Original Article

Intensive Insulin Therapy in Mixed Medical/Surgical Intensive Care Units

Benefit Versus Harm

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Intensive insulin therapy (IIT) improves the outcome of prolonged critically ill patients, but concerns remain regarding potential harm and the optimal blood glucose level. These questions were addressed using the pooled dataset of two randomized controlled trials. Independent of parenteral glucose load, IIT reduced mortality from 23.6 to 20.4% in the intention-to-treat group ($n = 2,748; P = 0.04$) and from 37.9 to 30.1% among long stayers ($n = 1,389; P = 0.002$), with no difference among short stayers (8.9 vs. 10.4%; $n = 1,359; P = 0.4$). Compared with blood glucose of 110–150 mg/dl, mortality was higher with blood glucose >150 mg/dl (odds ratio 1.38 [95% CI 1.10–1.75]; $P = 0.007$) and lower with <110 mg/dl (0.77 [0.61–0.96]; $P = 0.02$). Only patients with diabetes ($n = 407$) showed no survival benefit of IIT. Prevention of kidney injury and critical illness polyneuropathy required blood glucose strictly <110 mg/day, but this level carried the highest risk of hypoglycemia. Within 24 h of hypoglycemia, three patients in the conventional and one in the IIT group died ($P = 0.0004$) without difference in hospital mortality. No new neurological problems occurred in survivors who experienced hypoglycemia in intensive care units (ICUs). We conclude that IIT reduces mortality of all medical/surgical ICU patients, except those with a prior history of diabetes, and does not cause harm. A blood glucose target <110 mg/day was most effective but also carried the highest risk of hypoglycemia. *Diabetes* 55:3151–3159, 2006

W e previously performed two randomized controlled trials, one of surgical ($n = 1,548$) and one of medical ($n = 1,200$) intensive care unit (ICU) patients, investigating the impact of intensive insulin therapy (IIT) during critical illness (1,2). In both studies, mean blood glucose levels in the conventional and IIT groups were, on average, 150–160 vs. 90–100 mg/dl, respectively. In the surgical study, in-hospital mortality was lowered from 10.9 to 7.2% in the total group of 1,548 patients, which was explained by a much larger effect among patients treated at least a few days. Indeed, mortality was reduced from 20.6 to 13.6% among patients treated at least 3 days and from 26.3 to 16.8% for patients treated at least 5 days. The medical ICU study used an identical study protocol and, based on the results of the surgical study, was statistically powered for an effect among patients in ICUs for at least 3 days. The intention-to-treat analysis of all 1,200 medical patients showed no significant difference in hospital mortality (39.9% in the control group and 37.2% in the IIT group). However, among the 767 patients in the ICU ≥3 days, IIT significantly reduced hospital mortality from 52.5 to 43.0%. Among the patients treated <3 days, more deaths occurred in the IIT than in the conventional group, but the numbers were too small to draw definitive conclusions on causality.

Since the publication of these trials, concerns have risen about the benefit versus potential harm by IIT when implemented in ICUs with a medical/surgical case mix; on the impact in certain subgroups of patients, such as those with sepsis or short stayers; on the optimal blood glucose target; and on the role of parenteral nutrition (3–7). To address these issues, we pooled the databases of the two randomized controlled trials ($n = 2,748$). This created the statistical power to investigate potential harm evoked by brief (<3 days) treatment in mixed medical/surgical populations (8). Furthermore, the large sample size allowed attempts to identify subgroups of patients who may not benefit from IIT, to determine the optimal level of blood glucose control, and to study consequences of hypoglycemia.

RESEARCH DESIGN AND METHODS

The study design has been previously reported (1,2). In brief, upon ICU admission, patients were randomly assigned to IIT or the conventional approach. Assignment to treatment groups was done by blinded envelopes, stratified according to diagnostic category, and balanced with the use of permuted blocks of 10. In the conventional group, continuous insulin infusion of 50 IU Actrapid HM (Novo Nordisk, Bagsvaerd, Denmark) in 50 ml NaCl (0.9% using a Perfusor-FM pump [B. Braun, Melsungen, Germany]) was started only when blood glucose levels exceeded 215 mg/dl and adjusted to keep blood glucose between 180 and 200 mg/dl. When blood glucose fell <180 mg/dl, insulin infusion was tapered and eventually stopped. In the IIT group, insulin infusion was started when blood glucose levels exceeded 110 mg/day and adjusted to maintain normoglycemia (80–110 mg/day). Maximal insulin dose was arbitrarily set at 50 IU/h. At discharge from the ICU, a conventional approach was adopted (maintenance of blood glucose levels ≤200 mg/dl).

TABLE 1
Baseline patient characteristics

Insulin treatment	Intention to treat (n = 2,748)			In ICU at least 3 days (n = 1,389)			In ICU <3 days (n = 1,359)		
	Conventional	Intensive	P value	Conventional	Intensive	P value	Conventional	Intensive	P value
n	1,388	1,360		702	687		686	673	
Medical ICU	606 (43.6)	595 (43.8)	>0.9	381 (54.3)	386 (56.2)	0.5	224 (32.7)	209 (31.0)	0.5
Male sex	939 (67.7)	900 (66.2)	0.2	458 (65.2)	434 (63.2)	0.4	481 (70.1)	466 (69.2)	0.7
Age (years)	63 ± 15	63 ± 15	0.4	63 ± 16	62 ± 15	0.3	63 ± 14	65 ± 14	0.009
BMI (kg/m^2)	25.4 ± 4.9	25.7 ± 4.9	0.06	25.1 ± 5.3	25.6 ± 5.4	0.07	25.6 ± 4.5	25.8 ± 4.4	0.5
History of diabetes	200 (14.4)	207 (15.2)	0.5	95 (13.5)	95 (13.8)	0.9	105 (15.3)	112 (16.6)	0.5
Insulin treated	84 (6.1)	104 (7.6)		39 (5.6)	57 (8.3)		45 (6.6)	47 (6.9)	
Oral antidiabetic treatment and/or diet	116 (8.3)	103 (7.6)		56 (7.9)	38 (5.5)		60 (8.7)	65 (9.7)	
Diagnostic group			>0.9			0.8			0.5
Cardiovascular disease/high-risk cardiac or complicated vascular surgery	549 (39.6)	533 (39.2)		172 (24.5)	156 (22.7)		377 (54.9)	377 (56.0)	
Respiratory/complicated pulmonary or esophageal surgery	317 (22.8)	317 (23.3)		204 (29.1)	229 (33.3)		113 (16.5)	88 (13.1)	
Gastrointestinal or hepatic disease/complicated abdominal surgery	210 (15.1)	199 (14.6)		125 (17.8)	104 (15.1)		85 (12.4)	95 (14.1)	
Neurology/neurosurgery	61 (4.4)	63 (4.6)		42 (6.0)	42 (6.1)		19 (2.8)	21 (3.1)	
Hematology/oncology	51 (3.7)	46 (3.4)		37 (5.3)	39 (5.7)		14 (2.0)	7 (1.0)	
Solid organ transplants	44 (3.2)	46 (3.4)		15 (2.1)	18 (2.6)		29 (4.2)	28 (4.2)	
Polytrauma	35 (2.5)	33 (2.4)		29 (4.1)	28 (4.1)		6 (0.9)	5 (0.7)	
Renal/metabolic	31 (2.2)	33 (2.4)		21 (3.0)	18 (2.6)		10 (1.5)	15 (2.2)	
Other	90 (6.5)	90 (6.6)		57 (8.1)	53 (7.7)		33 (4.8)	37 (5.5)	
Sepsis	471 (33.9)	479 (35.2)	0.8	324 (46.1)	345 (50.2)	0.3	147 (21.5)	134 (19.9)	0.7
Active malignancy	247 (17.8)	256 (18.8)	0.5	152 (21.7)	155 (22.6)	0.7	95 (13.8)	101 (15.0)	0.5
Ventilated upon admission	1,186 (85.4)	1,152 (84.7)	0.6	644 (91.7)	627 (91.3)	0.8	542 (79.0)	525 (78.0)	0.7
Baseline APACHE II score	16 ± 9	15 ± 10	0.4	18 ± 9	18 ± 10	>0.9	13 ± 9	12 ± 8	0.2
On admission blood glucose (mg/dl)	152 ± 60	148 ± 59	0.2	157 ± 64	154 ± 61	0.5	146 ± 55	142 ± 57	0.2

Data are n (%) or means ± SD. Sepsis was defined using modified Bone criteria (ref. 21) as suspected or documented infection on ICU admission day and fulfilment of at least two of three systematic inflammatory response syndrome criteria for which data were available: *1*) receiving ventilatory support, *2*) white blood cell count ≤4,000 or ≥12,000/l, and *3*) temperature ≤36 or ≥38°C. Patients after cardiac surgery or trauma were excluded for this definition.

Insulin dose was adjusted according to whole blood glucose levels, measured at 1- to 4-h intervals in arterial blood (or when an arterial line was not available, capillary blood was used) using the ABL700 analyzer (Radiometer Medical, Copenhagen, Denmark) or a point-of-care glucometer (HemoCue B-glucose; HemoCue, Ángelholm, Sweden). Both were calibrated to plasma glucose. The normal nursing staff (one nurse taking care of two patients) performed the insulin titration.

When patients were hemodynamically stable, feeding was started according to European guidelines (9). In both studies, patients who were anticipated not to be able to take normal oral feeding within 5 days received enteral feeding as early as possible. When sufficient amount of calories could not be given enterally, parenteral supplements were given to meet estimated caloric needs. Written informed consent was obtained from the closest family member. The study protocols were approved by the institutional review board of the Catholic University of Leuven.

Outcome measures. Since the two previous studies had identical protocols and were performed sequentially between 2000 and 2005 in one academic center with randomization using permuted blocks of 10, pooling of the databases (n = 2,748) allowed us to address benefit versus harm in a larger sample. The impact of IIT in this mixed population was assessed by analysis of the intention-to-treat group (n = 2,748). To determine whether brief (<3 days) IIT caused harm, analyses were also done for the long-stay (≥3 days in ICU; n = 1,389) and short-stay (<3 days in ICU; n = 1,359) equal-sized subgroups. To define whether certain subgroups, identifiable upon ICU admission, may not benefit from IIT, the large diagnostic subgroups (containing at least 400 patients) were considered separately. These were patients with surgical or medical *1*) cardiovascular insults, *2*) respiratory insults, *3*) gastrointestinal insults as reason for ICU admission, *4*) sepsis, *5*) malignancy,

and *6*) with a prior history of diabetes. To address whether the major role of IIT may be to prevent toxicity of high-parenteral glucose load (4,5,7), we stratified patients into three tertiles of daily intravenous glucose load. The independent impact of blood glucose level (mean daily value <110 mg/day, 110–150 mg/day, or >150 mg/day) and of insulin dose was also evaluated.

For morbidity, we here focused on the two major end points that were not affected by the unblinded study design, including *1*) newly acquired kidney injury occurring during time in the ICU (defined using modified RIFLE [risk, injury, failure, loss, end-stage kidney disease] criteria as at least doubling of admission plasma creatinine [10]) and *2*) critical illness polyneuropathy. All patients still in the ICU on day 7 after admission (n = 825) were screened for critical illness polyneuropathy by electromyography (EMG) of all limbs. EMG was repeated weekly for the duration of ICU stay. Patients with preexisting neuromuscular disorders were excluded. EMGs had been evaluated by an independent investigator who was unaware of treatment allocation. The diagnosis of critical illness polyneuropathy was exclusively based on the presence of abundant spontaneous activity in the form of positive sharp waves and fibrillation potentials in multiple distal and proximal muscles in all extremities. Muscles innervated by nerves susceptible to pressure palsies were avoided.

Consequences of hypoglycemia (blood glucose ≤40 mg/dl) were assessed independently by two investigators (I.M. and B.B.) who were unaware of insulin treatment allocation. This analysis was done by reviewing all ICU and hospital charts of the patients with hypoglycemia. Actions taken upon diagnosis of hypoglycemia and time to normalization of blood glucose were noted. Sweating, hemodynamic collapse or arrhythmia, decreased consciousness, epilepsy, or coma within 8 h of hypoglycemia were considered to be possible immediate consequences. Altered neurological status, epilepsy,

TABLE 2
Insulin therapy, nutrition, blood glucose control, and hypoglycemia

	Intention to treat ($n = 2,748$)			In ICU at least 3 days ($n = 1,389$)			In ICU <3 days ($n = 1,359$)		
	Conventional	Intensive	P value	Conventional	Intensive	P value	Conventional	Intensive	P value
n	1,388	1,360		702	687		686	673	
Total amount of feeding (kcal $\cdot$ kg^{-1} $\cdot$ day^{-1})	15 ± 8	15 ± 8	0.2	20 ± 6	19 ± 7	0.06	10 ± 5	10 ± 5	0.7
Amount of parenteral calories (kcal $\cdot$ kg^{-1} $\cdot$ day^{-1})*	13 ± 7	13 ± 7	0.7	16 ± 7	16 ± 7	>0.9	10 ± 5	10 ± 5	0.7
Amount of enteral calories (kcal $\cdot$ kg^{-1} $\cdot$ day^{-1})†	2.3 ± 0.1	1.9 ± 0.1	0.1	4.2 ± 0.2	3.5 ± 0.2	0.08	0.4 ± 0.07	0.2 ± 0.04	0.4
Number of patients receiving predominantly parenteral calories‡	1,166 (85)	1,175 (87)	0.2	525 (75)	531 (77)	0.3	641 (96)	644 (97)	0.3
Average daily amount of intravenous glucose (g/day)*	160 ± 66	161 ± 64	0.8	179 ± 65	179 ± 64	>0.9	141 ± 62	143 ± 60	0.6
Number of patients receiving at least some enteral nutrition‡	555 (40)	511 (38)	0.2	468 (67)	443 (64)	0.4	87 (13)	68 (10)	0.1
Daily insulin dose (IU/day)	1 (0–24)	59 (37–84)	<0.0001	7 (0–36)	68 (47–96)	<0.0001	0 (0–12)	48 (30–73)	<0.0001
Mean blood glucose level (mg/dl)	152 ± 32	105 ± 24	<0.0001	152 ± 27	103 ± 21§	<0.0001	151 ± 35	107 ± 27§	<0.0001
In lowest tertile of intravenous glucose	149 ± 37‖	107 ± 26‖	<0.0001	147 ± 28¶	103 ± 14		150 ± 41	109 ± 31‖	<0.0001
In middle tertile of intravenous glucose	151 ± 30	105 ± 22	<0.0001	152 ± 27	105 ± 19	<0.0001	151 ± 32	104 ± 32‖	<0.0001
In highest tertile of intravenous glucose	154 ± 28‖	104 ± 24‖	<0.0001	155 ± 27¶	103 ± 24	<0.0001	153 ± 29	105 ± 22	<0.0001
Patients per strata of blood glucose control			<0.0001			<0.0001			<0.0001
>150 mg/dl	656 (47.5)	41 (3.0)		353 (50.3)	10 (1.5)		303 (44.5)	31 (4.6)	
110–150 mg/dl	639 (46.2)	374 (27.7)		322 (45.9)	160 (23.4)		317 (46.6)	214 (32.1)	
<110 mg/dl	87 (6.3)	935 (69.3)		27 (3.8)	514 (75.1)#		60 (8.8)	421 (63.2)#	
Hypoglycemia	25 (1.8)	154 (11.3)	<0.0001	20 (2.8)	130 (18.9)	<0.0001	5 (0.7)	24 (3.6)	0.0003
More than one hypoglycemic event	5 (0.4)	31 (2.3)	<0.0001	3 (0.4)	30 (4.4)	<0.0001	2 (0.3)	1 (0.2)	0.6
Level of blood glucose during hypoglycemia (mg/dl)	32 ± 7	33 ± 5	0.7	32 ± 7	33 ± 5	0.7	32 ± 8	32 ± 6	>0.99
Hypoglycmia without insulin	6 (0.4)	5 (0.4)	0.8	5 (0.7)	4 (0.6)	0.8	1 (0.1)	1 (0.1)	1.0
Mean daily amount of kilocal administered to patients with hypoglycemia (kcal $\cdot$ kg^{-1} $\cdot$ day^{-1})	20 ± 7	20 ± 7	>0.9	23 ± 5	22 ± 6	0.4	9 ± 5	11 ± 5	0.5
Mean daily amount of kilocal administered to patients without hypoglycemia (kcal $\cdot$ kg^{-1} $\cdot$ day^{-1})	15 ± 8	14 ± 7	0.0002	20 ± 6	19 ± 7	0.0002	10 ± 5	10 ± 5	0.5
Among patients with hypoglycemia (n)	25	154		20	130		5	24	
Immediate (8 h) symptoms	3 (12.0)	6 (3.9)	0.1	2 (10.0)	5 (3.8)	0.3	1 (20.0)	1 (4.2)	0.4
Death within 24 h of hypoglycemia	3 (12.0)	1 (0.6)	0.0004	3 (15.0)	0 (0.0)	<0.0001	0 (0.0)	1 (4.2)	0.6
Hospital mortality	13 (52.0)	78 (50.6)	0.9	13 (65.0)	71 (54.6)	0.4	0 (0.0)	7 (29.2)	0.2
Late neurological sequellae (survivors)	0 (0.0)	3 (3.9)**	0.5	0 (0.0)	3 (5.1)**	0.5	0 (0.0)	0 (0.0)	1.0

Data are n (%), means ± SD, or median (interquartile range) unless otherwise indicated. *All intravenous calories were counted, including those for nonnutritional purposes such as solutes for intravenous drugs and bolus injections for correction of hypoglycemia. †Non–normally distributed data are represented as means ± SE; P values calculated by Mann-Whitney-U test. ‡Less than one-third of administered calories via the enteral route. §$P = 0.02$ for the difference between blood glucose control between IIT groups treated at least 3 days and those treated <3 days. ‖$P < 0.05$ and ¶$P < 0.01$ for comparison between the two marked tertiles among one randomization goup. #$P < 0.0001$ for the difference in distribution of patients in the different strata of blood glucose control among short-stay patients compared with long-stay patients. **Suffering from coma or epilepsy prior to hypoglycemia.

coma, or death at any time thereafter, until hospital discharge, were noted as possible late sequelae.

Statistical analysis. Baseline and outcome variables were compared using Student's t test, χ^2 test, and Mann-Whitney U test. The effect of the intervention on mortality and morbidity was assessed by comparing crude proportions using χ^2 test. In addition, odds ratios (ORs) were calculated by logistic regression analysis, correcting for baseline APACHE (Acute Physiology and Chronic Health Evaluation) II score (11) and for malignancy.

To assess the impact of the level of blood glucose control, a similar regression analysis was performed, replacing the randomized intervention (conventional versus intensive insulin) by 1) one of three strata of mean morning blood glucose (<110 mg/day; 110–150 mg/day; or >150 mg/day) and 2) the mean daily insulin dose. Since a history of diabetes predisposed to being in the >150 mg/dl group, the outcome analysis per strata of blood glucose control was also corrected for the history of diabetes.

Time to in-hospital death was assessed by Kaplan-Meier estimates and

TABLE 3
Outcome of mixed medical/surgical patients

Insulin treatment	Intention to treat group			In ICU at least 3 days			In ICU <3 days		
	Conventional	Intensive	P value	Conventional	Intensive	P value	Conventional	Intensive	P value
n	1,388	1,360		702	687		686	673	
Deaths during intensive care	225 (16.2)	179 (13.2)	0.02	195 (27.8)	149 (21.7)	0.009	30 (4.4)	30 (4.4)	0.9
OR (95% CI)*		0.76 (0.60–0.96)	0.02		0.67 (0.51–0.87)	0.003		1.27 (0.69–2.31)	0.4
In-hospital deaths	327 (23.6)	277 (20.4)	0.04	266 (37.9)	207 (30.1)	0.002	61 (8.9)	70 (10.4)	0.4
OR (95% CI)*		0.80 (0.65–0.98)	0.03		0.65 (0.51–0.83)	<0.0001		1.42 (0.93–2.17)	0.2
New kidney injury	107 (7.7)	61 (4.5)	0.0005	101 (14.4)	56 (8.2)	0.0003	6 (0.9)	5 (0.7)	0.8
OR (95% CI)*		0.58 (0.42–0.80)	0.0009		0.53 (0.38–0.75)	0.0003		1.28 (0.34–4.81)	0.7

	In ICU at least 7 days		
	Conventional	Intensive	P value
n	436	389	
Critical illness polyneuropathy (% of screened)	216 (49.5)	127 (32.6)	<0.0001
OR (95% CI)*		0.49 (0.37–0.65)	<0.0001

Data are n (%) unless otherwise indicated. *Corrected for APACHE-II score and malignancy. P values calculated by χ^2.

log-rank testing. Patients discharged alive from the hospital were considered survivors. The effect on time to a positive EMG diagnosis of critical illness polyneuropathy was assessed by cumulative hazard estimates and log-rank testing, censoring for early deaths.

Data are presented as means ± SD or medians (25th–75th percentile) unless indicated otherwise. P values were not adjusted for multiple comparisons, and values <0.05 were considered significant.

RESULTS

Baseline patient characteristics are described in Table 1. The study groups were comparable at baseline.

Nutrition and blood glucose control. Details on nutritional intake, insulin doses, and blood glucose control are shown in Table 2.

Impact on outcome of the mixed medical/surgical population and the optimal level of blood glucose control. Morbidity and mortality were significantly lower in the IIT group than in the conventional group, in the intention-to-treat analysis, and even more so in the long-stay subgroup (Table 3 and Figs. 1 and 2).

In the intention-to-treat group, in-hospital mortality was higher when the mean blood glucose level was >150 mg/dl (OR 1.38 [95% CI 1.10–1.75]; $P = 0.007$) and lower when the mean blood glucose level was <110 mg/day (0.77 [0.61–0.96]; $P = 0.02$) compared with 110–150 mg/dl. The benefit of a mean blood glucose level <110 mg/day, compared with 110–150 mg/dl, was even larger in the long-stay subgroup (0.71 [0.54–0.94]; $P = 0.02$) (Fig. 1). In the intention-to-treat group, but not in the long-stay subgroup, a higher mean daily insulin dose for any given blood glucose level was associated with higher hospital mortality (per 10 units of insulin per day: 1.04 [1.03–1.06]; $P < 0.0001$).

In the intention-to-treat analysis, the OR for newly acquired kidney injury when on IIT was 0.56 ([95% CI 0.41–0.78]; $P = 0.0005$). The OR for developing critical illness polyneuropathy when treated with IIT was 0.49 ([0.37–0.65]; $P < 0.0001$) compared with conventional therapy. A blood glucose level <110 mg/day was most effective to achieve these morbidity benefits (Fig. 2).

Potential harm by brief (<3 days) IIT. Among patients treated <3 days, morbidity or mortality were similar in IIT and conventional therapy groups (Table 3 and Fig. 1) and similar for the three strata of blood glucose control (Fig. 1).

Impact of IIT among subgroups of patients: who may not benefit? In all large diagnostic subgroups, except patients with a prior history of diabetes, morbidity and mortality were lower in the IIT than in the conventional group (Table 4). Among patients with diabetes, risk of death for the three strata of blood glucose control mirrored the pattern observed among patients without diabetes (Fig. 3). Among patients with diabetes, in-hospital mortality was 21.2% when mean blood glucose was 110–150 mg/dl; it was 21.6% among patients with a mean blood glucose level >150 mg/dl (OR 0.98 [95% CI 0.54–1.77]; $P = 0.9$) compared with 110–150 mg/dl and 26.2% when mean blood glucose level was <110 mg/day (1.28 [0.69–2.35]; $P = 0.4$) compared with 110–150 mg/dl. The insulin dose was not significantly associated with risk of death among patients with diabetes. Also, incidence of hypoglycemia in patients with diabetes was not higher than in other large subgroups (Table 4). The cause of death in nonsurvivors with a prior history of diabetes was more often of cardiac origin than among patients without a history of diabetes ($P = 0.04$) in both the IIT and conventional groups. In
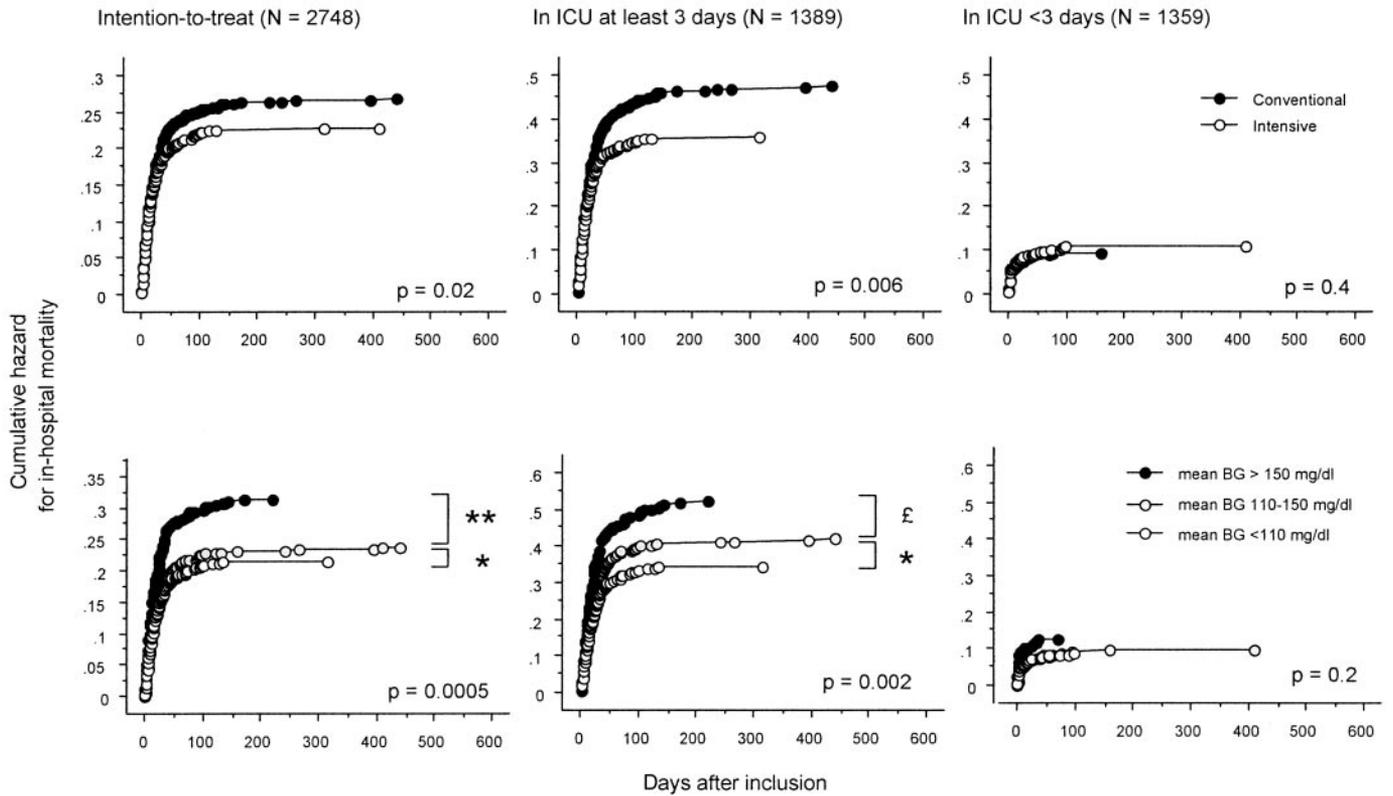
FIG. 1. Impact of IIT (*upper panels*) and of the level of blood glucose control (*lower panels*) on time to hospital mortality among short- and long-stay ICU patients. Numerical *P* values were obtained by log-rank test. Symbols reflect *P* values obtained by χ^2 testing for logistic regression analysis per level of blood glucose control. *$P = 0.02$; **$P = 0.007$; £$P = 0.07$.
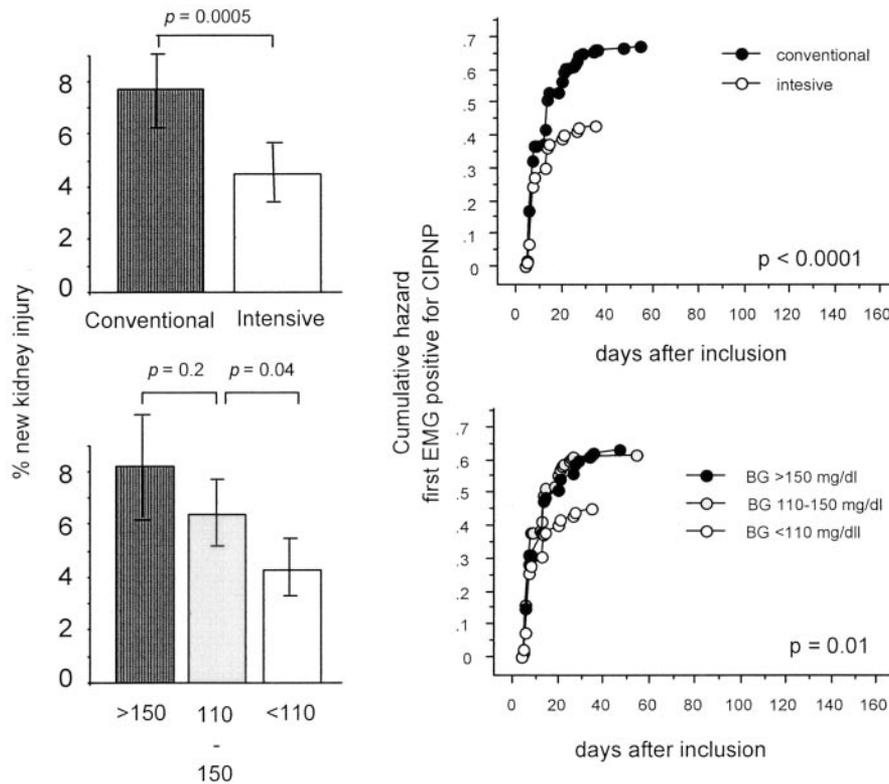

FIG. 2. Impact of IIT (*upper panels*) and of the level of blood glucose control (*lower panels*) on new kidney injury during ICU stay (*left panels*, $n = 2,748$) and on the time to a first positive EMG diagnosis of critical illness polyneuropathy among all screened patients (*right panels*, $n = 825$ in ICU at least 7 days). Compared with a mean blood glucose level of 110–150 mg/dl, the OR for new kidney injury when mean blood glucose was <110 mg/day was 0.66 (95% CI 0.44–0.97) and 1.25 (0.86–1.83) when mean blood glucose was >150 mg/dl. *P* values for kidney injury were obtained by χ^2 testing in the *lower panels* for logistic regression analysis per level of blood glucose control. Bars reflect proportions and 95% CIs. *P* values for critical illness polyneuropathy were obtained by log-rank testing.

TABLE 4
Outcome of subgroups

Insulin treatment	Conventional	Intensive
Cardiovascular disease/high-risk cardiac or complicated vascular surgery	549	533
New kidney injury	35 (6.4)	17 (3.2)
Critical illness polyneuropathy (% of screened)	41 (40.6)	17 (23.3)
ICU mortality	34 (6.2)	18 (3.4)
Hospital mortality	48 (8.7)	34 (6.4)
Hypoglycemia	3 (0.5)	21 (3.9)
Respiratory/complicated pulmonary or esophageal surgery	317	317
New kidney injury	36 (11.4)	20 (6.3)
Critical illness polyneuropathy (% of screened)	71 (52.9)	48 (35.0)
ICU mortality	83 (26.2)	68 (21.5)
Hospital mortality	128 (40.4)	103 (32.5)
Hypoglycemia	6 (1.9)	58 (18.3)
Gastrointestinal or hepatic disease/complicated abdominal surgery	210	199
New kidney injury	11 (5.2)	7 (3.5)
Critical illness polyneuropathy (% of screened)	38 (51.4)	18 (32.7)
ICU mortality	34 (16.2)	27 (13.6)
Hospital mortality	60 (28.6)	50 (25.1)
Hypoglycemia	6 (2.9)	22 (11.0)
Sepsis	471	479
New kidney injury	49 (10.4)	34 (7.0)
Critical illness polyneuropathy (% of screened)	114 (53.3)	69 (31.9)
ICU mortality	128 (27.2)	112 (23.3)
Hospital mortality	172 (36.5)	160 (33.4)
Hypoglycemia	14 (2.9)	94 (19.6)
Active malignancy	247	256
New kidney injury	23 (9.3)	16 (6.3)
Critical illness polyneuropathy (% of screened)	54 (54.5)	31 (30.7)
ICU mortality	77 (31.2)	62 (24.2)
Hospital mortality	105 (42.5)	95 (37.1)
Hypoglycemia	3 (1.2)	39 (15.2)
History of diabetes	200	207
New kidney injury	14 (7.0)	11 (5.3)
Critical illness polyneuropathy (% of screened)	25 (43.9)	14 (32.6)
ICU mortality	27 (13.5)	27 (13.0)
Hospital mortality	44 (22.0)	48 (23.2)
Hypoglycemia	8 (4.0)	29 (14.0)

Data are n or n (%). Sepsis was defined using modified Bone criteria (ref. 21) as suspected or documented infection on ICU admission day and fulfilment of at least two of three systematic inflammatory response syndrome criteria for which data were available: *1*) receiving ventilatory support, *2*) white blood cell count $\leq 4,000$ or $\geq 12,000/l$, and *3*) temperature ≤ 36 or $\geq 38°C$. Patients after cardiac surgery or trauma were excluded for this definition.

contrast, with the lack of effect on mortality, morbidity tended to be reduced when patients with diabetes received IIT (Table 4).

The benefit of IIT was independent of parenteral glucose load as mortality was lowered in the lowest and the highest tertile of parenteral glucose (Fig. 4). For long-stay patients, mortality in the three parenteral glucose subgroups treated conventionally was similar ($P = 0.6$) and IIT reduced it from 37 to 23% in the lowest tertile ($P = 0.0003$), from 36 to 29% in the middle tertile ($P = 0.05$), and from 39 to 34% in the highest tertile ($P = 0.04$) of parenteral glucose (Fig. 4). In the conventional groups, blood glucose levels were slightly higher in the highest than the lowest tertile. In the IIT group, blood glucose levels were identical or lower with higher parenteral glucose load (Table 2).

Potential consequences of hypoglycemia. Hypoglycemia occurred in 1.8% of patients treated conventionally and 11.3% of patients treated with IIT ($P < 0.0001$) (Table 2). Risk of hypoglycemia increased with lower mean blood glucose (2.9% at >150 mg/dl, 4.3% at 110–150 mg/dl, and 10.7% at <110 mg/day; $P < 0.0001$). Hypoglycemia occurred in patients who received more, not less, calories (Table 2).

In 62% of patients with hypoglycemia, blood glucose was normalized (by stopping the insulin infusion and/or administering extra glucose) within 1 h and in all but two patients within 4 h. Immediate symptoms (sweating or decreased consciousness) occurred in 5% of patients with hypoglycemia: three in the conventional group and six in the IIT group ($P = 0.1$); all fully recovered within 8 h. For seven patients, this evaluation was inconclusive due to deep sedation or presence of these symptoms before hypoglycemia. Within 24 h of first hypoglycemia, three (12%) patients in the conventional and one (0.6%) in the IIT group died ($P = 0.0004$) (Table 2).

Hospital mortality (percent) was comparable among hypoglycemic patients in the conventional and IIT groups (Table 2). Median time from hypoglycemia to death was 221 h (range 54–530) in the conventional and 152 h (87–407) in the IIT group ($P = 0.9$). Risk of hypoglycemia in both conventional and IIT groups coincided with a high risk of death (Table 2). Spontaneous hypoglycemia (occurring in patients not receiving insulin; $n = 11$) (Table 2) was associated with a 1.7-fold higher mortality than with insulin ($P = 0.03$).

Among survivors with hypoglycemia during intensive care, late neurological sequelae were absent in all but three IIT patients. However, these three patients suffered from coma or epilepsy before hypoglycemia; thus, no conclusions on causality were possible (Table 2).

DISCUSSION

Both previous randomized controlled trials (1,2) on the impact of IIT during critical illness clearly demonstrated reduced morbidity and mortality of patients treated at least a few days in the ICU. However, a substantial fraction of medical and surgical patients require intensive care only for 1 or 2 days. The previous medical ICU study had revealed a higher number of deaths in the group of short-stay patients on IIT. Although this difference was not statistically significant and likely explained by selection bias, it was of concern to the practicing clinician. Indeed, if IIT would be harmful when given only briefly, it would be difficult to direct this therapy to the target population
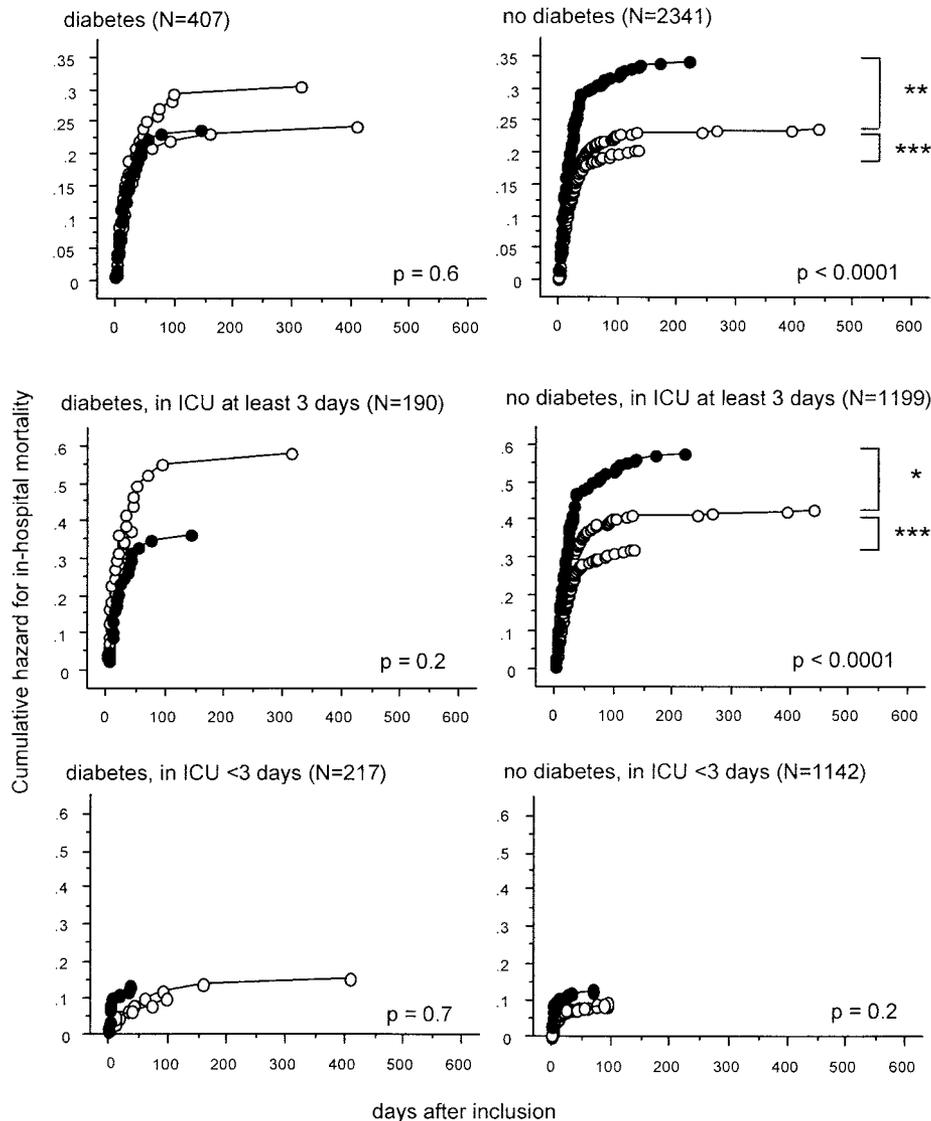
FIG. 3. Impact of the level of blood glucose control on time to hospital mortality among ICU patients with and without a history of diabetes. Numerical *P* values were obtained by log-rank testing. Symbols reflect *P* values obtained by χ^2 testing for logistic regression analysis per level of blood glucose control. *P* = 0.03; **P* = 0.002; ***P* ≤ 0.001. ●, patients with a mean blood glucose level >150 mg/dl; ◒, patients with a mean blood glucose level of 110–150 mg/dl; ○, patients with a mean blood glucose level <110 mg/day.

who would benefit from it, as long-stay patients cannot be identified with certainty on ICU admission. Hence, as benefit versus harm remained unclear, the question remained whether IIT should be applied to all ICU patients, including short stayers.

Pooling the two datasets of the randomized controlled trials generated equal-sized samples of long-stay and short-stay medical/surgical ICU patients. Hence, the current analysis had the statistical power to show the morbidity and mortality benefits of IIT in the intention-to-treat group, explained by a larger effect when continued for at least 3 days in ICU and to exclude harm by brief (<3 days) intervention. In the intention-to-treat group, avoiding blood glucose levels >150 mg/dl appeared to be most crucial to reduce mortality, but more survival benefit was achieved by strictly maintaining blood glucose levels <110 mg/day. When continued for at least a few days, the benefits of blood glucose control <110 mg/day further increased. A blood glucose level kept strictly <110 mg/day from ICU admission onwards was necessary to obtain the protective effect of IIT on the kidney and the peripheral

nervous system and did not cause harm to short-stay patients.

The somewhat higher proportion of patients among long stayers than short stayers, with blood glucose levels strictly <110 mg/dl, may have contributed to the lack of benefit with IIT for short stayers. However, although statistically significant, a mean difference in blood glucose of 4 mg/dl may not be clinically relevant. The underlying disease for which admission to ICU was needed also does not explain the absence of effect among short stayers, as short stayers more often suffered from diseases with a lower risk of death (cardiovascular subgroup) for which a clear benefit was shown.

Most subgroups of patients benefited from IIT, including patients with sepsis upon admission, with quite similar absolute risk reduction for mortality in all the subgroups. In view of the varying baseline risk of death among the different diagnostic subgroups, future and ongoing studies should take this effect size into account for power calculation. Only for patients with a history of diabetes was no survival benefit present, and the risk of death appeared
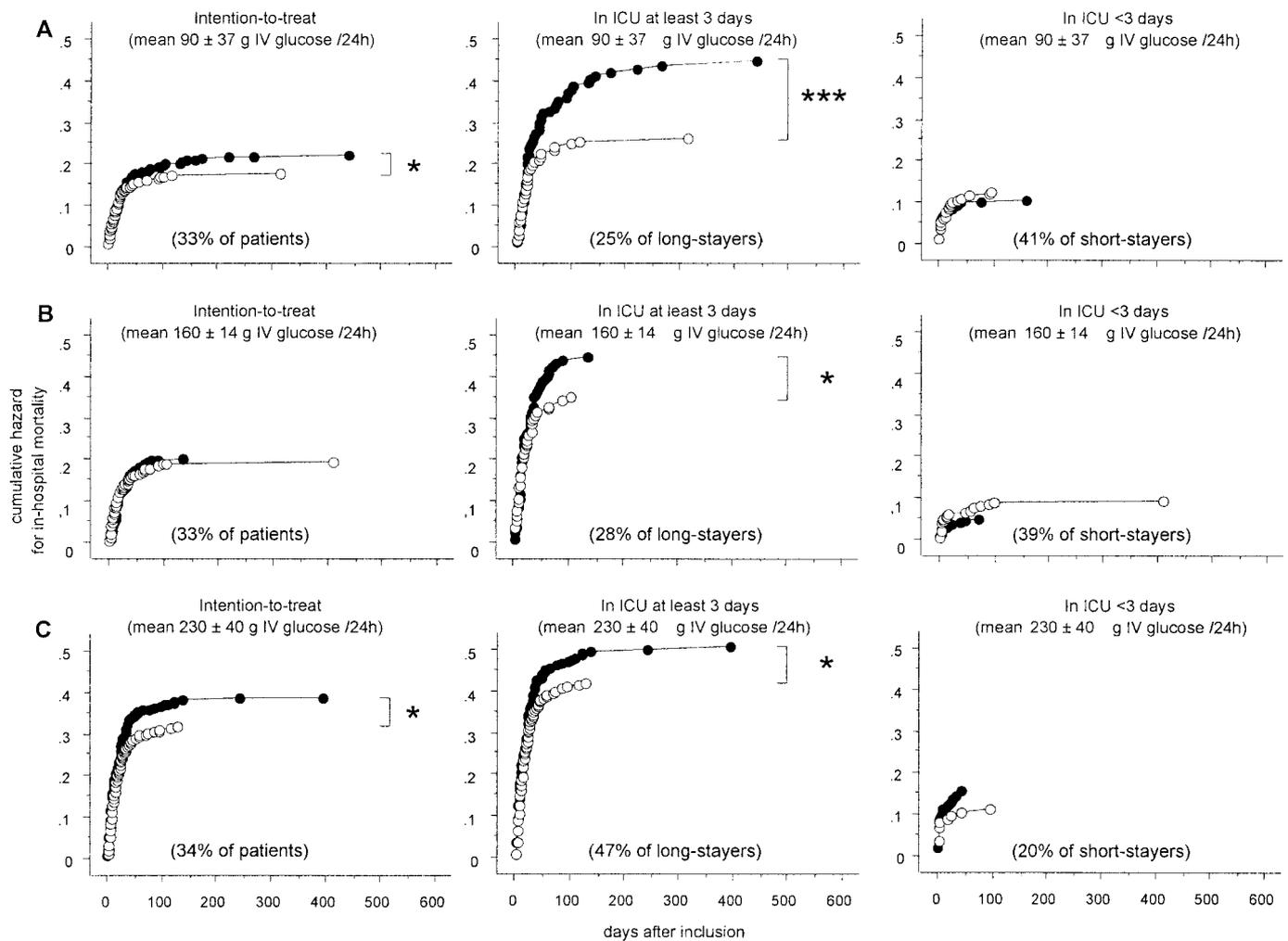
FIG. 4. Impact of IIT on time to hospital mortality among short- and long-stay ICU patients, stratified for tertiles of mean daily parenteral glucose load during ICU stay. The latter comprised all intravenous glucose, including those for nonnutritional purposes. Tertiles for daily parenteral glucose load were defined according to the distribution in the intention-to-treat group. The two insulin groups were comparable for mean daily amount of parenteral glucose and for the distribution among the three tertiles. Patients in the lowest tertile (*row A*) received a mean 90 g glucose per day (range 0–135); patients in the middle tertile (*row B*) received a mean 160 g glucose per day (range 136–185); patients in the highest tertile (*row C*) received a mean 230 g glucose per day (range 186–472). Symbols reflect *P* values obtained by χ^2 testing for logistic regression analysis. *$P \leq 0.05$; ***$P < 0.001$. ●, conventional; ○, IIT.

highest, albeit nonsignificantly, with blood glucose levels <110 mg/day. The latter was not explained by more hypoglycemia. When confirmed in larger samples, this observation could suggest that a rapid normalization of blood glucose levels of patients with diabetes, whose blood glucose levels presumably were elevated before ICU admission, could be deleterious. Adaptation to chronic hyperglycemia, via reduced expression of GLUT transporters in certain cell types, may play a role (12). Such a mechanism has been proposed to explain exacerbating complications with rapid metabolic control in patients with diabetes (13). While awaiting further studies, it may therefore be advisable to treat this subgroup of patients with diabetes to a blood glucose target similar to what the patient had before the acute insult, rather than at a level of <110 mg/day. Such a strategy would be comparable with blood pressure management of ICU patients with prior hypertension. The data call for specific attention to the population with a prior history of diabetes at the time of interim analyses of ongoing multicenter trials investigating IIT in ICU patients (14,15).

IIT works irrespective of parenteral glucose load. Long-stay patients receiving no or small amounts of parenteral glucose appeared to benefit most, which negates the suggestion raised in recent editorials that IIT would only antagonize side effects of excessive parenteral feeding (4,5). The analysis also suggests that higher mortality, previously associated with higher amounts of parenteral feeding (16), an association at first sight that was also present in our intention-to-treat groups, is explained by more feeding given to long-stay and, thus, sicker patients and does not reflect a causal association. Indeed, among long-stay patients treated conventionally, mortality was similar for the three strata of intravenous feeding.

There were more episodes of hypoglycemia during IIT than with conventional therapy and more so when blood glucose levels were <110 mg/day. This risk was higher among long-stay compared with short-stay patients. As most benefit was gained with the tightest blood glucose control, the risk of hypoglycemia should thus be weighed against improved outcome. Indeed, our data cannot completely resolve whether increased risk of brief hypoglycemia with IIT, in ICU conditions and treated promptly as in our studies, caused any harm. There was no immediate lethality associated with hypoglycemia, and only rarely were there immediate transient symptoms. However, im-

paired counterregulatory responses may mask these immediate symptoms and signs in ICU patients. It was reassuring to document that among survivors, no morbidity was associated with hypoglycemia and that the risk of hospital death among patients with hypoglycemia was equal in the conventional and the IIT groups. However, as more patients in the IIT group experienced hypoglycemia, it cannot be entirely excluded that hypoglycemia evoked morbidity or mortality. If this were the case, avoiding hypoglycemia while maintaining blood glucose levels <110 mg/day would further increase the benefit of IIT because, even in the group with the highest risk of hypoglycemia (the <110 mg/day stratum), most lives were saved. Sepsis, organ failure, and hemodialysis have been reported as risk factors for developing hypoglycemia with IIT (17). A recent nested case-control study (18) by the same group elegantly revealed no causal link between hypoglycemia in the ICU and death, when case and control subjects were matched for baseline conditions and for time in the ICU. Hence, as previously suggested (19), hypoglycemia during IIT in ICU patients may merely identify patients at high risk of dying rather then representing a risk in its own right. Our observation that spontaneous hypoglycemia had a higher mortality than hypoglycemia occurring during insulin infusion corroborates such an interpretation. Less overt consequences evoked by hypoglycemia during critical illness and the impact of time to normalization of the blood glucose level, as well as of the depth of hypoglycemia, remain to be explored in animal models of critical illness (20).

The statistical association between a high insulin dose for any given blood glucose level and risk of death can be interpreted in two ways. Either it points to the known association between severity of illness and degree of insulin resistance, or it may suggest that hyperinsulinemia is deleterious. Our recent animal studies addressed this question in detail and showed that not hyperinsulinemia, but rather hyperglycemia, is causing morbidity and mortality in critical illness (20), thus not supporting the latter interpretation.

In conclusion, IIT significantly reduced morbidity and mortality in mixed medical/surgical ICU patients in an intention-to-treat analysis and more so when continued for at least 3 days, independent of parenteral glucose load, and without causing harm to patients treated for <3 days. Only the subgroup of patients with a prior history of diabetes did not appear to benefit. Blood glucose maintained at <110 mg/day was more effective than at 110–150 mg/dl but also carried the highest risk of hypoglycemia. Hypoglycemia did not cause early deaths, only minor immediate and transient morbidity in a minority of patients, and no late neurological sequellae among hospital survivors. However, as risk of hypoglycemia in both conventional and intensive insulin groups coincided with a higher risk of death, it cannot be completely excluded that hypoglycemia counteracted some of the survival benefit of IIT.

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