ORIGINAL ARTICLE

Early versus Late Parenteral Nutrition in Critically Ill Adults

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ABSTRACT

BACKGROUND

Controversy exists about the timing of the initiation of parenteral nutrition in critically ill adults in whom caloric targets cannot be met by enteral nutrition alone.

METHODS

In this randomized, multicenter trial, we compared early initiation of parenteral nutrition (European guidelines) with late initiation (American and Canadian guidelines) in adults in the intensive care unit (ICU) to supplement insufficient enteral nutrition. In 2312 patients, parenteral nutrition was initiated within 48 hours after ICU admission (early-initiation group), whereas in 2328 patients, parenteral nutrition was not initiated before day 8 (late-initiation group). A protocol for the early initiation of enteral nutrition was applied to both groups, and insulin was infused to achieve normoglycemia.

RESULTS

Patients in the late-initiation group had a relative increase of 6.3% in the likelihood of being discharged alive earlier from the ICU (hazard ratio, 1.06; 95% confidence interval [CI], 1.00 to 1.13; P=0.04) and from the hospital (hazard ratio, 1.06; 95% CI, 1.00 to 1.13; P=0.04), without evidence of decreased functional status at hospital discharge. Rates of death in the ICU and in the hospital and rates of survival at 90 days were similar in the two groups. Patients in the late-initiation group, as compared with the early-initiation group, had fewer ICU infections (22.8% vs. 26.2%, P=0.008) and a lower incidence of cholestasis (P<0.001). The late-initiation group had a relative reduction of 9.7% in the proportion of patients requiring more than 2 days of mechanical ventilation (P=0.006), a median reduction of 3 days in the duration of renal-replacement therapy (P=0.008), and a mean reduction in health care costs of €1,110 (about $1,600) (P=0.04).

CONCLUSIONS

Late initiation of parenteral nutrition was associated with faster recovery and fewer complications, as compared with early initiation. (Funded by the Methusalem program of the Flemish government and others; EPaNIC ClinicalTrials.gov number, NCT00512122.)

Critical illness induces anorexia and the inability to eat normally, predisposing patients to serious nutritional deficits, muscle wasting, weakness, and delayed recovery. Whether artificial nutritional support improves the outcome for critically ill patients is unclear. The administration route, the time until the initiation of artificial nutrition, the number of calories, and the type of nutrients may be important.[1-3]

Enteral nutrition is associated with fewer complications than parenteral nutrition and is less expensive to administer.[4-6] However, the use of enteral nutrition alone often does not achieve caloric targets.[7] In addition, underfeeding is associated with weakness, infection,[8] an increased duration of mechanical ventilation,[9,10] and death.[11] Combining parenteral nutrition with enteral nutrition constitutes a strategy to prevent nutritional deficit but may risk overfeeding, which has been associated with liver dysfunction, infection, and prolonged ventilatory support.[12-15] The increased levels of blood glucose that are associated with parenteral nutrition could contribute to such complications[5,16,17] and have been hypothesized to explain the failure of parenteral nutrition to prevent muscle wasting.[18,19]

Current clinical practice guidelines for nutritional support in critically ill patients are largely based on expert opinion and differ substantially across continents. The guidelines of the European Society of Parenteral and Enteral Nutrition (ESPEN) recommend that practitioners consider initiating parenteral nutrition within 2 days after admission to the intensive care unit (ICU) for patients who cannot be adequately fed enterally.[20] In contrast, the American and Canadian guidelines recommend early initiation of enteral nutrition but suggest that parenteral nutrition not be initiated concomitantly, thus advising that hypocaloric nutrition be tolerated during the first week in patients who are not malnourished at baseline.[21,22]

In this study, we compared the effect of late initiation of parenteral nutrition (American and Canadian guidelines) with early initiation (ESPEN guidelines) on rates of death and complications in adults in the ICU who were nutritionally at risk but who were not chronically malnourished (body-mass index [the weight in kilograms divided by the square of the height in meters], ≥17).[23] Since all the participating ICUs followed the guidelines for early initiation of parenteral nutrition, the active intervention was late initiation. In this study, we investigated whether preventing a caloric deficit during critical illness by providing parenteral nutrition to supplement enteral nutrition early in the disease course would reduce the rate of complications or whether withholding parenteral nutrition for 1 week would be clinically superior.

METHODS

STUDY DESIGN AND OVERSIGHT

The Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) study was a prospective, randomized, controlled, parallel-group, multicenter trial that was initiated by the investigators. The protocol and consent forms were approved by the institutional review boards at University Hospitals Leuven and Jessa Hospitals and by the Belgian authorities. The study protocol and statistical analysis plan are available with the full text of this article at NEJM.org, and the methods have been reported previously.[24] The first author and last author vouch for the fidelity of the study to the protocol.

Baxter Healthcare provided an unrestricted research grant that covered less than a third of the costs of the study. The company was not involved in the design of the study; in the collection, analysis, or interpretation of the data; in the preparation of the manuscript, or in the decision to submit the manuscript for publication.

PATIENTS

From August 1, 2007, through November 8, 2010, all adults who were admitted to one of the seven participating ICUs were eligible for inclusion in the study if they had a score of 3 or more on nutritional risk screening (NRS) (on a scale of 1 to 7, with a score ≥3 indicating that the patient was nutritionally at risk)[23] and did not meet any of the exclusion criteria (Fig. 1). Written informed consent was provided by all patients or their designated representatives.

Consecutive patients were stratified according to 16 diagnostic categories (see Table 1 in the Supplementary Appendix, available at NEJM.org) and randomly assigned in a 1:1 ratio to early or late initiation of parenteral nutrition, with the use of sequentially numbered, sealed, opaque envelopes. Envelopes were replaced by an identical digital system at all sites after the addition of the Jessa Hospitals study sites. Treatment assignments were made in permuted blocks of 10 per stratum.

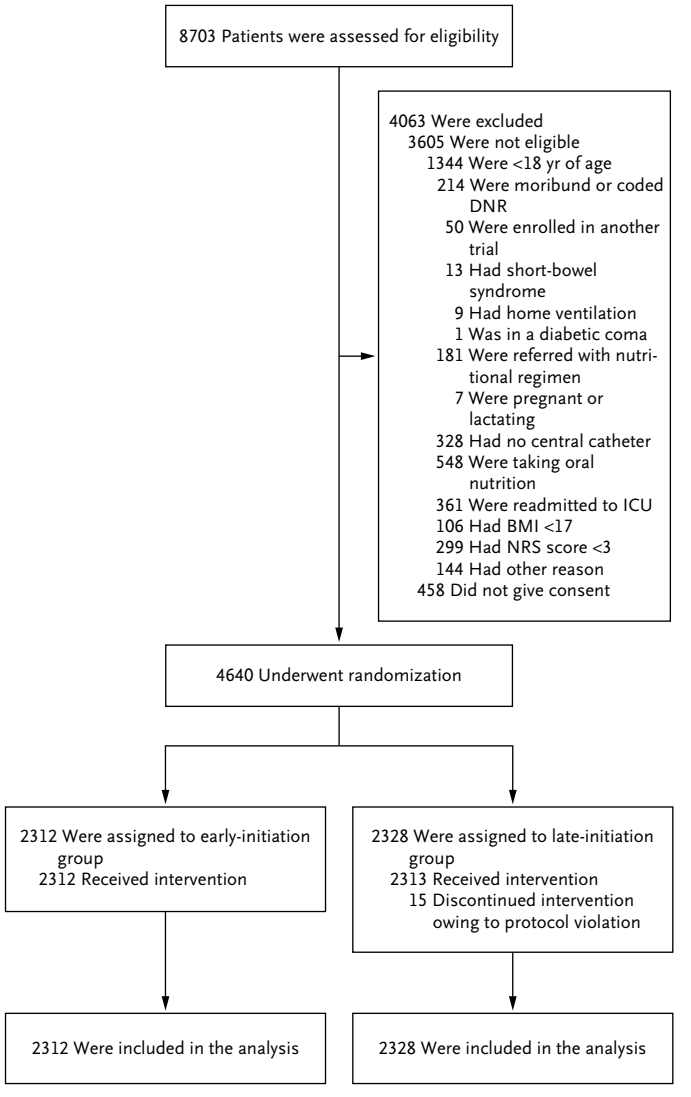

Figure 1. Enrollment and Outcomes.

Patients were excluded for a number of medical reasons, including chronic malnourishment (defined as a body-mass index [BMI] of <17) before admission to an intensive care unit (ICU) and referral from another ICU with an established regimen of enteral or parenteral nutrition. For 15 patients who were assigned to the late-initiation group, the study protocol was considered to have been violated because of inadvertent administration of at least 1 liter of parenteral nutrition per day for at least 2 days during the intervention window. DNR denotes do not resuscitate, and NRS nutritional risk screening.

The treating physicians and nurses did not know the block size. All outcome adjudicators were unaware of study-group assignments.

One interim safety analysis was performed after the first 1500 patients had been discharged from the ICU. The independent data and safety monitoring board then advised that the study be continued to completion. Because the primary efficacy end point was not analyzed, no correction of the significance level at the final analysis was required.

STUDY PROCEDURES

Patients who were assigned to the early-initiation group received intravenous 20% glucose solution; the target for total energy intake was 400 kcal per day on ICU day 1 and 800 kcal per day on day 2 (Fig. 2, and Table 2 in the Supplementary Appendix).[24] On day 3, parenteral nutrition (OliClinomel or Clinimix, Baxter) was initiated, with the dose targeted to 100% of the caloric goal through combined enteral and parenteral nutrition (except when clinicians predicted that the patient would tolerate sufficient enteral nutrition or oral feeding on day 3). The amount of parenteral nutrition was calculated daily as the difference between the total energy intake that was effectively delivered by enteral nutrition and the calculated caloric goal. Calculations regarding the caloric goal included protein energy and were based on corrected ideal body weight, age, and sex[25] (Table 3 in the Supplementary Appendix). The maximum caloric goal for all patients was 2880 kcal per day. When enteral nutrition covered 80% of the calculated caloric goal or when the patient was judged to be able to resume oral nutrition, parenteral nutrition was reduced and eventually stopped. Parenteral nutrition was restarted whenever enteral or oral intake fell to less than 50% of the calculated caloric needs.

Patients who were assigned to the late-initiation group received 5% glucose solution in a volume equal to that of the parenteral nutrition administered in the early-initiation group in order to provide adequate hydration, with the delivered volume of enteral nutrition taken into account. If enteral nutrition was insufficient after 7 days in the ICU, parenteral nutrition was initiated on day 8 to reach the caloric goal.

All patients who were unable to eat by day 2 received enteral nutrition (mainly Osmolite, Abbott), while being maintained in a semirecumbent position unless medically contraindicated (Table 4 in the Supplementary Appendix). Standing orders for enteral nutrition for all patients specified a twice-daily increase in the infusion rate for enteral nutrition and the use of prokinetic agents and duodenal feeding tubes. Patients in the two study groups received parenteral trace elements, miner-

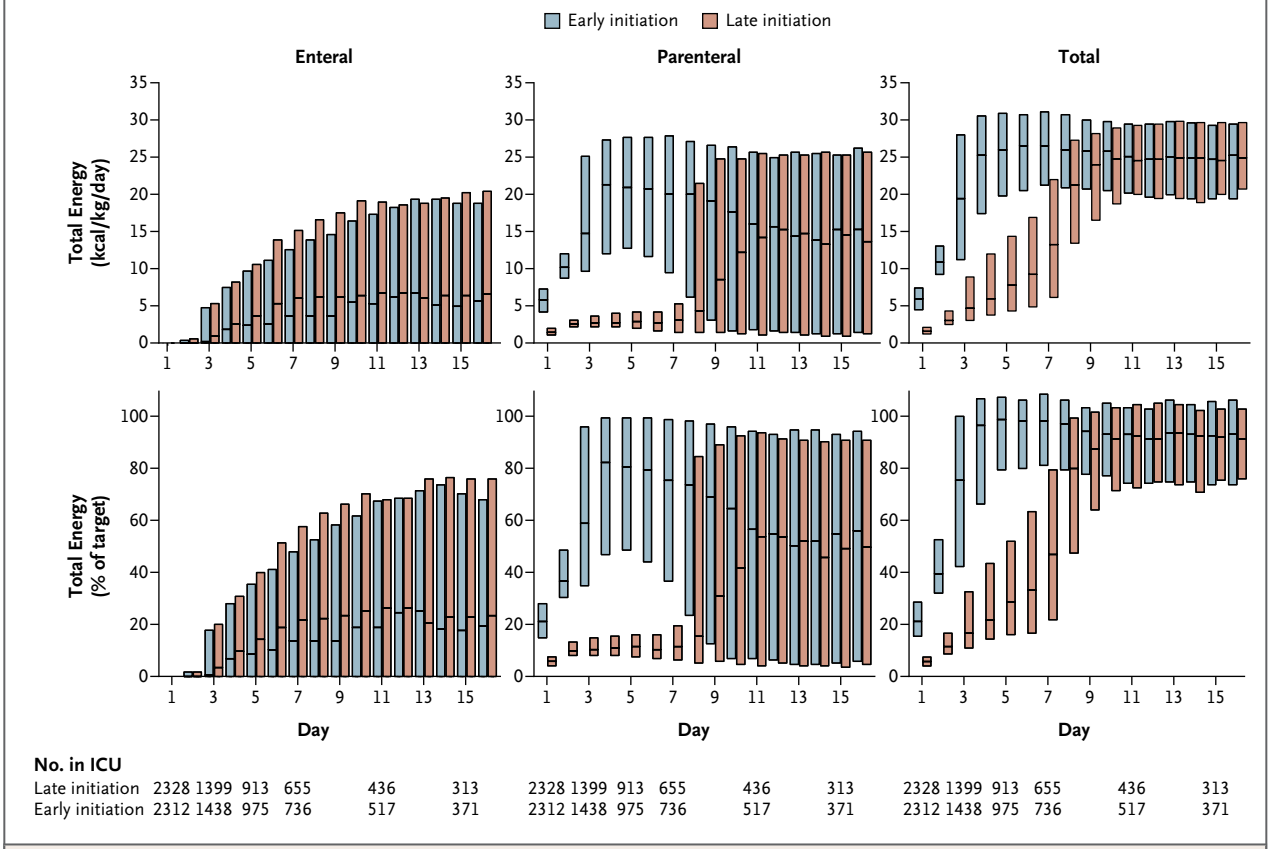

Figure 2. Total Energy Levels.

The upper panels show total energy levels, expressed in kilocalories per kilogram of body weight, that were administered in the intensive care unit (ICU) by the enteral route, the parenteral route, or both from day 1 through day 16. The lower panels show the percentages of the calculated nutritional goal administered from day 1 through day 16. The data on total energy intake include oral nutrition. Nutrition after discharge from the ICU was at the discretion of the attending physicians on the regular wards. The boxes represent interquartile ranges, and the horizontal lines within the boxes represent the medians. If no horizontal line is present within the box, the median value is the same as the 25th percentile.

als (potassium, phosphate, and magnesium), and vitamins early in their ICU stay[24] in order to avoid problems due to micronutrient depletion on refeeding (Table 2 in the Supplementary Appendix).

A patient-data–management system (MetaVision, iMDsoft) was used to calculate the daily volumes of enteral and parenteral nutrition to be administered to each patient, according to the protocol. Nutritional management after discharge from the ICU was at the discretion of the attending ward physicians. Continuous insulin infusion was adjusted to obtain a blood glucose level of 80 to 110 mg per deciliter (4.4 to 6.1 mmol per liter).[16,26] Arterial blood glucose levels were monitored, with chemical analysis performed every 1 to 4 hours on a blood gas analyzer (Radiometer ABL 715 and 725, Radiometer Medical) and corrected as required. Guidelines for ventilator weaning were followed in all participating ICUs. When continued intensive care was considered to be futile, two senior ICU physicians and the referring specialist made end-of-life decisions by consensus.

DATA COLLECTION

Baseline demographic and clinical characteristics of the patients were well matched between the two study groups (Table 1, and Table 1 in the Supplementary Appendix). We quantified the severity of illness according to the score on the Acute Physiology and Chronic Health Evaluation II (APACHE II) (on a scale of 0 to 71, with higher scores indi-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Late-Initiation Group (N=2328)	Early-Initiation Group (N=2312)	P Value
Male sex — no. (%)	1486 (63.8)	1486 (64.3)	0.75
Age — yr	64±15	64±14	0.53
Weight — kg	75±15	76±16	0.05
Body-mass index — no. (%)†			0.34
<20	141 (6.1)	134 (5.8)	
20 to <25	890 (38.2)	854 (36.9)	
25 to <30	864 (37.1)	852 (36.9)	
30 to <40	405 (17.4)	430 (18.6)	
≥40	28 (1.2)	42 (1.8)	
Diabetes mellitus — no. (%)	417 (17.9)	391 (16.9)	0.36
Dialysis-dependent kidney failure before ICU admission — no. (%)	35 (1.5)	34 (1.5)	0.92
Cancer — no. (%)	457 (19.6)	437 (18.9)	0.52
Score on nutritional risk screening — no. (%)‡			0.71
3	1050 (45.1)	1014 (43.9)	
4	862 (37.0)	851 (36.8)	
5	207 (8.9)	231 (10.0)	
6	171 (7.3)	178 (7.7)	
7	38 (1.6)	38 (1.6)	
Sepsis — no. (%)	505 (21.7)	510 (22.1)	0.76
Emergency admission — no. (%)	970 (41.7)	956 (41.3)	0.82
APACHE II score§	23±10	23±11	0.85

* Plus–minus values are means ±SD. The proportions of patients in various diagnostic categories at the time of admission to the intensive care unit (ICU) were similar in the two study groups. (For details, see Table 1 in the Supplementary Appendix.) Percentages may not total 100 because of rounding.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on nutritional risk screening range from 0 to 7, with higher scores indicating a higher risk of malnutrition.[23]
§ Scores on the Acute Physiology and Chronic Health Evaluation II (APACHE II) range from 0 to 71, with higher scores indicating a greater severity of illness.[27]

cating a greater severity of illness).[27] The criteria of the American College of Chest Physicians–Society of Critical Care Medicine were used for the diagnosis of sepsis.[28] Organ-failure and sepsis scores were calculated by trained experts.

Daily records were kept regarding all intensive care treatments and procedures, new bacterial or fungal infections, the results of blood and urine chemical analyses and hematologic studies, and markers of inflammation. Also recorded were the total energy intake delivered daily by means of enteral and parenteral nutrition, interruptions of delivery of enteral nutrition, and feeding-related complications. In addition, whenever practically feasible, the functional status of patients before hospital discharge was quantified. All direct health care costs were retrieved from the invoices for patients and analyzed from the perspective of the health care payer. Government and patient costs were aggregated. Vital status 90 days after randomization was obtained from the Belgian National Registry for all Belgian citizens.

OUTCOME MEASURES

Safety End Points

Safety end points included vital status (the proportion of patients who were alive at discharge from the ICU in ≤8 days, the rates of death in the ICU

and the hospital, and the rates of survival up to 90 days, regardless of ICU and hospital discharge status) and the rates of complications and hypoglycemia. Hypoglycemia that was resistant to parenteral glucose administration during the intervention window was considered to be a serious adverse event.

Primary Efficacy End Point

The primary end point was the duration of dependency on intensive care, assessed as the number of ICU days (for survivors and nonsurvivors) and the time to discharge from the ICU. To reduce bias that might result from variability in the availability of beds on regular wards, we defined the time to discharge from the ICU as the time by which patients were ready for ICU discharge, according to prespecified objective criteria[24] (Table 2).

Secondary Efficacy End Points

Secondary end points were the number of patients with new infections; the infection site (airways or lungs, bloodstream, urinary tract, or wounds)[29,30]; the duration of antibiotic therapy; inflammation, as reflected by the maximum level of plasma C-reactive protein; the time to final weaning from mechanical ventilatory support and the need for tracheostomy; the rate of incident acute kidney injury, which was defined according to RIFLE criteria[31] (risk of renal dysfunction, injury to the kidney, failure or loss of kidney function, and end-stage kidney disease) as at least a doubling of the serum creatinine level recorded on admission; the proportion of patients requiring renal-replacement therapy and the duration of such therapy in the ICU; and the need for and duration of pharmacologic or mechanical hemodynamic support. We compared the two study groups with respect to the proportion of patients during the study intervention and during the entire ICU stay who presented with liver dysfunction, which was defined as a total bilirubin level of more than 3 mg per deciliter (51 μmol per liter), a γ-glutamyltransferase level of more than 79.5 U per liter, an alkaline phosphatase level of more than 405 U per liter, or a pronounced elevation in the level of either alanine aminotransferase (>123 U per liter) or aspartate aminotransferase (>114 U per liter). Finally, we compared the duration of the hospital stay and time to discharge from the hospital between the two study groups. Before hospital discharge, we quantified functional status according to the distance walked in 6 minutes[32] and the proportion of patients who were independent in all activities of daily living.[33] We also compared the two groups with respect to the total incremental health care costs from randomization to hospital discharge.

STATISTICAL ANALYSIS

The sample-size calculation was based on the ability to detect a between-group change of 1 day in the ICU stay with a power of at least 80% and to concomitantly detect a change of 3% in the rate of death in the ICU with a power of at least 70%.[24] All analyses were performed on an intention-to-treat basis. Variables were summarized as frequencies and percentages, means and standard deviations, or medians and interquartile ranges, as appropriate. Data were compared with the use of the chi-square test, Student's t-test, or nonparametric testing (median test, Wilcoxon rank-sum test, or Mann–Whitney U test), as appropriate. Health care costs were reported as means with interquartile ranges and were analyzed with the use of Student's t-test.[34] We used Kaplan–Meier methods to perform time-to-event analyses, and the time-to-event effect size was estimated with the use of Cox proportional-hazards analysis. In the analysis of survival to 90 days, data for 69 of 83 non-Belgian citizens who had been discharged from the hospital before 90 days were censored at the time of discharge. For the time to discharge from the ICU and hospital, data for patients who died were censored at the time of death, and data for one patient who was still in the hospital 90 days after the enrollment of the last patient were censored at 90 days. For the analysis of the time to discharge alive from the ICU or hospital, data for patients who died were censored at a time point after the last surviving patient had been discharged.[35] All outcomes were analyzed both with no adjustment for baseline variables and with adjustment for prespecified risk factors (type and severity of illness, age, body-mass index, and NRS score). Data for the type of illness included diagnostic categories on admission (Table 1, and Table 1 in the Supplementary Appendix) and the presence or absence of cancer.

We performed prespecified subgroup analyses[24] for patients at increased risk as indicated by the body-mass index (<25 or ≥40)[11,36-38] or

NRS score (≥5), those who had undergone cardiac surgery, and those with sepsis on admission. These subgroup analyses were performed for the primary outcome and one safety end point. Interactions in the fully adjusted models were tested at a significance level of less than 0.10. For all end points, a two-sided P value of less than 0.05 was considered to indicate statistical significance, without correction for multiple testing. All analyses were performed with the use of JMP software, version 8.0.1 (SAS Institute).

RESULTS

STUDY INTERVENTION

A total of 4640 patients underwent randomization and were included in the analysis (Fig. 1). Details regarding the patients' nutrition, which was administered according to the study protocol, are shown in Figure 2 (also Fig. 1 in the Supplementary Appendix). Patients in the late-initiation group required a median of 31 IU of insulin (interquartile range, 19 to 48) per day to reach the target blood

Table 2. Outcomes.*

Variable	Late-Initiation Group (N=2328)	Early-Initiation Group (N=2312)	P Value
Safety outcome			
Vital status — no. (%)			
Discharged live from ICU within 8 days	1750 (75.2)	1658 (71.7)	0.007
Death			
In ICU	141 (6.1)	146 (6.3)	0.76
In hospital	242 (10.4)	251 (10.9)	0.63
Within 90 days after enrollment†	257 (11.2)	255 (11.2)	1.00
Nutrition-related complication — no. (%)	423 (18.2)	434 (18.8)	0.62
Hypoglycemia during intervention — no. (%)‡	81 (3.5)	45 (1.9)	0.001
Primary outcome			
Duration of stay in ICU§			
Median (interquartile range) — days	3 (2–7)	4 (2–9)	0.02
Duration >3 days — no. (%)	1117 (48.0)	1185 (51.3)	0.02
Hazard ratio (95% CI) for time to discharge alive from ICU	1.06 (1.00–1.13)		0.04
Secondary outcome			
New infection — no. (%)			
Any	531 (22.8)	605 (26.2)	0.008
Airway or lung	381 (16.4)	447 (19.3)	0.009
Bloodstream	142 (6.1)	174 (7.5)	0.05
Wound	64 (2.7)	98 (4.2)	0.006
Urinary tract	60 (2.6)	72 (3.1)	0.28
Inflammation			
Median peak C-reactive protein level during ICU stay (interquartile range) — mg/liter	190.6 (100.8–263.2)	159.7 (84.3–243.5)	<0.001
Mechanical ventilation			
Median duration (interquartile range) — days	2 (1–5)	2 (1–5)	0.02
Duration >2 days — no. (%)	846 (36.3)	930 (40.2)	0.006
Hazard ratio (95% CI) for time to definitive weaning from ventilation	1.06 (0.99–1.12)		0.07
Tracheostomy — no. (%)	134 (5.8)	162 (7.0)	0.08

Table 2. (Continued.)

Variable	Late-Initiation Group (N=2328)	Early-Initiation Group (N=2312)	P Value
Kidney failure			
Modified RIFLE category — no. (%)¶	104 (4.6)	131 (5.8)	0.06
Renal-replacement therapy — no. (%)	201 (8.6)	205 (8.9)	0.77
Median duration of renal-replacement therapy (interquartile range) — days	7 (3–16)	10 (5–23)	0.008
Duration of hospital stay			
Median (interquartile range) — days	14 (9–27)	16 (9–29)	0.004
Duration >15 days — no. (%)	1060 (45.5)	1159 (50.1)	0.001
Hazard ratio (95% CI) for time to discharge alive from hospital	1.06 (1.00–1.13)		0.04
Functional status at hospital discharge			
Distance on 6-min walk test			
No. of patients evaluated	624	603	
Distance (interquartile range) — m	277 (210–345)	283 (205–336)	0.57
Activities of daily living			
No. of patients evaluated	1060	996	
Independent in all activities — no. (%)	779 (73.5)	752 (75.5)	0.31
Mean total incremental health care cost (interquartile range) — €‖	16,863 (8,793–17,774)	17,973 (8,749–18,677)	0.04

* All hazard ratios and 95% confidence intervals (CI) were calculated with the use of Cox proportional-hazards analysis of the effect of late initiation of parenteral nutrition, with adjustment for risk factors. ICU denotes intensive care unit.
† Data on vital status at 90 days were available for 2289 patients in the late-initiation group and 2268 in the early-initiation group.
‡ Hypoglycemia was defined as a glucose level of less than 40 mg per deciliter (2.2 mmol per liter).
§ The duration of time in the ICU was defined as the time from admission of patients until they were ready for discharge. Patients were considered ready for discharge as soon as all clinical conditions for ICU discharge were fulfilled (i.e., no more need for vital-organ support and receipt of at least two thirds of caloric requirements as oral feedings) even if they were not actually discharged that day. The "ready for discharge" day coincided with the actual day of discharge for all patients except for 104 patients in the late-initiation group and 95 patients in the early-initiation group.
¶ The Modified RIFLE classification (risk of renal dysfunction, injury to the kidney, failure or loss of kidney function, and end-stage kidney disease) was used to define new kidney injury or failure as at least a doubling of the creatinine level at admission. Values were available for 2264 patients in the late-initiation group and 2248 patients in the early-initiation group.
‖ Total incremental health care costs included costs billed to either the government or the patient. Since the Belgian reimbursement system provides a daily flat compensation for the administration of intravenous fluids (including parenteral nutrition), the reported values do not include a deduction of the cost of parenteral nutrition in the late-initiation group.

glucose level, with a mean (±SD) blood glucose level of 102±14 mg per deciliter (5.7±0.8 mmol per liter), as compared with a median of 58 IU of insulin (interquartile range, 40 to 85) for a mean blood glucose level of 107±18 mg per deciliter (5.9±1.0 mmol per liter) in the early-initiation group ($P<0.001$ for both comparisons). Levels of serum potassium, phosphorus, and magnesium were similar in the two study groups (data not shown).

SAFETY OUTCOMES

The two study groups had similar rates of death in the ICU and the hospital and at 90 days (Table 2, and Fig. 2 in the Supplementary Appendix). However, the proportion of patients who were discharged alive from the ICU within 8 days was higher in the late-initiation group, even though hypoglycemia developed in more patients in this group. The rates of nutrition-related complications were similar in the two groups, and there were no serious adverse events that could be attributed to the study interventions.

PRIMARY OUTCOME

The median stay in the ICU was 1 day shorter in the late-initiation group than in the early-initia-

tion group, which was reflected in a relative increase of 6.3% in the likelihood of earlier discharge alive from the ICU (hazard ratio, 1.06; 95% confidence interval [CI], 1.00 to 1.13; P=0.04) (Table 2 and Fig. 3). This effect size was similar (an increase in likelihood of 6.9%) after adjustment for hypoglycemia.

SECONDARY OUTCOMES

Fewer patients in the late-initiation group acquired a new infection (in the airways or lungs, bloodstream, or wound) in the ICU, but the acute inflammatory response was more pronounced than in the early-initiation group (Table 2). The duration of mechanical ventilation and the course of renal-replacement therapy were shorter in the late-initiation group. More patients in the late-initiation group had hyperbilirubinemia (>3 mg per deciliter), and fewer had a clinically important increase in levels of γ-glutamyltransferase or alkaline phosphatase. The numbers of patients with pronounced elevations in aminotransferase levels were similar in the two groups (Table 5 in the Supplementary Appendix).

The median duration of hospitalization was 2 days shorter in the late-initiation group than in the early-initiation group, which was reflected in a relative increase of 6.4% in the likelihood of earlier discharge from the hospital (hazard ratio, 1.06; 95% CI, 1.00 to 1.13; P=0.04) (Table 2). Functional status, as assessed by the 6-minute walk distance and activities of daily living at the time of imminent hospital discharge, was similar in the two study groups. Late initiation of parenteral nutrition resulted in a mean reduction in total health care costs of €1,110 (about $1,600) per patient (Table 2).

SUBGROUP ANALYSES

Predefined subgroup analyses revealed no heterogeneity for the primary outcome or for the safety outcomes (Table 6 in the Supplementary Appendix). In post hoc subgroup analyses, we compared late initiation of parenteral nutrition with early initiation in patients for whom early enteral nutrition was surgically contraindicated (517 patients who had undergone complicated pulmonary, esophageal, abdominal, or pelvic surgery and who had a mean APACHE II score of 27±11). Together, these high-risk subgroups predictably received a median of 0 kcal (interquartile range, 0 to 163) per day of enteral nutrition by day 7. Among these patients, the rate of infection was lower in the late-initiation group (29.9%) than in the early-initiation group (40.2%, P=0.01). In the late-initiation group, there was a relative increase of 20% in the likelihood of earlier discharge alive from the ICU (hazard ratio, 1.20; 95% CI, 1.00 to 1.44; P=0.05; P=0.11 for interaction) (Table 6 in the Supplementary Appendix).

DISCUSSION

We found that there was no significant difference in mortality between late initiation and early initiation of parenteral nutrition among patients in the ICU who were at risk for malnutrition, despite the use of early enteral feeding plus micronutrients in a protocol that prevented hyperglycemia. However, withholding of parenteral nutrition until day 8 was associated with fewer ICU infections but a higher degree of acute inflammation. Late initiation of parenteral nutrition was also associated with a shorter duration of mechanical ventilation and a shorter course of renal-replacement therapy, a shorter ICU stay despite a slight increase in hypoglycemic episodes, a shorter hospital stay without a decrease in functional status, and reduced health care costs.

Our results do not support the conclusions from previous observational studies[9-11] that earlier achievement of nutritional targets improves the outcome for critically ill patients. Such observational studies could not differentiate between cause and consequence, since the sickest patients were often those who could not tolerate enteral nutrition. Such associations also formed the basis of the recommendation that critically ill patients should undergo early initiation of enteral tube feeding and that patients with insufficient enteral nutrition should receive early parenteral supplementation. In our study, although patients' vital status was unaffected, all primary and secondary morbidity end points indicated that early parenteral nutrition was not beneficial. Such factors as the body-mass index, severity of nutritional risk, and presence or absence of sepsis on admission did not influence the results, indicating that our findings have general application. Furthermore, the effect of late initiation of parenteral nutrition in the large cohort of patients who had undergone cardiac surgery was identical to that in other diagnostic groups.

The subgroup of patients for whom early en-

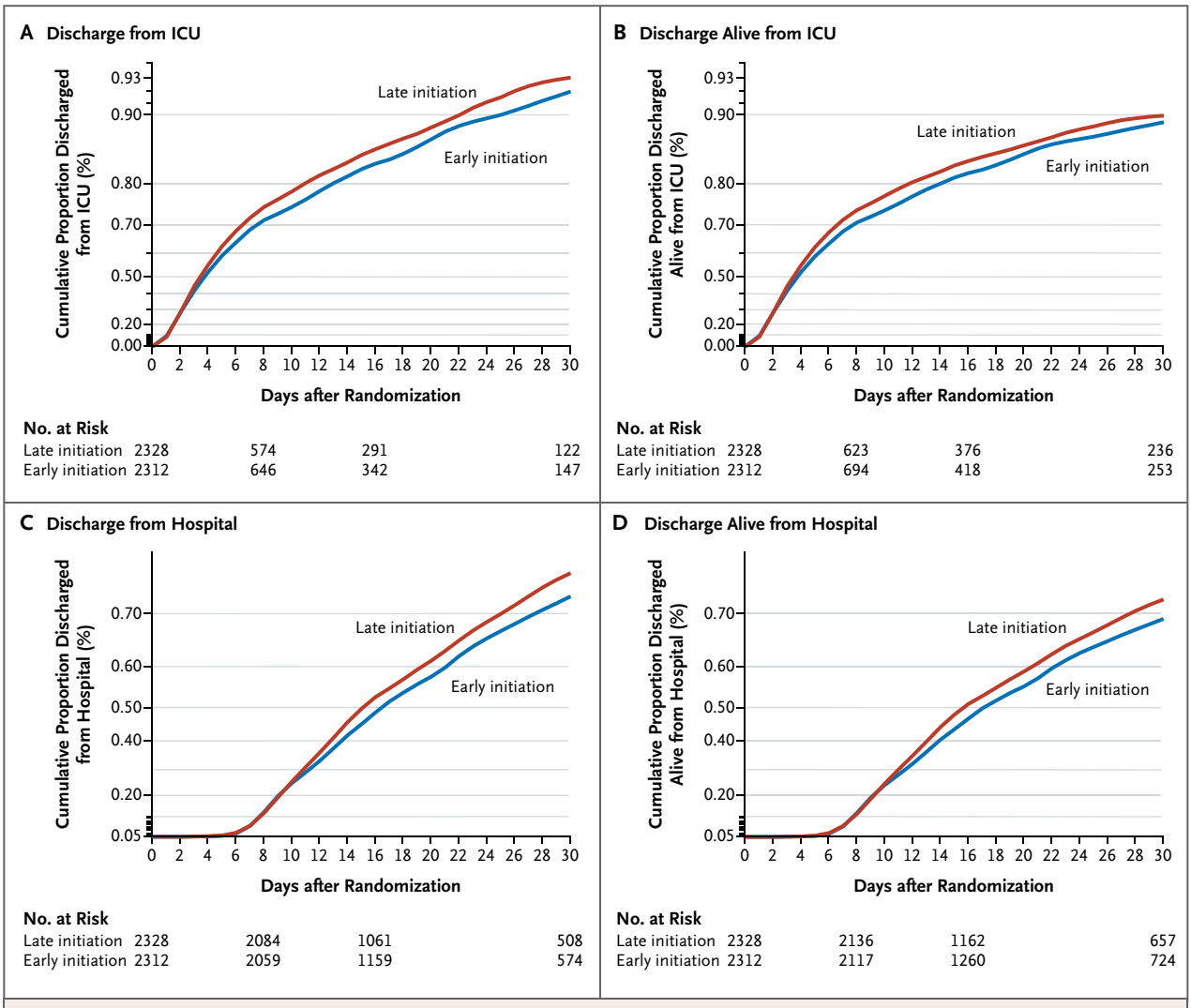

Figure 3. Kaplan–Meier Estimates of the Time to Discharge from the Intensive Care Unit (ICU) and from the Hospital.

Shown are the cumulative proportions of patients who were discharged from the ICU (Panel A), discharged alive from the ICU (Panel B), discharged from the hospital (Panel C), and discharged alive from the hospital (Panel D). For the analysis of the time to discharge from the ICU and the hospital, data for patients who died were censored at the time of death. For the analysis of the time to discharge alive from the ICU and the hospital, data for patients who died were censored at a time point after the last surviving patient had been discharged.[35] Plots were drawn for the first 30 days after randomization, for the sake of clarity. The effect size was calculated by Cox proportional-hazards analysis for the entire stay in the ICU and the hospital, except for one patient who was still in the hospital 90 days after the enrollment of the last patient, whose data were censored at 90 days.

teral nutrition was surgically contraindicated appeared to have a greater benefit from late initiation of parenteral nutrition than did other patients, perhaps because such patients in the early-initiation group received the largest amount of parenteral nutrition. Alternatively, withholding of macronutrients in the early stages of a critical illness, regardless of the route of nutrition, may enhance recovery.[39] We speculate that the increased rates of infection and delayed recovery from organ failure that are associated with the early administration of parenteral nutrition may be explained by a suppression of autophagy, with inadequate clearance of cell damage and microorganisms.[40-46] The protocol for our study targeted normoglycemia. Whether an increased blood glucose target would have affected the outcome of the trial remains speculative. However, the expected increase in

blood glucose levels could add to the risk of early parenteral nutrition.[16,17,26]

Our study has certain limitations. First, the parenteral nutrition that we used contained neither glutamine[47] nor specific immune-modulating compounds,[48] but rather reflected the parenteral nutrition given in common daily practice.[49] The data favoring the administration of glutamine remain controversial.[50,51] Second, the use of standardized, premixed parenteral-nutrition products resulted in a relatively low protein-to-energy ratio (Fig. 1 in the Supplementary Appendix). However, high-level evidence of an improved outcome with increased protein doses is currently lacking. Third, the amount of nutrition was calculated without measurement of energy expenditure with the use of indirect calorimetry, a technique that is not recommended by evidence-based guidelines.[21] Finally, because of the nature of the study, patients or their designated representatives and their ICU providers were aware of study-group assignments.

In conclusion, the early initiation of parenteral nutrition to supplement insufficient enteral nutrition during the first week after ICU admission in severely ill patients at risk for malnutrition appears to be inferior to the strategy of withholding parenteral nutrition until day 8 while providing vitamins, trace elements, and minerals. Late parenteral nutrition was associated with fewer infections, enhanced recovery, and lower health care costs.

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