. Of 1200 patients in the intention-to-treat population, 9 were treated for septic shock with activated protein C, 5 in the conventional-treatment group and 4 in the intensive-treatment group ($P=0.8$). Of 644 patients receiving corticosteroid therapy, 327 were in the conventional-treatment group and 317 were in the intensive-treatment group ($P=0.8$). The corticosteroid therapy consisted largely of immunosuppressive or anti-inflammatory treatment with methylprednisolone (at a median dose of 40 mg [interquartile range, 24 to 75] per treatment day among 233 patients in the conventional-treatment group and a median dose of 40 mg [interquartile range, 29 to 65] per day among 249 patients in the intensive-treatment group; $P>0.9$). Hydrocortisone was given for presumed adrenal failure at a median dose of 125 mg (interquartile range, 100 to 193) per day to 129 patients in the conventional-treatment group and at a median dose of 135 mg (interquartile range, 100 to 240) per day to 118 patients in the intensive-treatment group ($P=0.2$). Five patients, two in the conventional-treatment group and three in the intensive-treatment group, received a median daily dose of 10 mg of dexamethasone ($P>0.9$).

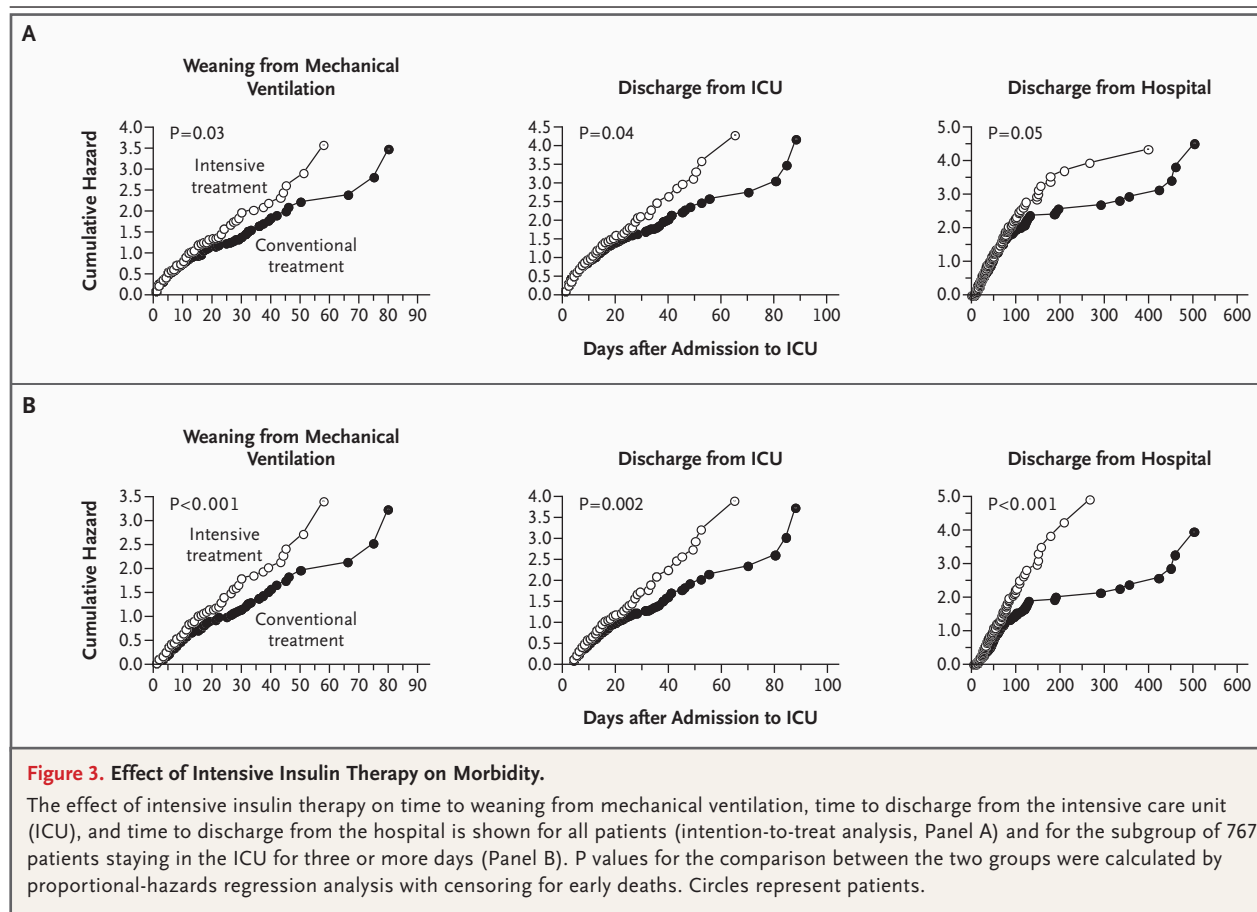
Morbidity was reduced in the intensive-treatment group, as reflected by a reduction in newly acquired kidney injury (8.9 to 5.9 percent, $P=0.04$) and in earlier weaning from mechanical ventilation, as compared with the conventional-treatment group (hazard ratio, 1.21; 95 percent con-

fidence interval, 1.02 to 1.44; $P=0.03$), along with earlier discharge from the ICU (hazard ratio, 1.15; 95 percent confidence interval, 1.01 to 1.32; $P=0.04$) and from the hospital (hazard ratio, 1.16; 95 percent confidence interval, 1.00 to 1.35; $P=0.05$) (Fig. 3). There was no significant effect on bacteremia (reduction, 7 to 8 percent; $P=0.5$), prolonged requirement of antibiotic agents (reduction, 24 to 21 percent; $P=0.2$), hyperbilirubinemia (reduction, 27 to 25 percent; $P=0.4$), hyperinflammation (reduction, 61 to 56 percent; $P=0.1$), or cumulative TISS-28 scores (reduction, 308 ± 16 to 272 ± 13 ; $P=0.08$). Rates of readmission to the ICU were similar (6.3 percent) in the two groups.

Stays in ICU Longer Than Three Days

Among the 767 patients who stayed for more than three days in the ICU, there was no significant difference between the two groups in the use of any medications other than insulin. Among the 386 patients in the intensive-treatment group, intensive insulin therapy for at least a third day, as compared with conventional therapy, accelerated weaning from mechanical ventilation (hazard ratio, 1.43; 95 percent confidence interval, 1.16 to 1.75; $P<0.001$), discharge from the ICU (hazard ratio, 1.34; 95 percent confidence interval, 1.12 to 1.61; $P=0.002$), and discharge from the hospital (hazard ratio, 1.58; 95 percent confidence interval, 1.28 to 1.95; $P<0.001$) (Fig. 3).

In the conventional-treatment group, 28.6 percent of patients received dialysis therapy, as compared with 27.2 percent of those in the intensive-treatment group ($P=0.7$). The use of dialysis in patients who did not require dialysis before admission to the ICU was not significantly reduced (22.7 percent in the conventional-treatment group and 20.8 percent in the intensive-treatment group, $P=0.5$). However, acquired kidney injury occurring after randomization, as defined by a serum creatinine level at least twice that present on admission to the ICU (12.6 percent in the conventional-treatment group and 8.3 percent in the intensive-treatment group, $P=0.05$) and the fraction of patients reaching a peak serum creatinine level greater than 2.5 mg per deciliter (39.4 and 32.5 percent, respectively; $P=0.04$), was reduced. Hyperbilirubinemia was present in 55.2 percent of patients in the conventional-treatment group and 47.3 percent of those in the intensive-treatment group ($P=0.04$). The levels of alanine aminotransferase or aspartate aminotransferase were similar in the two groups.



The proportion of patients who had bacteremia (11.3 percent) or secondary bacteremia (7.3 percent) or received prolonged antibiotic therapy (37.6 percent in the conventional-treatment group and 31.9 percent in the intensive-treatment group, $P=0.09$) was not significantly reduced. However, intensive insulin therapy reduced the incidence of hyperinflammation from 74 percent in the conventional-treatment group to 67 percent in the intensive-treatment group ($P=0.03$).

Intensive insulin therapy reduced the cumulative TISS-28 scores among patients in the ICU by 20 percent (454 ± 22 in the conventional-treatment group vs. 388 ± 17 in the intensive-treatment group, $P=0.02$), reflecting a reduction in the costs of intensive care.^{19,20} Among patients who underwent randomization and stayed in the ICU less than three days, none of the morbidity end points were significantly different in the two treatment groups. Beyond the fifth day of intensive insulin therapy, all the morbidity end points studied were

also beneficially affected, with no effect among those treated for less than five days.

MORTALITY

Among the 1200 patients included in the intention-to-treat analysis, ICU and in-hospital mortality were not significantly reduced by intensive insulin therapy (Table 2 and Fig. 4). For all patients, mortality in the ICU at day 3 (2.8 percent vs. 3.9 percent, $P=0.31$) and in-hospital mortality at day 3 (3.6 percent vs. 4.0 percent, $P=0.72$) were not significantly different in the two treatment groups. Beyond the third day of intensive insulin therapy, the in-hospital mortality was reduced from 52.5 to 43.0 percent (Fig. 4 and Table 2). Death from all causes in the ICU appeared to be reduced. The effect on mortality among patients staying for more than three days in the ICU was shown in most of the subgroups stratified according to diagnostic category, but it was much less pronounced

Table 2. Mortality in the Study Groups.*

| Variable | Intention-to-Treat Group | | | Group in ICU for ≥3 Days | | |
|--|--------------------------------|-----------------------------|---------|--------------------------------|-----------------------------|---------|
| | Conventional Treatment (N=605) | Intensive Treatment (N=595) | P Value | Conventional Treatment (N=381) | Intensive Treatment (N=386) | P Value |
| Total deaths during intensive care — no. (%) | 162 (26.8) | 144 (24.2) | 0.31 | 145 (38.1) | 121 (31.3) | 0.05 |
| Causes of death during intensive care — no. (% of patients in the category) | | | 0.90 | | | 0.70 |
| Persistent MOF after septic or SIRS-induced shock | 59 (51.3) | 56 (48.7) | | 55 (51.4) | 52 (48.6) | |
| Respiratory failure | 50 (54.3) | 42 (45.7) | | 49 (55.7) | 39 (44.3) | |
| Therapy-resistant septic shock | 21 (50.0) | 21 (50.0) | | 14 (53.8) | 12 (46.2) | |
| Cardiovascular collapse | 18 (54.5) | 15 (45.5) | | 16 (66.7) | 8 (33.3) | |
| Severe brain damage | 14 (58.3) | 10 (41.7) | | 11 (52.4) | 10 (47.6) | |
| In-hospital deaths — no. (%) | 242 (40.0) | 222 (37.3) | 0.33 | 200 (52.5) | 166 (43.0) | 0.009 |
| Hazard ratio (95% CI) | | 0.94 (0.84–1.06) | 0.31 | | 0.84 (0.73–0.97) | 0.02† |
| In-hospital deaths, according to diagnostic category — no. (% of patients in the category) | | | | | | |
| Respiratory | 115 (44.1) | 98 (39.0) | | 100 (58.1) | 78 (41.7) | |
| Gastrointestinal or liver disease | 49 (32.2) | 41 (45.6) | | 39 (43.8) | 23 (32.4) | |
| Hematologic or oncologic disease | 33 (64.7) | 28 (60.9) | | 26 (70.3) | 23 (58.9) | |
| Other sepsis | 13 (28.9) | 19 (42.2) | | 11 (36.7) | 16 (47.0) | |
| Cardiovascular | 8 (33.3) | 14 (53.8) | | 6 (40.0) | 11 (61.1) | |
| Neurologic | 9 (29.0) | 9 (30.0) | | 6 (42.8) | 5 (35.7) | |
| Renal | 8 (40.0) | 6 (25.0) | | 7 (63.6) | 4 (30.8) | |
| Metabolic | 4 (36.4) | 2 (22.2) | | 4 (40.0) | 2 (40.0) | |
| Other | 3 (30.0) | 5 (50.0) | | 1 (33.3) | 4 (80.0) | |
| In-hospital deaths, according to APACHE II quartile — no. (% of patients in the category) | | | | | | |
| <17 | 25 (19.5) | 28 (19.7) | | 25 (34.7) | 20 (24.1) | |
| 17 to 22 | 63 (37.1) | 54 (32.1) | | 51 (51.5) | 38 (38.8) | |
| 23 to 29 | 74 (44.6) | 66 (44.0) | | 63 (55.8) | 51 (47.7) | |
| >29 | 79 (58.1) | 73 (55.3) | | 61 (62.9) | 57 (58.2) | |
| In-hospital deaths, according to history of diabetes — no. (% of patients in the category) | | | | | | |
| No history of diabetes | 208 (40.9) | 180 (36.8) | | 173 (53.4) | 137 (41.9) | |
| History of diabetes | 34 (35.0) | 42 (39.6) | | 27 (47.4) | 29 (49.2) | |
| 28-Day mortality — no. (%) | 182 (30.0) | 178 (29.9) | 0.95 | 149 (39.1) | 133 (34.5) | 0.18 |
| 90-Day mortality — no. (%) | 228 (37.7) | 214 (35.9) | 0.53 | 187 (49.1) | 163 (42.2) | 0.06 |
| Deaths in ICU on day 3 — no. (%) | 17 (2.8) | 23 (3.9) | 0.31 | | | |
| Deaths in hospital on day 3 — no. (%) | 22 (3.6) | 24 (4.0) | 0.72 | | | |

* ICU denotes intensive care unit, MOF multiple organ failure, SIRS systemic inflammatory response syndrome, and CI confidence interval. P values were calculated by the chi-square test, uncorrected for the crude mortality data and corrected for baseline risk factors for the odds ratios for in-hospital death obtained by proportional-hazards regression analysis. Clinically relevant baseline risk factors for death included severity of illness scores (APACHE II and Therapeutic Intervention Scoring System-28 scores), a history of diabetes, active cancer and kidney failure before admission to the ICU, dialysis dependence, signs of liver necrosis (alanine aminotransferase level, >150 IU per liter), baseline plasma urea level >150 mg per deciliter, and hyperinflammation (C-reactive protein level, >150 mg per deciliter).

† The P value has been corrected for the risk factors.

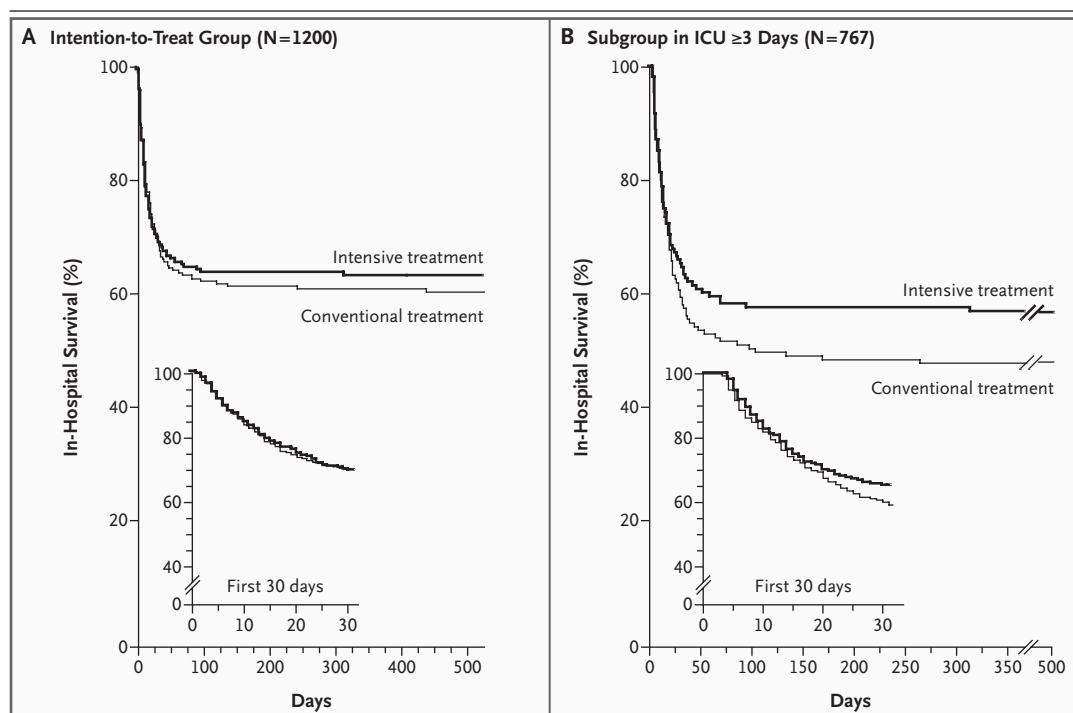


Figure 4. Kaplan–Meier Curves for In-Hospital Survival.

The effect of intensive insulin treatment on the time from admission to the intensive care unit (ICU) until death is shown for the intention-to-treat group (Panel A) and the subgroup of patients staying in the ICU for three or more days (Panel B). Patients discharged alive from the hospital were considered survivors. P values calculated by the log-rank test were 0.40 for the intention-to-treat group and 0.02 for the subgroup staying in the ICU for three or more days. P values calculated by proportional-hazards regression analysis were 0.30 and 0.02, respectively.

in the highest APACHE II quartile (Table 2). Among the 433 patients who stayed in the ICU less than three days and for whom data were censored after randomization, 56 of those in the intensive-treatment group and 42 in the conventional-treatment group died, but the statistical significance of this finding varied depending on the analytical approach ($P=0.05$ with the chi-square test; hazard ratio, 1.09; 95 percent confidence interval, 0.90 to 1.32; $P=0.35$ by uncorrected proportional-hazards analysis; hazard ratio, 1.09; 95 percent confidence interval, 0.89 to 1.32; $P=0.41$ after correcting for baseline risk factors listed in Table 2).

Beyond the fifth day of intensive insulin therapy, mortality was reduced from 54.9 to 45.9 percent ($P=0.03$), with no significant effect among patients staying less than five days in the ICU ($P=0.50$).

Post Hoc Exploratory Mortality Analysis

Of the 1200 patients in the total study group, a post hoc analysis censored data on 65 patients for

whom intensive care had been limited or withdrawn within 72 hours after admission to the ICU (26 patients in the conventional-treatment group and 39 in the intensive-treatment group). Of these 65 patients, 29 had long stays in the ICU (16 in the conventional-treatment group and 13 in the intensive-treatment group), and 36 had short stays (10 and 26, respectively). After censoring, the in-hospital mortality in the intention-to-treat population was 37.8 percent in the conventional-treatment group versus 33.5 percent in the intensive-treatment group ($P=0.1$); among those with long stays in the ICU, the in-hospital mortality was 50.9 percent versus 41.5 percent ($P=0.01$); and among those with short stays, it was 15.4 percent versus 16.9 percent ($P=0.7$).

DISCUSSION

Intensive insulin therapy during intensive care prevented morbidity but did not significantly reduce the risk of death among all patients in the

medical ICU included in the intention-to-treat population. However, among those who stayed in the ICU for three or more days, intensive insulin therapy reduced morbidity and mortality.

The reduced morbidity resulted from the prevention of acquired kidney injury, earlier weaning from mechanical ventilation, and earlier discharge from the medical ICU and the hospital in patients who received intensive insulin therapy as compared with those who did not. In contrast to patients in the surgical ICU,⁵ however, those in the medical ICU had no detectable reduction in bacteremia, which may be explained by the fact that among medical patients sepsis often triggers admission to the ICU, irrespective of the disease necessitating hospital admission. Although infections other than bacteremia were not analyzed for our study and may have been missed, the anti-inflammatory effect⁸ and the protection of organ function⁹ appeared to be independent of prevention of infection. Possible mechanisms of action include the prevention of cellular hypoxia by means of reduced endothelial damage¹⁰ and the prevention of cytopathic hypoxia.¹¹

Analysis of the subgroup treated in the ICU for three or more days showed not only a beneficial effect on morbidity but also a reduction in mortality that was absent in the total study population. However, since the length of stay in the ICU cannot be predicted for an individual patient and therefore the analysis based on length of stay inevitably requires post-randomization stratification, there is a risk of bias. It is unclear whether intensive insulin therapy received for less than three days caused harm, as might be inferred from the greater number of deaths among patients staying less than three days in the ICU. Post hoc exploratory analysis, with its inherent limitations, suggested that this apparent difference in mortality among those staying a shorter time in the ICU could be explained by the higher number of patients in the intensive-treatment group for whom intensive care was limited or withdrawn for reasons of futility within 72 hours after admission. In our previous study, brief exposure to insulin therapy had no significant effect on the risk of death.⁵ Why 48 hours or less of insulin therapy would cause harm, whereas sustained treatment would be beneficial, is unclear.

An alternative and more likely explanation for the difference in the effect of intensive insulin therapy in the intention-to-treat population, as

compared with patients staying in the ICU for at least three days, is that the benefit from intensive insulin therapy requires time to be realized. Indeed, the intervention is aimed not at curing disease but at preventing complications that occur during and, perhaps in part as a result of, intensive care. Prevention probably does not occur when the patient has a high risk of death from the disease causing admission to the ICU and when the intervention is administered for a relatively short time. However, among patients in whom complications resulting from intensive care contribute to an adverse outcome, such a preventive strategy, if continued long enough, is likely to be effective. This would explain why patients with long stays in the medical ICU benefit more than those with short stays, as shown in a surgical ICU.⁵

Among patients staying for at least three days in the ICU, the absolute reduction in in-hospital mortality associated with intensive insulin therapy was similar to that in our previous report⁵ and exceeded the effect on mortality in the ICU, indicating that intensive insulin therapy during intensive care had a carryover effect. Such a longer-term effect is in line with our previous finding of superior long-term rehabilitation among patients with brain injury who received intensive insulin therapy during intensive care.²⁴ Mortality in a subgroup with a diagnosis of diabetes appeared to be unaffected by intensive insulin therapy, although the numbers were small. This finding may be explained in part by the fact that the target blood glucose level was not reached in this subgroup. Indeed, achieving normoglycemia appears crucial to obtaining the benefit of intensive insulin therapy.⁶

In the present study, normoglycemia was achieved with insulin titrated by the attending nurses in the ICU. Despite the use of guidelines similar to those used in the surgical study,⁵ an episode of biochemical hypoglycemia occurred more often among the patients in the medical ICU. Liver failure and kidney failure, which increase the vulnerability to hypoglycemia, may partly explain this observation. However, logistic-regression analysis identified hypoglycemia as an independent risk factor for death. Hence, it is possible that hypoglycemia induced by intensive insulin therapy may have reduced a portion of the potential benefit.

This study has certain limitations. Like our previous study of the surgical ICU,⁵ this was a single-center study; and as in previous studies in

patients with diabetes mellitus,^{25,26} it was not possible to achieve strict blinding, because safe insulin titration requires monitoring of blood glucose levels. However, because physicians on the general wards were unaware of the treatment assignments of patients receiving intensive care and had no access to the results of blood glucose testing, bias in the analysis of the effect on length of stay in the hospital and in the analysis of in-hospital mortality was prevented. Furthermore, since there was no survival benefit in the intention-to-treat group, as compared with the subgroup staying in the ICU for three or more days, the use of intensive insulin therapy in all patients in the medical ICU, including those staying less than three days, could be questioned. Because patients who will have a prolonged stay in the ICU cannot be identified with certainty on admission, adequately powered trials are needed to address this important issue. On the basis of our current data, such studies would require at least 5000 patients in the medical ICU.

Thus, targeting blood glucose levels to below 110 mg per deciliter with insulin therapy prevented morbidity but did not significantly reduce mortality among all patients in our medical ICU. However, intensive insulin therapy in patients who stayed in the ICU for at least three days was associated with reduced morbidity and mortality. Large multicenter trials are needed to confirm these preliminary results.

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REFERENCES

- Mizock BA. Alterations in carbohydrate metabolism during stress: a review of the literature. *Am J Med* 1995;98:75-84.
- McCowan KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. *Crit Care Clin* 2001;17:107-24.
- Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000;355:773-8.
- Cely CM, Arora P, Quartin AA, Kett DH, Schein RMH. Relationship of baseline glucose homeostasis to hyperglycemia during medical critical illness. *Chest* 2004;126:879-87.
- Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359-67.
- Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med* 2003;31:359-66.
- Weekers F, Giulietti A-P, Michalaki M, et al. Metabolic, endocrine, and immune effects of stress hyperglycemia in a rabbit model of prolonged critical illness. *Endocrinology* 2003;144:5329-38.
- Hansen TK, Thiel S, Wouters PJ, Christiansen JS, Van den Berghe G. Intensive insulin therapy exerts anti-inflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. *J Clin Endocrinol Metab* 2003;88:1082-8.
- Van den Berghe G. How does blood glucose control with insulin save lives in intensive care? *J Clin Invest* 2004;114:1187-95.
- Langouche L, Vanhorebeek I, Vlasselaers D, et al. Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest* 2005;115:2277-86.
- Vanhorebeek I, De Vos R, Mesotten M, Wouters PJ, De Wolf-Peters C, Van den Berghe G. Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. *Lancet* 2005;365:53-9.
- Evans TW. Hemodynamic and metabolic therapy in critically ill patients. *N Engl J Med* 2001;345:1417-8.
- Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care* 2004;27:553-91. [Errata, *Diabetes Care* 2004;27:856, 2004;27:1255.]
- Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995;26:57-65.
- Malmberg K, Ryden L, Wedel H, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005;26:650-61.
- Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2003;125:1007-21.
- Souba WW. Nutritional support. *N Engl J Med* 1997;336:41-8.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818-29.
- Miranda DR, de Rijk A, Schaefeli W. Simplified Therapeutic Intervention Scoring System: the TISS-28 items — results from a multicenter study. *Crit Care Med* 1996;24:64-73.
- Keene AR, Cullen DJ. Therapeutic Intervention Scoring System: update 1983. *Crit Care Med* 1983;11:1-3.
- Weinstein MP, Towns ML, Quartey SM, et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. *Clin Infect Dis* 1997;24:584-602.
- Weinstein MP, Mirrett S, Van Pelt L, et al. Clinical importance of identifying coagulase-negative staphylococci isolated from blood cultures: evaluation of MicroScan Rapid and Dried Overnight Gram-Positive panels versus a conventional reference method. *J Clin Microbiol* 1998;36:2089-92.
- Bellomo R, Ronco C, Kellum JA, et al.

Acute renal failure: definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004;8:R204–R212.

24. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin

therapy protects the central and peripheral nervous system of intensive care patients. *Neurology* 2005;64:1348-53.

25. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.

26. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53. [Erratum, *Lancet* 1999;354:602.]

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