

# Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control\*

Greet Van den Berghe, MD, PhD; Pieter J. Wouters, MSc; Roger Bouillon, MD, PhD; Frank Weekers, MD; Charles Verwaest, MD; Miet Schetz, MD, PhD; Dirk Vlasselaers, MD; Patrick Ferdinande, MD, PhD; Peter Lauwers, MD

**Objectives:** Maintenance of normoglycemia with insulin reduces mortality and morbidity of critically ill patients. Here we report the factors determining insulin requirements and the impact of insulin dose vs. blood glucose control on the observed outcome benefits.

**Design:** A prospective, randomized, controlled trial.

**Setting:** A 56-bed predominantly surgical intensive care unit in a tertiary teaching hospital

**Patients and Intervention:** A total of 1,548 patients were randomly assigned to either strict normalization of blood glucose (80–110 mg/dL) with insulin infusion or the conventional approach, in which insulin is only given to maintain blood glucose levels at 180–200 mg/dL.

**Measurements and Main Results:** It was feasible and safe to achieve and maintain blood glucose levels at <110 mg/dL by using a titration algorithm. Stepwise linear regression analysis identified body mass index, history of diabetes, reason for intensive care unit admission, at-admission hyperglycemia, caloric intake, and time in intensive care unit as independent determinants of insulin requirements, together explaining 36% of its variation. With nutritional intake increasing from a mean of 550 to 1600 calories/day during the first 7 days of intensive care, normoglycemia was reached within 24 hrs, with a mean daily insulin dose of 77 IU and maintained with 94 IU on day 7. Insulin requirements were highest and most variable

during the first 6 hrs of intensive care (mean, 7 IU/hr; 10% of patients required >20 IU/hr). Between day 7 and 12, insulin requirements decreased by 40% on stable caloric intake. Brief, clinically harmless hypoglycemia occurred in 5.2% of intensive insulin-treated patients on median day 6 (2–14) vs. 0.8% of conventionally treated patients on day 11 (2–10). The outcome benefits of intensive insulin therapy were equally present regardless of whether patients received enteral feeding. Multivariate logistic regression analysis indicated that the lowered blood glucose level rather than the insulin dose was related to reduced mortality ( $p < .0001$ ), critical illness polyneuropathy ( $p < .0001$ ), bacteremia ( $p = .02$ ), and inflammation ( $p = .0006$ ) but not to prevention of acute renal failure, for which the insulin dose was an independent determinant ( $p = .03$ ). As compared with normoglycemia, an intermediate blood glucose level (110–150 mg/dL) was associated with worse outcome.

**Conclusion:** Normoglycemia was safely reached within 24 hrs and maintained during intensive care by using insulin titration guidelines. Metabolic control, as reflected by normoglycemia, rather than the infused insulin dose *per se*, was related to the beneficial effects of intensive insulin therapy. (Crit Care Med 2003; 31:359–366)

**KEY WORDS:** critical illness; intensive care; critical care; glucose; insulin; algorithm; sepsis; polyneuropathy; acute renal failure; inflammation

**H**yperglycemia and insulin resistance are common in critically ill patients, even when glucose homeostasis has previously been normal. Increased gluconeogenesis, despite abundantly released insulin, is probably central to this

disruption of glucoregulation (1, 2). Hence, the liver seems to be a major site of insulin resistance. Reduced insulin-stimulated glucose uptake also exists in skeletal muscle and heart (1, 3). Overall glucose uptake, however, is increased but takes place mainly in insulin-indepen-

dent tissues such as the brain, the red blood cells, and in wounds. The increased glucose turnover and insulin-resistance of hyperglycemia were previously interpreted as a plea for tolerating moderately elevated (up to 200 mg/dL) blood glucose levels during critical illness (4, 5). More pronounced hyperglycemia in diabetic surgical patients has been associated with high prevalence of postoperative infections (6) after stroke and head injury, with poor prognosis (7, 8). In diabetic patients with acute myocardial infarction, blood glucose control of <215 mg/dL has been shown to improve long-term outcome (9–11). We recently hypothesized that even moderate hyperglycemia, between 110 and 200 mg/dL, in diabetic and in nondiabetic critically ill

\*See also p. 634.

From the Department of Intensive Care Medicine (GVdB, PJW, FW, CV, MS, DV, PF, PL) and Laboratory for Experimental Medicine and Endocrinology (RB), Catholic University of Leuven, Belgium.

Supported, in part, by research grants from the Belgian Fund for Scientific Research (G. 0144.00 and G.3C05.95N, G. Van den Berghe), the Research Council of the University of Leuven (OT 99/32, G. Van den Berghe), the Belgian Foundation for Research in Congenital Heart Diseases (G. Van den Berghe), and an unrestricted research

grant from Novo Nordisk, Denmark (G. Van den Berghe).

R. Bouillon holds a J.J. Servier Diabetes Research Chair.

Address requests for reprints to: Greet Van den Berghe, MD, PhD, Department of Intensive Care Medicine, University Hospital Gasthuisberg, University of Leuven, B-3000 Leuven, Belgium. E-mail: greta.vandenbergh@med.kuleuven.ac.be

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DOI: 10.1097/01.CCM.0000045568.12881.10

patients is directly or indirectly harmful to vital organs and systems (12), thus contributing to adverse outcome. A prospective, randomized, controlled study of 1,548 predominantly surgical intensive care unit (ICU) patients confirmed this hypothesis by showing that strict glycemic control at <110 mg/dL with insulin infusion substantially reduces morbidity and mortality (12). Indeed, intensive insulin therapy reduced overall ICU mortality from 8% to 4.6% and from 20.2% to 10.6% among patients requiring >5 days of intensive care. Intensive insulin therapy also halved the prevalence of blood stream infections, prolonged inflammation, acute renal failure requiring dialysis or hemofiltration, critical illness polyneuropathy, and transfusion requirements. Patients receiving intensive insulin therapy were also less likely to require prolonged mechanical ventilation and intensive care. It remained an open question, however, whether the benefits are brought about directly by the infused insulin *per se* or by the prevention of hyperglycemia, as both occurred concomitantly. As an extension of our previous study (12), we here report to what extent insulin requirement to maintain normoglycemia in an intensive care patient can be predicted and the impact of insulin dose vs. blood glucose level on the observed outcome benefits.

## MATERIALS AND METHODS

### Study Objectives

The primary clinical results of this study, which involved 1,548 patients (783 treated conventionally and 765 treated with intensive insulin therapy), were published previously (12). The aims of the current analysis were 1) to report on feasibility and safety of intensive insulin therapy in the ICU by providing details of feeding strategy, insulin requirements, and blood glucose control over time; 2) to statistically define the factors that independently determine insulin requirements; 3) to analyze the separate impact of glycemic control and amount of exogenous insulin infused on mortality and morbidity outcome measures (development of critical illness polyneuropathy as diagnosed by blinded weekly systematic electromyographic screenings, acute renal failure requiring dialysis, bacteremia, and prolonged and severe inflammatory responses as defined by C-reactive protein level of >150 mg/L for >3 days), and transfusion requirements; and 4) to *post hoc* analyze the impact on outcome measures of strict normoglycemia (<110 mg/dL) compared with an intermediate level of

blood glucose control (110–150 mg/dL) among long-stay patients.

### Study Population

The study population (mechanically ventilated adults admitted to our predominantly surgical ICU during a 1 yr period) has been described elsewhere (12). Informed consent was obtained from the closest family member at ICU admission. The study protocol was approved by the Institutional Ethical Review Board.

### Study Design

The complete study design has previously been described (12, 13). At intensive care admission, all patients were started on partial nutritional support with mainly intravenous glucose (8–12 g/hr) and from the next day onward with a standardized feeding schedule, intended to deliver 20–30 nonprotein calories·kg<sup>-1</sup>·24 hrs<sup>-1</sup> with a balanced composition (0.13–0.26 g nitrogen·kg<sup>-1</sup>·24 hrs<sup>-1</sup> and 20–40% of nonprotein calories as lipids) (14) of total parenteral, combined parenteral/enteral, or full enteral feeding. Enteral feeding was attempted as early as possible, at the discretion of the attending physician.

At ICU admission, patients were randomly assigned to either intensive or conventional insulin treatment. Assignment to treatment groups was done by blinded envelopes, stratified according to type of critical illness (cardiac surgery; neurologic disease, isolated cerebral trauma, or brain surgery; thoracic surgery or respiratory insufficiency; abdominal surgery or peritonitis; vascular surgery; multiple trauma and severe burns; transplantation; and others) and balanced with the use of permuted blocks of ten. Adjustment of the insulin dose was based on measurement of whole blood glucose in undiluted arterial blood every 1 to 4 hrs with the use of a glucose analyzer (ABL700, Radiometer Medical A/S, Copenhagen, Denmark; the coefficient of variation was 2.84% at 90 mg/dL and 3.57% at 220 mg/dL). The dose was adjusted according to a titration algorithm, as stipulated below, by the intensive care nurses, supervised by a study physician who was not involved in the clinical care of the patients. The nurses were advised to consider the titration algorithm as directives rather than strict numerical instructions.

Insulin was given exclusively by continuous intravenous infusion through a central venous catheter by using a 50-mL syringe-driven pump (Perfusor-FM pump, B. Braun, Melsungen, Germany). The standard concentration was 50 IU of Actrapid HM (Novo Nordisk, Copenhagen, Denmark) in 50 mL of 0.9% NaCl. Prepared solutions, stable for up to

24 hrs when kept at <25°C, were not to be used beyond that time.

Whole blood glucose levels were measured on site in undiluted arterial blood. Undiluted samples were obtained by removing at least four times the flush volume in the arterial catheter between the sampling point and the arterial puncture site before the actual sample was taken. During the first 12 to 24 hrs after admission to the ICU, until the targeted range of blood glucose level was reached, measurement of blood glucose was advised every 1 to 2 hrs. Thereafter, blood glucose was measured every 4 hrs, unless steep falls or rises in blood glucose level occurred, for which hourly control after each dose adjustment was advised.

Attention was drawn to always assure adequate administration of the prescribed nutrients. To avoid fluctuating blood glucose levels and too frequent need for readjustment of the insulin dose, intravenous glucose-containing solutions were always administered by infusion pump. At the time of planned interruptions of feeding, the insulin dose was reduced proportionately to avoid hypoglycemia. Hence, in a patient receiving total enteral nutrition, insulin was virtually stopped during the twice daily 2-hr interruptions of tube feeding. In some patients, however, including those with diabetes and requiring insulin before ICU admission, a low maintenance dose was needed during that time. At the time of patient transportation to an investigation or to the operating room for surgery, all intravenous and enteral administration of feeding was usually stopped, and insulin infusion was temporarily discontinued. Blood glucose level was measured to ensure an adequate level before transport. Whenever a patient was extubated and assumed to re-start (limited) oral food intake, the intravenous or tube feeding was usually reduced to allow appetite to re-occur. The insulin dose was proportionately reduced, often temporarily discontinued.

When glucocorticoids were given in high doses (>90 mg/day hydrocortisone or its equivalent), insulin dose was increased to overcome the associated insulin resistance. The total daily dose of glucocorticoids was administered as a continuous infusion to avoid fluctuating insulin requirements occurring with intermittent bolus injections.

Patients at risk for acute renal failure often received hourly substitution of urinary fluid loss to avoid fluctuating intravascular filling status. To co-adjust insulin dose with the variable amounts of glucose-containing solutions (glucose 5%, glucose 3.3%, or glucose 2.5%) infused to substitute the variable hourly urine output, 16, 12, or 10 IU of insulin per liter of substitution fluid, respectively, were added to the infusion bag. This insulin administration was additional to the hourly dose, which was given separately by infusion pump.

## Intensive Insulin Therapy

**Initiation of Insulin Infusion and Initial Stabilization of Blood Glucose Level.** When blood glucose level exceeded 110 mg/dL (6.1 mmol/L), insulin was started at 2 IU/hr (4 IU/hr if the first blood glucose level exceeded 220 mg/dL). When the next blood glucose was >140 mg/dL, the insulin dose was increased by 1–2 IU/hr. When the next blood glucose level was 110–140 mg/dL, insulin was increased by 0.5 to 1 IU/hr. When blood glucose approached 80–110 mg/dL, insulin was adjusted by 0.1 to 0.5 IU/hr. When blood glucose level was 80–110 mg/dL, the insulin dose was unaltered.

**Dose Adjustments After Initial Stabilization.** Dose adjustments were always proportionate to the observed change in blood glucose. When blood glucose decreased by >50%, the dose was reduced to half and the blood glucose level was checked within the next hour. When blood glucose was 60–80 mg/dL, insulin was reduced depending on the previous blood glucose level and the blood glucose level was checked within the next hour. When blood glucose was 40–60 mg/dL, insulin infusion was stopped, adequate baseline glucose intake was ensured, and the blood glucose level was checked within the next hour. When the blood glucose was <40 mg/dL, insulin infusion was stopped, adequate baseline glucose intake was assured, glucose was administered via 10-g intravenous boluses, and the blood glucose level was checked within the next hour. When blood glucose started to decrease within the normal range in a stable patient, recovery of insulin sensitivity was assumed and the insulin dose was reduced by 20%. Additional blood glucose controls were advised whenever changes in body temperature or infection occurred.

At discharge from the ICU, a less strict approach was adopted (glycemia  $\leq$  200 mg/dL) to avoid hypoglycemia in the less well-controlled setting of a regular ward. When a (previously non-insulin requiring) patient was normoglycemic when receiving <2 IU/hr insulin, the insulin infusion was stopped. The blood glucose level before discharge was targeted below 200 mg/dL. When insulin was required to maintain the blood glucose level below 200 mg/dL, the patient was presumed to have preexisting diabetes, and a follow-up by an endocrinologist was planned.

## Conventional Insulin Therapy

**Initiating and Dose Adjustment of Insulin Infusion.** As soon as the blood glucose level exceeded 215 mg/dL (12 mmol/L), insulin infusion was initiated at a starting dose of 1 IU/hr. When a control blood glucose level was >200 mg/dL, the insulin dose was increased by increments of 1 IU/hr. Once the blood glucose level was between 180 and 200 mg/dL, the insulin dose was kept constant. When the blood glucose level decreased to <180 mg/dL,

insulin infusion was decreased until the blood glucose level was between 180 and 200 mg/dL. The insulin dose was further decreased and eventually completely stopped when blood glucose levels decreased further. Insulin infusion was only re-started when blood glucose exceeded 215 mg/dL.

## Statistical Analysis

Data are presented as mean  $\pm$  SEM for precision and medians (25th to 75th percentiles) for distribution, unless indicated otherwise. Difference between study groups were analyzed by chi-square test, unpaired Student's *t*-test, Mann-Whitney U test, and Mantel-Cox log-rank test, when appropriate. Bonferroni's correction was applied for multiple testing. Pearson's product-moment correlation coefficients (*R*), determination coefficients (*R*<sup>2</sup>), and Spearman's (Rho) correlation coefficients were calculated for quantifying the relation between variables. Multivariate logistic regression analysis was performed to assess the impact of blood glucose level vs. insulin dose on the observed outcome benefits. After univariate simple regression analysis, stepwise linear regression analysis was done to define the independent determinants of the insulin dose required to maintain normoglycemia. Two-sided *p* values <.05 were considered significant.

## RESULTS

**Detailed Description of Daily Caloric Intake, Insulin Doses, and Blood Glucose Control over Time in Conventionally Treated Patients and in Patients Receiving Intensive Insulin Therapy.** Daily caloric intake, insulin requirements, and blood glucose levels (including the at-admission blood glucose level and the highest blood glucose level reached during the first 24 hrs in the ICU) are depicted in Figure 1.

All patients underwent a gradual transition from mainly intravenous glucose infusion at ICU admission ( $120 \pm 1$  g of glucose administered during the, on average, 15 hrs from admission until the next morning) to normocaloric balanced nutrition comprising glucose (mean, 200–260g/24 hrs from day 2 onward), proteins, and lipids, preferably administered via the enteral route. Hence, daily caloric intake progressively increased until ICU day 7, equally in both study groups, starting from a mean of 8 calories·kg<sup>-1</sup>·day<sup>-1</sup> and reaching a mean of 24 calories·kg<sup>-1</sup>·day<sup>-1</sup> (Fig. 1, *top panel*). This strategy resulted in comparable amounts of calories, glucose, proteins, and lipids in both study groups at

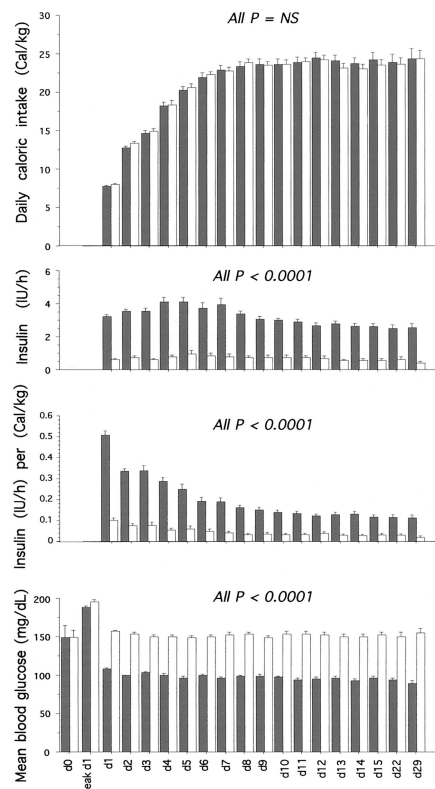


Figure 1. Daily caloric intake (calories per day and kilograms of body weight, *top panel*), insulin requirements (insulin dose per day expressed as mean amount of units per hour, *second panel from top*; insulin dose per hour corrected for caloric intake per kilogram of body weight, *second panel from bottom*), and mean blood glucose levels (including the at-admission blood glucose level [d0] and the highest blood glucose level reached during the first 24 hrs in the intensive care unit [peak d1], *bottom panel*) for the first 4 wks in the intensive care unit. Filled bars represent patients receiving intensive insulin therapy, and open bars indicate patients receiving conventional therapy. Data are presented as mean  $\pm$  SEM. The *p* values were obtained by Mann-Whitney U test at the different time points and corrected for multiple testing by using Bonferroni's method. Caloric intake was increased progressively during the first 7 days, and insulin doses corrected for caloric intake progressively decreased over time in the intensive care unit. For the intensive insulin-treated patients, in view of their virtually identical blood glucose levels, this indicated a progressively improving insulin resistance or endogenous insulin secretion.

all times, a prerequisite for attributing observations to intensive insulin therapy.

Of all patients in the ICU for >5 days (*n* = 451), the group among whom intensive insulin therapy reduced mortality, 60% (*n* = 267) received combined parenteral-enteral feeding with up to a mean of 68% of nutrients administered enterally. After 7 days in the ICU, 85% of

the patients received at least partial enteral nutrition. Intensive insulin therapy was equally effective regardless of whether patients received enteral feeding in the ICU: mortality was reduced from 18.8% to 10.2% ( $p < .05$ ) in the group in the ICU for  $>5$  days and receiving combined parenteral-enteral feeding and from 22.3% to 11.1% ( $p < .05$ ) in the parenterally fed only group. Effects on morbidity were equally independent of feeding regimen.

With the nutritional strategy applied, 99% of patients in the intensive insulin group required exogenous insulin to maintain mean blood glucose levels at  $103 \pm 1$  mg/dL. In the conventionally treated group, only 39% of patients revealed blood glucose levels peaking at  $>215$  mg/dL and thus required exogenous insulin. Mean blood glucose level for the entire conventionally treated group therefore was  $153 \pm 1$  and  $173 \pm 2$  mg/dL for the subgroup requiring insulin. In both study groups, targeted ranges of blood glucose were reached within 24 hrs of intensive care.

Daily insulin dose was  $68 \pm 2$  units in the patients randomized to receive intensive insulin therapy ( $70 \pm 2$  units/day in the patients actually receiving insulin) and  $12 \pm 1$  units/day in the conventionally treated patients ( $41 \pm 3$  units/day in the patients actually receiving insulin). The mean hourly doses on a daily basis are depicted in Figure 1, *second panel from top*. Insulin requirements to reach normoglycemia were highest and most variable among patients during the first 6 hrs after admission (mean, 7 units/hr; in 10% of the patients,  $>20$  units/hr). Normoglycemia was reached within 24 hrs with, for a 70 kg patient, a mean of 77 units/day, for a mean of 550 calories on the first day and 94 units/day on ICU day 7 when full nutrition was given (a mean of 1600 calories). After day 7, caloric intake remained constant, although insulin doses decreased by 40% from day 7 to day 12, remaining stable thereafter. At all times, the within-patient variability of the insulin dose remained within a mean of 75% (95% confidence interval of 25% to 125%) of the insulin dose on day 1.

In 0.8% of conventionally treated patients and 5.2% of intensive insulin-treated patients ( $p < .0001$ ), hypoglycemia ( $<40$  mg/dL) occurred after a median of 11 (2–20) and 6 (2–14) days, respectively ( $p = .6$ ). In 18% of the intensive insulin-treated patients who encountered hyperglycemia, such an event

occurred at more than one (median, 3 [2–4]) occasion. More than one hypoglycemic event did not occur in conventionally treated patients. Of all episodes of hypoglycemia, 90% occurred after stable blood glucose levels within the targeted range had been reached, and 62% of those occurred in association with interruption of enteral feeding, which was inadvertently done without adequately reducing the insulin dose. Because of the frequent insulin dose adjustments, particularly when blood glucose levels dropped steeply, hypoglycemia episodes were always brief and serious complications, such as hemodynamic deteriorations, convulsions, or permanent consequences, did not occur.

**Factors Determining Insulin Requirements.** On univariate analysis, the factors significantly correlated with the hourly insulin dose required to maintain normoglycemia were body mass index ( $R = .34$ ,  $R^2 = .12$ ), history of diabetes, which was present in 13% of patients in both study groups ( $Rho = 0.50$ ), reason for ICU admission ( $Rho = 0.08$ ), Acute Physiology and Chronic Health Evaluation (APACHE)-II at admission ( $Rho = 0.10$ ), blood glucose level at admission ( $R = .34$ ,  $R^2 = .12$ ), mean daily caloric intake ( $R = .23$ ,  $R^2 = .05$ ), concomitant treatment with glucocorticoids ( $Rho = 0.37$ ), and time in ICU ( $R = -.14$ ,  $R^2 = .02$ ) (Figs. 1 and 2). Stepwise linear regression analysis revealed that they were all independent determinants, except for APACHE-II score (15) (positively correlated with at-admission glycemia;  $Rho = 0.14$ ,  $p < .0001$ ) and concomitant treatment with glucocorticoids (related to reason for ICU admission;  $>86\%$  of the transplanted patients received glucocorticoids vs. 24–30% among all other patient groups;  $p < .0001$ ). Taken together, the independent factors (in order of impact: history of diabetes, body mass index, blood glucose level at admission, caloric intake, time in the ICU, and reason for ICU admission) explained 36% of the variability in mean hourly insulin requirements to maintain normoglycemia.

Caloric intake, an independent determinant of insulin dose required to maintain normoglycemia, varied according to the type of illness (more calories were given to vascular surgery patients, brain surgery, or cerebral trauma patients and multiple trauma patients compared with the other subgroups) and with time in the ICU (Fig. 1, *top panel*). Hence, assessment of differences in insulin requirement to maintain the preset glycemic

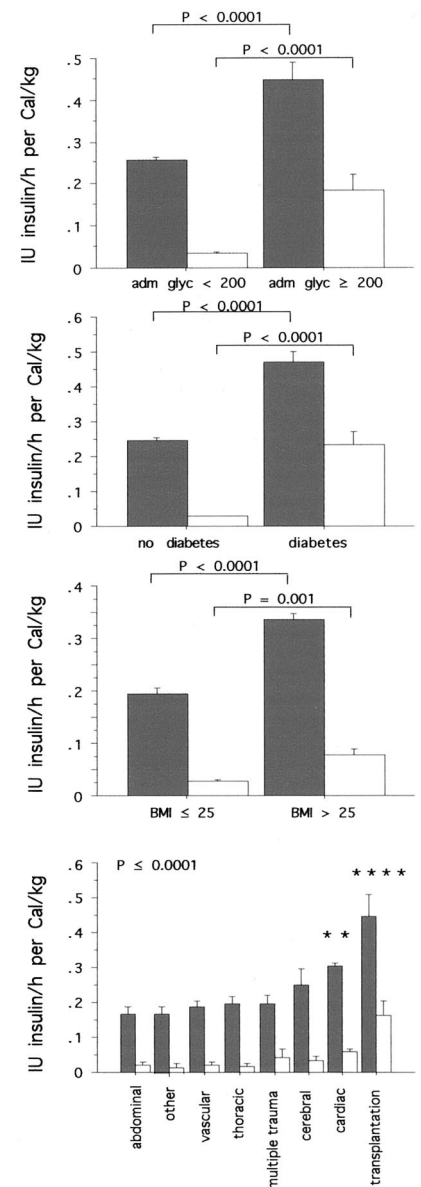


Figure 2. Mean daily insulin doses (units per hour) corrected for caloric intake per kilogram of body weight for the different independent at-admission determinants of outcome (hyperglycemia of  $>200$  mg/dL at intensive care unit admission, a history of diabetes, a high body mass index, and reason for intensive care unit admission) in both study groups (intensive insulin-treated patients in filled bars; conventionally treated patients in open bars). The higher insulin requirements to maintain normoglycemia in the transplantation group ( $p < .0001$  vs. all other groups) were explained at least partially by the concomitant administration of high doses of glucocorticoids. Data are expressed as mean  $\pm$  SEM. The  $p$  values were obtained using Mann-Whitney U test or analysis of variance, when appropriate, and were corrected for multiple comparisons.  $****p < .0001$ ;  $**p = .005$  vs. all other groups.

range with time in the ICU (Fig. 1, *second panel from bottom*) and among the different patient groups (Fig. 2) was done by

comparing the ratio of hourly insulin dose (IU/hr) over caloric intake (calories/kg body weight<sup>-1</sup>·24 hrs<sup>-1</sup>). In the intensive insulin-treated patients, in whom blood glucose levels were tightly “clamped” between 80 and 110 mg/dL, and hence virtually similar at all times, this ratio of insulin dose over caloric intake is also a surrogate marker of insulin resistance. In both study groups, this ratio continued to decrease significantly over time ( $p < .0001$ ) (Fig. 1, second panel from bottom).

Among patients in the ICU for >5

days, the route of feeding determined this ratio: the insulin dose required to maintain normoglycemia, corrected for caloric intake per kilogram of body weight, was a median 26% higher in exclusively parenterally fed patients compared with those receiving at least some enteral nutrition ( $p = .007$ ).

*Analysis of the Impact of Actual Glycemic Control Vs. Amount Of Infused Insulin On Mortality and Morbidity.* For the entire study group, the mean daily insulin dose and the mean blood glucose

level were entered into a multivariate logistic regression model together with all other univariate determinants of adverse outcome (age, delayed ICU admission, at-admission APACHE-II score, reason for ICU admission, history of malignancy and diabetes, at-admission hyperglycemia) (5, 7, 16). For ICU mortality (Table 1), both the mean daily amount of infused insulin ( $p = .005$ ) and the mean level of blood glucose during ICU stay ( $p < .0001$ ) were independent positive risk factors. For critical illness polyneuropathy ( $p <$

Table 1. Multivariate logistic regression analysis of all univariate determinants of intensive care unit (ICU) mortality

	OR	95% CI	p Value
Age (per 10 yrs added)	1.360	1.140–1.580	.001
Delayed ICU admission	1.882	1.069–3.314	.03
At-admission APACHE II >9	5.054	2.524–10.120	<.0001
Reason for ICU admission (vs. cardiac surgery OR 1)			
Multiple trauma or severe burns	4.851	1.664–14.141	.004
Neurologic disease, cerebral trauma, or brain surgery	4.814	2.044–11.339	.0003
Thoracic surgery and/or respiratory insufficiency	2.966	1.242–7.084	.01
Abdominal surgery and/or peritonitis	2.466	1.017–5.979	.05
Transplantation	0.746	0.197–2.820	.7
Vascular surgery	1.336	0.433–4.123	.6
Other	1.904	0.642–5.644	.2
History of malignancy	1.504	0.779–2.905	.2
At-admission hyperglycemia ( $\geq 200$ mg/dL)	1.128	0.601–2.116	.7
History of diabetes	0.356	0.158–0.803	.01
Daily insulin dose (per 10 units added)	1.060	1.020–1.090	.005
Mean blood glucose level (per 20 mg/dL added)	1.300 <sup>a</sup>	1.180–1.420	<.0001

OR, odds ratio; CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation.

<sup>a</sup>An adjusted odds ratio of 1300 for mean blood glucose level (per 20 mg/dL added) indicates that for every 20 mg/dL increase in blood glucose concentration, the risk of death increases by 30%. In other words, for a blood glucose level of 200 mg/dL, the risk of death is 2.5 times higher than for a blood glucose level of 100 mg/dL. Identifying daily insulin dose as a positive rather than a negative risk factor for death in the ICU indicates that it was not the amount of infused insulin per se that mediated the reduction of ICU mortality with intensive insulin therapy.

Table 2. Multivariate regression analysis of the impact of insulin dose vs. blood glucose level on morbidity, after correction for age, reason for intensive care unit admission and admission delay, Acute Physiology and Chronic Health Evaluation II, history of malignancy and diabetes, and for at-admission hyperglycemia

	OR	95% CI	p Value
Critical illness polyneuropathy			
Daily insulin dose (per 10 units added)	0.990	0.950–1.030	.7
Mean blood glucose level (per 20 mg/dL added)	1.240 <sup>a</sup>	1.140–1.360	<.0001
Bacteremia			
Daily insulin dose (per 10 units added)	1.000	0.960–1.040	.9
Mean blood glucose level (per 20 mg/dL added)	1.140	1.020–1.280	.02
>3 days CRP > 150 mg/L			
Daily insulin dose (per 10 units added)	1.040	1.010–1.070	.02
Mean blood glucose level (per 20 mg/dL added)	1.160	1.060–1.240	.0006
Acute renal failure requiring renal replacement therapy			
Daily insulin dose (per 10 units added)	0.940	0.880–1.000	.03
Mean blood glucose level (per 20 mg/dL added)	1.001	0.880–1.140	.9
>2 red cell transfusions			
Daily insulin dose (per 10 units added)	0.980	0.940–1.020	.3
Mean blood glucose level (per 20 mg/dL added)	1.100	1.000–1.220	.06

OR, odds ratio; CI, confidence interval; CRP, C-reactive protein.

<sup>a</sup>An adjusted odds ratio of 1.240 for mean blood glucose level (per 20 mg/dL added) indicates that for every 20 mg/dL increase in blood glucose concentration, the risk of critical illness polyneuropathy increases by 24%. In other words, for a blood glucose level of 200 mg/dL, the risk of critical illness polyneuropathy is 2.2 times higher than for a blood glucose level of 100 mg/dL.

.0001), bacteremia ( $p = .02$ ), and need for red cell transfusion ( $p = .06$ ) (Table 2), only the mean level of blood glucose during ICU stay, and not the insulin dose, seemed to be an independent risk factor. For the occurrence of prolonged inflammation (defined as  $>3$  days with a C-reactive protein level of  $>150$  mg/L), the insulin dose ( $p = .02$ ) and the level of blood glucose ( $p = .0006$ ) were independent positive risk factors. In contrast, for acute renal failure and the need for renal replacement therapy, not the actual level of blood glucose but the dose of insulin was an independent negative predictor ( $p = .03$ ).

Among the long-stay patients (ICU stay of  $>5$  days), the group in which intensive insulin therapy reduced mortality and morbidity (12), a *post hoc* analysis suggested a gradual decrease in risk of ICU (Fig. 3) and hospital death (Fig. 4), with decreasing blood glucose levels ( $<110$  mg/dL, 110–150 mg/dL,  $>150$  mg/dL) without an identifiable threshold below which no further risk reduction occurred. Also for the occurrence of critical illness polyneuropathy, bacteremia, need for red cell transfusion, and acute renal failure, the risk was lower among patients with maintained strict normoglycemia compared with patients in whom the blood glucose level was moderately elevated (110–150 mg/dL). There was no identifiable threshold blood glucose level below which no further reduction of risk of these complications occurred (Fig. 3). In contrast, for prevention of prolonged inflammation, as defined by a C-reactive protein-level of  $>150$  mg/L for  $>3$  days, the threshold blood glucose level may be higher than 110 mg/dL (Fig. 3).

## DISCUSSION

Strict maintenance of normoglycemia with intensive insulin therapy has been shown to reduce intensive care and hospital mortality and morbidity of critically ill adult patients in a surgical ICU (12). We report here that lowering of blood glucose, achieved with insulin titration according to a simple algorithm, rather than the actual amount of insulin given, was most significantly related to the observed reduction in mortality, critical illness polyneuropathy, bacteremia, inflammation, and anemia but not to the prevention of acute renal failure for which the insulin dose was an independent determinant.

Normoglycemia could be effectively and safely reached within 24 hrs after ICU admission and maintained throughout ICU stay by medically-supervised, nurse-controlled insulin titration, guided by a simple titration algorithm. A few at-admission patient- and disease-related factors (body mass index, history of diabetes, reason for ICU admission, at-admission hyperglycemia) (5, 7, 16, 17), the mean daily amount of calories per kilogram of body weight, the time in ICU and concomitant medication such as glucocorticoids were able to predict insulin requirements for 36%. This indicates that 64% of the insulin dose adjustments were not predictable by the studied variables and thus were based on the frequently measured blood glucose levels and empirically guided by factors such as the time course of the previous changes in blood glucose level, an eventual rise in body temperature, and intercurrent infections,

as advised in the insulin titration guidelines.

Episodes of hypoglycemia occurred infrequently, although more often with intensive insulin therapy than with conventional insulin therapy. Hypoglycemic episodes were never accompanied by serious adverse events because the algorithm guaranteed quick detection and correction. Hypoglycemia occurred in the stable phase, mostly after the first week of intensive care, and was often attributable to human error such as inadequate insulin dose reduction during interruption of enteral feeding. After implementation of intensive insulin therapy as part of routine clinical patient care in our ICU, these errors seemed avoidable with progressively increasing experience of the nursing team. Targeting blood glucose control tightly below 110 mg/dL seemed necessary to optimally prevent ICU and in-hospital deaths, critical illness polyneuropathy, bacteremia, anemia, and

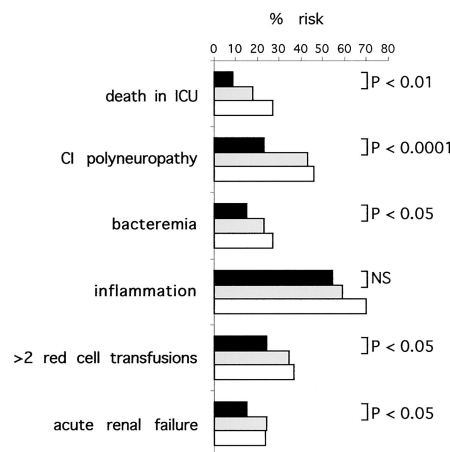


Figure 3. *Post hoc* analysis of the percentage of risk of death in the intensive care unit (ICU), development of critical illness (CI) polyneuropathy, bacteremia, inflammation (C-reactive protein-level higher than 150 mg/L for  $>3$  days), need for more than two red cell transfusions, and acute renal failure requiring hemofiltration/dialysis among long-stay ( $>5$  days) patients stratified for mean blood glucose levels. Filled bars represent patients with a mean blood glucose level of  $<110$  mg/dL; shaded bars represent patients with a mean blood glucose level between 110 and 150 mg/dL; unfilled bars represent patients with a mean blood glucose level higher than 150 mg/dL. At baseline, the three groups were comparable for the independent risk factors for adverse outcome, as determined by multivariate logistic regression analysis (Table 1). The  $p$  values were obtained using the chi-square test and indicate the level of significance of the difference between the  $<110$  mg/dL and the 110–150 mg/dL groups.

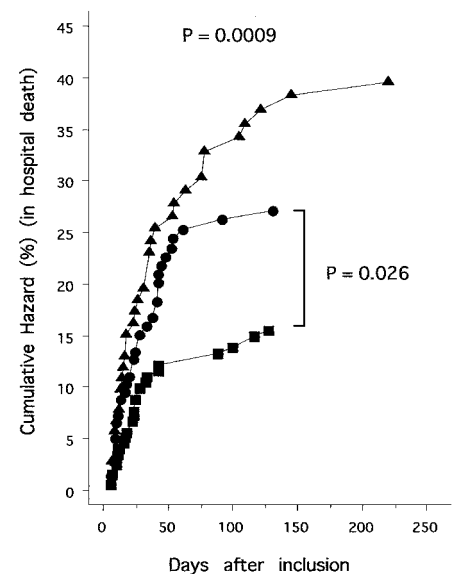


Figure 4. Kaplan-Meier cumulative risk of in-hospital death among long-stay ( $>5$  days) patients in the intensive care unit) patients with a mean blood glucose level of  $<110$  mg/dL (squares), with a mean blood glucose level between 110 and 150 mg/dL (circles), and in patients with a mean blood glucose level of  $>150$  mg/dL (triangles). At baseline, the three groups were comparable for the independent risk factors for adverse outcome as determined by multivariate logistic regression analysis (Table 1). A  $p$  value of .0009, obtained with Mantel-Cox log-rank test, indicates the significance level of the overall difference in risk of death among the groups, and a  $p$  value of .026 indicates the significance level of the difference between the  $<110$  mg/dL and the 110–150 mg/dL groups.

**N**ormoglycemia was safely reached within 24 hrs and maintained during intensive care by using insulin titration guidelines.

acute renal failure, as even moderate hyperglycemia (110–150 mg/dL) was associated with higher risk of these complications. Hence, the higher risk of brief hypoglycemia was clearly outweighed by the observed benefits of intensive insulin therapy.

In the studied population that received progressively increasing amounts of nutritional support, from a mean of 550 calories to a mean of 1600 calories during the first 7 days of intensive care administered via the parenteral or enteral route, the lowering of blood glucose rather than the amount of infused insulin was related to the observed benefits of the intervention, as indicated by the multivariate logistic regression analysis. Although the study was not specifically designed to evaluate the separate impact of infused insulin and of metabolic control, these results point to an important role of the latter. Indeed, although direct effects of insulin such as anti-inflammatory effects through suppression of cytokine production or signaling (18) or anabolic effects (19) may have played a role, favorable effects mediated specifically by the prevention of hyperglycemia seem to have dominated. Examples of the latter are improvement of coagulation and fibrinolysis (20) and of macrophage function (21), acting alone or together. Whether the lowering of the blood glucose was the primary effector or rather a simple reflection of other metabolic effects of intensive insulin therapy, such as improved clearance and, hence, less toxicity of circulating fatty acids, remains unclear.

The results also indicate that the observed benefits of our strategy to maintain normoglycemia with insulin (mean,  $0.04 \text{ IU}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ ) during normal intake of glucose (mean, 9 g/hr) and calories (mean,  $19 \text{ calories}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ ) probably differ from those of glucose-insulin-potassium solutions, used for improve-

ment of cardiac performance during and after myocardial injury (22, 23). The goal of glucose-insulin-potassium infusions is to stimulate myocardial metabolism of glucose instead of fatty acids when oxygen supply is compromised. Hence, glucose-insulin-potassium solutions include a much higher dose of both insulin (ranging from 0.1 to  $1 \text{ IU}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ , depending on the protocol used) and glucose (ranging from 30 to 80 g/hr) than what we provided, and most importantly, these solutions are infused without targeting normoglycemia. In fact, most studies on glucose-insulin-potassium have reported substantial hyperglycemia. We found that it was a low level of blood glucose, rather than a high insulin dose, that apparently protected against most ICU complications and death, without an identifiable threshold, below which no further risk reduction occurred. Together, these observations suggest that perhaps glucose-insulin-potassium infusions may be more beneficial in the absence of hyperglycemia. Our data are in line with the absence of a glycemic threshold for the prevention of most long-term complications with intensive insulin therapy in patients with type-I diabetes, as was shown in the Diabetes Control and Complications Trial (24, 25). However, for prevention of prolonged inflammatory responses during critical illness, here defined as C-reactive protein levels higher than 150 mg/L for >3 days, blood glucose levels somewhat higher than 110 mg/dL may still be effective.

The prevention of acute renal failure, for which the insulin dose was an independent determinant, seemed a notable exception. This observation may either point to a direct protective effect of insulin on the kidney or to the fact that insulin is to a large extent cleared through the kidney (26), which may reduce the need for exogenous insulin in patients with acute renal failure. Alternatively, the lower insulin requirements to maintain normoglycemia in patients on hemofiltration can also be explained by the fact that hemofiltration clears glucose from the blood proportionately to the hemofiltration volume and thus to a much greater extent than does the normal kidney.

Insulin requirements, particularly when corrected for caloric intake, decreased steadily with time in the ICU. Insulin doses were highest and varied substantially among patients during the first 6 hrs after ICU admission. Within

the first 24 hrs, normoglycemia was reached (on average, for a 70 kg patient) with 70 units of insulin per 500 calories. Maintenance of normoglycemia was achieved with insulin doses progressively decreasing to about 20 units per 500 calories on day 7 of intensive care. Besides this progressively decreasing insulin requirement, within-patient insulin dose variations remained limited. Because the majority (87%) of the patients were not previously diabetic, and because blood glucose levels in the intensive insulin group were indeed adequately clamped around 100 mg/dL from day 1 until the last day in the ICU, the decreasing insulin requirements with time in the ICU reflect several-fold improvement of either insulin resistance or endogenous insulin production.

We observed a 26% higher insulin requirement to maintain normoglycemia for identical amounts of calories in patients who received exclusively parenteral feeding compared with those who received enteral nutrition. This can be explained by the incretin effects on insulin secretion with enteral feeding in nondiabetic subjects (27). Furthermore, endogenous insulin released by enteral feeding is likely to induce more pronounced suppression of hepatic gluconeogenesis and more hepatic glucose uptake than peripherally infused insulin (28).

The higher insulin requirements to obtain normoglycemia in patients fed with parenteral compared with enteral feeding indicates that parenterally fed patients are more at risk for hyperglycemia. Furthermore, the outcome benefits of intensive insulin therapy were present regardless of the feeding regimen. Hence, our observations have implications for the controversy on early enteral feeding (29, 30). Indeed, some of the reported benefits of early enteral feeding may be explained by the concomitant lower risk of hyperglycemia. Our data suggest that the outcome advantage of early enteral nutrition as compared with parenteral feeding may fade when intensive insulin therapy is given to avoid hyperglycemia.

In conclusion, normoglycemia was safely reached within 24 hrs and maintained during intensive care by using simple insulin titration guidelines. The lowering of blood glucose levels, or effects reflected by normoglycemia, rather than the amount of infused insulin *per se* was related to the observed protective effects of intensive insulin therapy on morbidity and mortality.

## CONCLUSIONS

Normoglycemia was safely reached within 24 hrs and maintained during intensive care by using simple insulin titration guidelines. The lowering of blood glucose levels, or effects reflected by normoglycemia, rather than the amount of infused insulin *per se*, was related to the observed protective effects of intensive insulin therapy on morbidity and mortality.

We thank Ilse Milants, Jenny Gielens, An Andries, Myriam Vandenberg, and Viviane Celis for sample handling and data entering; Dr. Bruyninckx and the clinical fellows of the Department of Physical Medicine and Rehabilitation for the systematic electromyographic screening; the clinical ICU fellows for daily Acute Physiology and Chronic Health Evaluation II scoring; the nurses for excellent clinical care and protocol compliance; and Drs. Catherine Ingels, Jan Muller, Lars Desmet, An Wallijn, Herbert Fannes, Heidi Weyns, David Van Roosbroeck, and Carine Van Dijcke for patient care.

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