ORIGINAL ARTICLE

Tight Blood-Glucose Control without Early Parenteral Nutrition in the ICU

J. Gunst, Y. Debaveye, F. Güiza, J. Dubois, A. De Bruyn, D. Dauwe, E. De Troy, M.P. Casaer, G. De Vlieger, R. Haghedooren, B. Jacobs, G. Meyfroidt, C. Ingels, J. Muller, D. Vlasselaers, L. Desmet, L. Mebis, P.J. Wouters, B. Stessel, L. Geebelen, J. Vandenbrande, M. Brands, I. Gruyters, E. Geerts, I. De Pauw, J. Vermassen, H. Peperstraete, E. Hoste, J.J. De Waele, I. Herck, P. Depuydt, A. Wilmer, G. Hermans, D.D. Benoit, and G. Van den Berghe, for the TGC-Fast Collaborators*

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Van den Berghe can be contacted at greet.vandenberghe@kuleuven.be or at the Clinical Department of Intensive Care Medicine, University Hospitals of KU Leuven, and the Department of Cellular and Molecular Medicine, KU Leuven, Herestraat 49, B-3000, Leuven, Belgium.

*A complete list of the TGC-Fast collaborators is provided in the Supplementary Appendix, available at NEJM.org.

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ABSTRACT

BACKGROUND

Randomized, controlled trials have shown both benefit and harm from tight blood-glucose control in patients in the intensive care unit (ICU). Variation in the use of early parenteral nutrition and in insulin-induced severe hypoglycemia might explain this inconsistency.

METHODS

We randomly assigned patients, on ICU admission, to liberal glucose control (insulin initiated only when the blood-glucose level was >215 mg per deciliter [>11.9 mmol per liter]) or to tight glucose control (blood-glucose level targeted with the use of the LOGIC-Insulin algorithm at 80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]); parenteral nutrition was withheld in both groups for 1 week. Protocol adherence was determined according to glucose metrics. The primary outcome was the length of time that ICU care was needed, calculated on the basis of time to discharge alive from the ICU, with death accounted for as a competing risk; 90-day mortality was the safety outcome.

RESULTS

Of 9230 patients who underwent randomization, 4622 were assigned to liberal glucose control and 4608 to tight glucose control. The median morning blood-glucose level was 140 mg per deciliter (interquartile range, 122 to 161) with liberal glucose control and 107 mg per deciliter (interquartile range, 98 to 117) with tight glucose control. Severe hypoglycemia occurred in 31 patients (0.7%) in the liberal-control group and 47 patients (1.0%) in the tight-control group. The length of time that ICU care was needed was similar in the two groups (hazard ratio for earlier discharge alive with tight glucose control, 1.00; 95% confidence interval, 0.96 to 1.04; P=0.94). Mortality at 90 days was also similar (10.1% with liberal glucose control and 10.5% with tight glucose control, P=0.51). Analyses of eight prespecified secondary outcomes suggested that the incidence of new infections, the duration of respiratory and hemodynamic support, the time to discharge alive from the hospital, and mortality in the ICU and hospital were similar in the two groups, whereas severe acute kidney injury and cholestatic liver dysfunction appeared less prevalent with tight glucose control.

CONCLUSIONS

In critically ill patients who were not receiving early parenteral nutrition, tight glucose control did not affect the length of time that ICU care was needed or mortality. (Funded by the Research Foundation–Flanders and others; TGC-Fast ClinicalTrials.gov number, NCT03665207.)

In critically ill patients who have been admitted to the intensive care unit (ICU), hyperglycemia is common and is associated with a poor outcome.[1-3] Whether this association reflects causality remains debated, because randomized, controlled trials have shown divergent effects of blood-glucose lowering.[4-11] In three single-center, randomized, controlled trials, patients in whom the blood-glucose level was lowered with insulin to the healthy, age-adjusted fasting range (tight glucose control) had better outcomes than those in whom hyperglycemia was permitted.[4-6] Mechanistic studies attributed this benefit to prevention of glucose toxicity in cells such as neurons, renal tubular cells, hepatocytes, and immune cells that take up glucose in a manner that is insulin-independent and gradient-dependent (the gradient is created by a difference between extracellular and intracellular glucose levels).[12-15] However, a benefit of tight glucose control was not confirmed in subsequent multicenter, randomized, controlled trials, and the largest trial showed increased mortality[9] that was attributed to a substantially increased incidence of severe hypoglycemia (glucose level, <40 mg per deciliter [<2.2 mmol per liter]).[16]

These opposite outcome effects might be explained by two important methodologic differences.[17] First, the trial showing harm from tight glucose control has been criticized for unstandardized blood-glucose measurements and insulin adjustments that may have increased the incidence of hypoglycemia, and the generalizability of the trial findings has been questioned. Second, the generalizability of the benefit shown in the earlier trials has been questioned because of the early use of parenteral nutrition.[4-6,18] Subsequent randomized, controlled trials have shown that early parenteral nutrition not only does not improve outcomes but may increase the risk of infections and delay recovery from critical illness.[19,20] These findings resulted in revised clinical practice guidelines that no longer advocate for early parenteral nutrition.[21] The nonuse of early parenteral nutrition also appears to reduce the severity of hyperglycemia and preserves autophagy-dependent removal of cell damage; the effect of this preservation may increase the threshold for hyperglycemic toxicity.[19,20,22-24] Moreover, the risk of hypoglycemia with tight glucose control may increase among patients who do not receive early parenteral nutrition.[19,20] However, there is evidence that hypoglycemia can be largely avoided with use of the LOGIC-Insulin computer algorithm, which provides guidance to bedside nurses on how to adjust insulin infusion, as shown in a single-center study and subsequently confirmed in a multicenter, randomized, controlled trial.[25,26]

On the basis of this evidence, we hypothesized that in critically ill patients who are not receiving early parenteral nutrition, tight glucose control with insulin infusion adjusted with the use of a high-performance computer algorithm would safely reduce the length of time that ICU care was needed, calculated on the basis of time to discharge alive from the ICU, although with a smaller effect size than previously reported in patients receiving early parenteral nutrition.

A Quick Take is available at NEJM.org

Methods

Trial Design and Oversight

TGC-Fast was an investigator-initiated, prospective, multicenter, randomized, controlled, parallel-group trial. The trial protocol (available with the full text of this article at NEJM.org) and informed-consent forms were approved by the ethics committees of the participating centers and by Belgian authorities. A description of the trial protocol and statistical analysis plan has been published previously.[27] Written informed consent was obtained from each patient or a legal representative. The first and last authors designed the trial protocol, analyzed the data, and wrote the first draft of the manuscript; they vouch for the accuracy and completeness of the data, the accuracy of the analyses, and the fidelity of the trial to the protocol. The other authors gathered the data, approved the decision to submit the manuscript for publication, and read and provided revisions. More information about author contributions is provided in the Supplementary Appendix, available at NEJM.org. No confidentiality agreements, except the agreement to maintain data confidentiality before publication, were in place between KU Leuven (the lead site) and the authors or other institutions.

Patients

From September 2018 through August 2022, consecutive adult patients admitted to one of 11 ICUs at two university hospitals and one district hospital in Belgium were screened for eligibility. During the first wave of coronavirus disease

2019 (Covid-19) in 2020, recruitment was temporarily halted as mandated by the central ethics committee. On resumption of recruitment, patients who were admitted to closed Covid-19 units were no longer assessed for eligibility.

Eligible patients were assigned in a 1:1 ratio to liberal glucose control or tight glucose control by centralized computer randomization that used a permuted block size of 10 and were stratified according to center and diagnostic category on ICU admission. Bedside nurses and physicians were unaware of the block size.

TRIAL PROCEDURES

In the patients assigned to tight glucose control, the blood-glucose level was targeted at 80 to 110 mg per deciliter (4.4 to 6.1 mmol per liter). The insulin doses, glucose doses in case of hypoglycemia, and frequency of blood-glucose measurement (ranging from every 1 to 4 hours and more frequently after hypoglycemia) were adjusted in accordance with the computer algorithm.[25,26]

In the patients assigned to liberal glucose control, insulin was initiated only when the blood-glucose level exceeded 215 mg per deciliter (>11.9 mmol per liter) on two consecutive measurements (or one measurement in patients with type 1 diabetes), after which bedside physicians and nurses adjusted the insulin dose to a target blood-glucose level between 180 and 215 mg per deciliter (10.0 and 11.9 mmol per liter). To maximize protocol adherence, a simple alert was integrated into the patient data management systems of each center to inform physicians and nurses about when to administer or discontinue insulin. The blood-glucose level was measured at least four times daily. Hypoglycemia was managed at the discretion of the attending physician in each ICU.

In both groups, blood-glucose levels were measured in arterial blood with use of a blood gas analyzer, and insulin was administered only as a continuous intravenous infusion through a central venous catheter. When the arterial catheter was removed, capillary blood could be used for blood-glucose measurements.

The trial intervention was stopped when the patient started to eat, no longer had a central venous catheter, or was discharged from the ICU, whichever came first. In patients who were readmitted to the ICU within 48 hours after discharge, the initial randomly assigned intervention was resumed.

All the patients received enteral nutrition as soon as possible. When enteral nutrition was insufficient to meet the caloric target, parenteral nutrition was initiated only after 1 week in the ICU. In all patients who did not receive 80% of the nutritional intake enterally, parenteral micronutrients were administered according to local practice in order to prevent refeeding syndrome.

OUTCOMES

The primary outcome was the length of time that ICU care was needed, calculated on the basis of time to discharge alive from the ICU, or the time until readiness for discharge from the ICU, with readiness for discharge defined as the time at which patients were no longer at risk or in need of vital-organ support or the time they were actually discharged, whichever came first. The safety outcome was mortality at 90 days after randomization. The incidence of severe hypoglycemia (glucose level, <40 mg per deciliter) that was resistant to intravenous glucose administration was considered to be a serious adverse event.

Eight secondary outcomes were prespecified. These outcomes included ICU-acquired kidney injury, which was defined as the incidence of severe (stage 3) acute kidney injury according to the creatinine criteria of the Kidney Disease: Improving Global Outcomes guidelines[28] and by new use of kidney-replacement therapy. Another secondary outcome was liver dysfunction as revealed by cholestatic or cytolytic liver dysfunction markers (γ-glutamyltransferase level, ≥90 U per liter [1.5 times the upper limit of the normal range]; alkaline phosphatase level, ≥195 U per liter [1.5 times the upper limit of the normal range]; bilirubin level, >3 mg per deciliter; aspartate aminotransferase level, ≥111 U per liter [3 times the upper limit of the normal range]; or alanine aminotransferase level, ≥123 U per liter [3 times the upper limit of the normal range]).[19] The six other secondary outcomes were new infections, respiratory support, hemodynamic support, time to discharge alive from the hospital, mortality in the ICU, and mortality in the hospital.

STATISTICAL ANALYSIS

In patients who had not received early parenteral nutrition, we expected small differences in blood-glucose levels between the tight glucose control group and the liberal glucose control group, so we hypothesized much smaller outcome benefits of tight glucose control than those we had found

in our previous randomized, controlled trials. Therefore, to obtain 80% statistical power with an alpha level of 0.05, we calculated that a sample of 9230 patients would need to be enrolled to detect a 1-day difference in the length of time that ICU care was needed, calculated on the basis of time to discharge alive from the ICU (the primary outcome), and to exclude a 1.5 percentage-point increase in mortality with tight glucose control (the safety outcome).

The independent data and safety monitoring board performed two preplanned interim analyses.[27] The first was performed after inclusion of 25% of the preplanned sample, in order to assess any need for repowering based on the real versus estimated duration of ICU stay in the control group (liberal glucose control). The second was performed to assess the effect of tight glucose control on the safety outcome (mortality) after inclusion of 50% of the patients. At both time points, the data and safety monitoring board allowed continuation of recruitment as planned.

Analyses of differences between the randomized treatment groups were performed with use of JMP Pro software, version 17.0.0 (SAS Institute). Data were summarized as frequencies and percentages and medians (interquartile range) unless indicated otherwise. Mortality in the two groups was compared with the use of the chi-square test. The cumulative survival and the cumulative incidence of discharge alive from the ICU were analyzed with the use of Kaplan–Meier plots. The time-to-event analyses were performed with the use of a Cox proportional-hazards model, after ensuring, with the Schoenfeld residuals method, that the proportional-hazards assumption was met. For time-to-event analyses, data for nonsurvivors were censored at a time point beyond that of the last surviving patient to account for death as a competing risk.[29]

We investigated potential heterogeneity in treatment effects in six prespecified subgroups: patients with a history of diabetes,[3,30] those who had undergone cardiac surgery or who had complications after cardiac surgery, those who had undergone surgery (or who had complications after surgery) or trauma, those with a neurologic or neurosurgical admission diagnosis,[30-32] those with sepsis, and those with a predicted ICU stay of more than 1 week (through random-forest modeling with use of data available on ICU admission). Details regarding methods and performance measures are provided in the Supplementary Appendix and Figures S1 through S6 and Tables S1 and S2 in the Supplementary Appendix. In general, patients with long stays in the ICU who receive insufficient enteral nutrition are expected to receive supplemental parenteral nutrition from day 8 onward, which increases blood-glucose levels and insulin requirements and may hamper recovery from cell damage.[19,22-24] In our trial, the interaction between the randomized treatment and the yes–no level in these subgroups (i.e., whether patients were classified as being part of a prespecified subgroup as compared with all other patients) was determined with use of Cox proportional-hazards and logistic-regression models, followed by forest-plot visualization of the treatment effects in the subgroups.

All the analyses were performed in the intention-to-treat population, which consisted of all the patients who had undergone randomization. Two-sided P values of less than 0.05 were considered to indicate statistical significance. For secondary outcomes and subgroups, point estimates and 95% confidence intervals of the difference were not adjusted for multiplicity and may not be used in place of hypothesis testing.

RESULTS

PATIENTS AND TRIAL INTERVENTIONS

Of the 24,195 patients who were assessed for eligibility, 9230 underwent randomization, and 4622 were assigned to the liberal glucose control group and 4608 to the tight glucose control group; all 9230 patients were included in the intention-to-treat analysis (Fig. 1). Baseline characteristics were similar in the two groups (Table 1). Table S3 describes the representativeness of the trial population.

Blood-glucose levels were similarly elevated on ICU admission in both groups (Table 1). Thereafter, patients in the tight-control group had lower blood-glucose levels and received higher insulin doses than those in the liberal-control group (Table 2 and Fig. 2A and 2B). In the liberal-control group, blood-glucose levels and insulin requirements became substantially higher in the second week in the ICU in parallel with the increased nutritional intake from day 8 onward (Fig. 2A through 2D). The incidence of severe hypoglycemia was low (in 31 of 4622 patients [0.7%] in the liberal-control group and 47

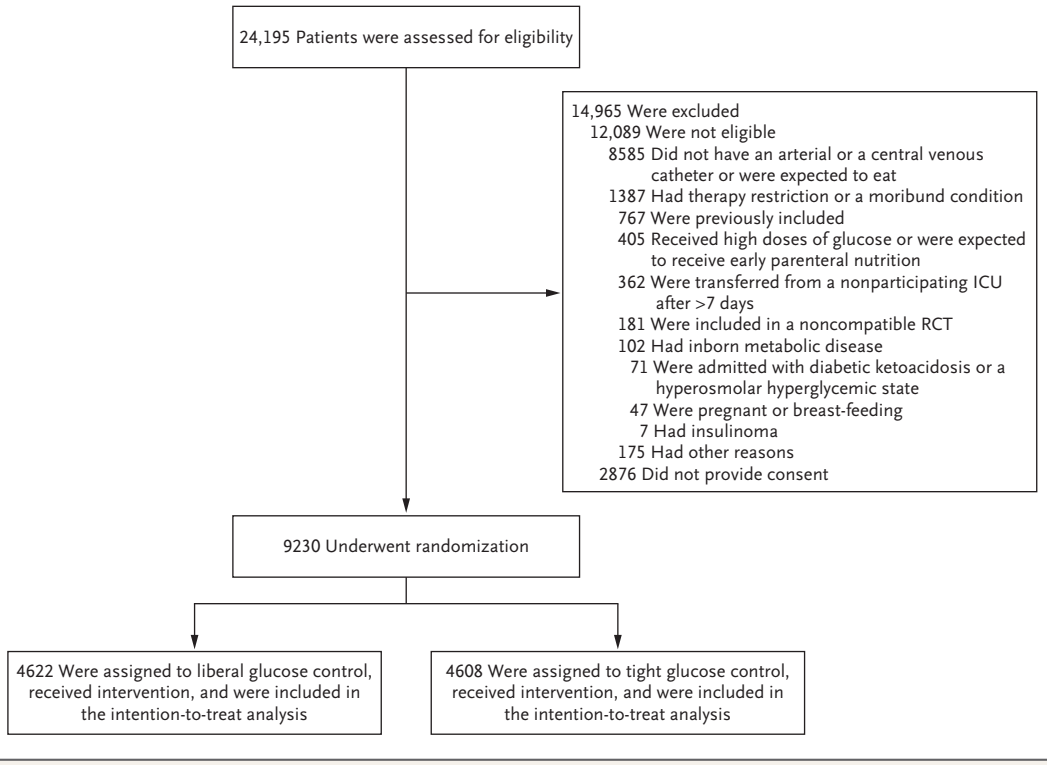


Figure 1. Screening and Randomization.
ICU denotes intensive care unit, and RCT randomized, controlled trial.

of 4608 patients [1.0%] in the tight-control group) (relative risk with tight control vs. liberal control, 1.52; 95% confidence interval [CI], 0.97 to 2.39) (Table 2). None of the patients had therapy-resistant hypoglycemia.

PRIMARY AND SAFETY OUTCOMES

The length of time that ICU care was needed was not significantly different in the two groups (hazard ratio for earlier discharge alive with tight glucose control, 1.00; 95% CI, 0.96 to 1.04; P=0.94) (Fig. 2E). Within 90 days after randomization, 468 of 4621 patients in the liberal-control group (10.1%) and 486 of 4607 patients in the tight-control group (10.5%) had died (P=0.51) (Fig. 2F and Table 2).

SECONDARY OUTCOMES

Severe acute kidney injury developed in 387 of 4500 patients in the liberal-control group (8.6%) and in 326 of 4507 patients in the tight-control group (7.2%) (relative risk, 0.84; 95% CI, 0.73 to 0.97). New use of kidney-replacement therapy was initiated in 259 of 4500 patients in the liberal-control group (5.8%) and in 212 of 4507 patients in the tight-control group (4.7%) (relative risk, 0.82; 95% CI, 0.68 to 0.98) (Table 2). Biochemical markers of cholestatic liver dysfunction, but not cytolytic liver dysfunction, were lower in the tight-control group than in the liberal-control group (Table 2). A total of 1370 of 4170 patients (32.9%) in the liberal-control group and 1175 of 4146 patients in the tight-control group (28.3%) had plasma γ-glutamyltransferase levels of at least 90 U per liter (relative risk, 0.86; 95% CI, 0.81 to 0.92). In the liberal-control group, 498 of 3818 patients (13.0%) had plasma alkaline phosphatase levels of at least 195 U per liter as compared with 437 of 3787 patients in the tight-control group (11.5%) (relative risk, 0.88; 95% CI, 0.78 to 0.99). The incidence of new infections, the duration of respiratory and hemodynamic support, the time to discharge alive from the hospital, and mortality in the ICU and hospital were similar in the two groups (Table 2 and Table S4).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Liberal Glucose Control (N=4622)	Tight Glucose Control (N=4608)
Median age (IQR) — yr	67 (56–75)	67 (57–75)
Male sex — no. (%)	2902 (62.8)	2930 (63.6)
Median weight (IQR) — kg	75 (65–86)	76 (65–88)
Median body-mass index (IQR)†	26 (23–29)	26 (23–29)
History of diabetes mellitus — no. (%)	955 (20.7)	933 (20.2)
Median Charlson comorbidity index score (IQR)‡	4 (2–6)	4 (2–5)
Sepsis — no. (%)§	1307 (28.3)	1313 (28.5)
Median APACHE II score (IQR)¶	21 (15–30)	21 (15–30)
Predicted ICU stay >1 wk — no. (%)	1605 (34.7)	1625 (35.3)
Diagnostic category — no. (%)		
Cardiac surgery or complications thereafter	2084 (45.1)	2086 (45.3)
Neurologic or neurosurgical	528 (11.4)	525 (11.4)
Abdominal or pelvic surgery, or complications thereafter	522 (11.3)	505 (11.0)
Solid-organ transplantation	319 (6.9)	314 (6.8)
Lung or esophageal surgery, or complications thereafter	168 (3.6)	179 (3.9)
Trauma or burns	172 (3.7)	175 (3.8)
Gastrointestinal or hepatic	151 (3.3)	158 (3.4)
Respiratory	139 (3.0)	137 (3.0)
Vascular surgery or complications thereafter	117 (2.5)	117 (2.5)
Cardiovascular	106 (2.3)	103 (2.2)
Hematologic or oncologic	70 (1.5)	65 (1.4)
Metabolic or renal	40 (0.9)	40 (0.9)
Other	206 (4.5)	204 (4.4)
Median blood-glucose level (IQR) — mg/dl‖	143 (120–170)	142 (121–168)

* ICU denotes intensive care unit.
† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 4 patients (2 patients in each group).
‡ Scores on the Charlson comorbidity index range from 0 to 37, with higher scores indicating a greater burden of coexisting conditions.[33]
§ Sepsis was defined according to the Sepsis-3 criteria.[34]
¶ Acute Physiology and Chronic Health Evaluation (APACHE) II scores range from 0 to 71, with higher scores indicating a greater severity of illness.[35]
‖ To convert blood-glucose values to millimoles per liter, multiply by 0.05551.

ANALYSES OF HETEROGENEITY IN TREATMENT EFFECTS

For the safety outcome, mortality at 90 days (see Fig. 3B), there was a possible interaction between randomization to tight glucose control versus liberal glucose control and the baseline variable "neurologic or neurosurgical admission diagnosis versus other diagnoses." The results suggest the possibility of lower mortality with tight glucose control in the subgroup of patients with a neurologic or neurosurgical admission diagnosis. No other apparent treatment heterogeneity was observed.

DISCUSSION

In this large, multicenter, randomized, controlled trial, hyperglycemia was much less pronounced in critically ill adult patients in whom parenteral nutrition was withheld for 1 week in the ICU than in those in previous randomized, controlled trials who received early parenteral

Table 2. Blood-Glucose Management, Nutrition, and Outcomes.*

Variable	Liberal Glucose Control (N=4622)	Tight Glucose Control (N=4608)	Relative Risk, Difference, or Hazard Ratio (95% CI)†	P Value
Protocol compliance: glucose metrics and nutrition				
Treatment with insulin — no. (%)	2122 (45.9)	4551 (98.8)	2.15 (2.08 to 2.22)	
Median daily insulin dose (IQR) — units/day‡	0.0 (0.0–5.6)	24.8 (14.8 to 39.9)	21.0 (20.5 to 21.5)	
Median blood-glucose level (IQR) — mg/dl				
Peak level in ICU	189 (162–230)	170 (146 to 204)	–19 (–21 to –17)	
Daily level‡	145 (128–165)	115 (107 to 126)	–28 (–29 to –27)	
Morning level‡§	140 (122–161)	107 (98 to 117)	–32 (–33 to –32)	
Severe hypoglycemia, glucose level <40 mg/dl — no. (%)	31 (0.7)	47 (1.0)	1.52 (0.97 to 2.39)	
Median caloric intake of parenteral nutrition (IQR) — average kcal/day, day 1–day 7	101 (77 to 160)	101 (76 to 162)	0 (–2 to 2)	
Primary and safety outcomes				
Length of time that ICU care was needed				
Time to discharge alive from ICU			1.00 (0.96 to 1.04)	0.94
Duration of stay in ICU — days				
Mean	7±13	6±12	0 (–1 to 0)	
Median (IQR)	3 (1 to 6)	3 (1 to 6)	0 (0 to 0)	
Death within 90 days — no. (%)	468/4621 (10.1)	486/4607 (10.5)	1.04 (0.92 to 1.17)	0.51
Secondary outcomes				
Acute kidney injury — no. (%)¶				
Severe acute kidney injury	387/4500 (8.6)	326/4507 (7.2)	0.84 (0.73 to 0.97)	
New use of kidney-replacement therapy	259/4500 (5.8)	212/4507 (4.7)	0.82 (0.68 to 0.98)	
Liver dysfunction, plasma levels — no. (%)				
Peak γ-glutamyltransferase level ≥90 U/liter‖	1370/4170 (32.9)	1175/4146 (28.3)	0.86 (0.81 to 0.92)	
Peak alkaline phosphatase level ≥195 U/liter‖	498/3818 (13.0)	437/3787 (11.5)	0.88 (0.78 to 0.99)	
Peak bilirubin level >3 mg/dl	458/4545 (10.1)	409/4526 (9.0)	0.90 (0.79 to 1.02)	
Peak AST level ≥111 U/liter**	1013/4584 (22.1)	1020/4578 (22.3)	1.01 (0.93 to 1.09)	
Peak ALT level ≥123 U/liter**	723/4583 (15.8)	677/4574 (14.8)	0.94 (0.85 to 1.03)	
New infection — no. (%)	664 (14.4)	634 (13.8)	0.96 (0.87 to 1.06)	
Time to live weaning from mechanical respiratory support			0.99 (0.95 to 1.03)	
Time to live weaning from hemodynamic support			0.98 (0.94 to 1.02)	
Time to discharge alive from hospital			1.00 (0.96 to 1.04)	
Death — no. (%)				
In ICU	247 (5.3)	267 (5.8)	1.08 (0.92 to 1.28)	
In hospital	421 (9.1)	443 (9.6)	1.06 (0.93 to 1.20)	

* Plus–minus values are means ±SD. To convert blood-glucose levels to millimoles per liter, multiply by 0.05551. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and CI confidence interval.

† For continuous variables, between-group differences are presented as differences in medians (Hodges–Lehman estimate) or differences in means; for proportions, between-group differences are presented as relative risks. For time-to-event analyses, the hazard ratio is shown. The relative risk or hazard ratio is for tight glucose control versus liberal glucose control. The widths of the 95% confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

‡ The medians shown for each group are based on the mean values for the individual patients.

§ Data were missing for 91 patients.

¶ In the analysis of incidence of severe (stage 3) acute kidney injury and the use of new kidney-replacement therapy, 223 patients receiving long-term dialysis or having received kidney-replacement therapy before randomization were excluded.

‖ This value is a minimum of 1.5 times the upper limit of the normal range.

** This value is a minimum of 3 times the upper limit of the normal range.

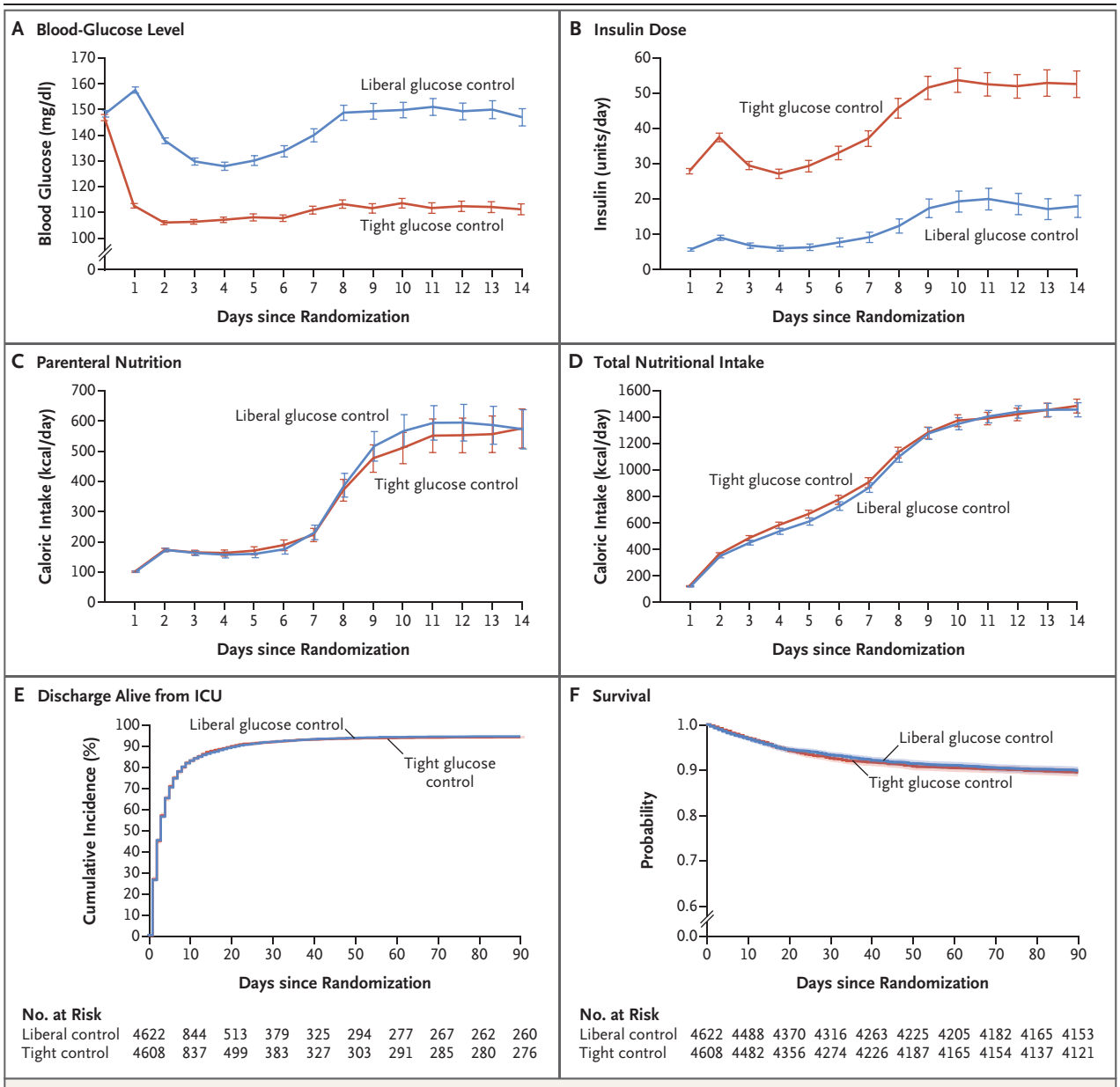


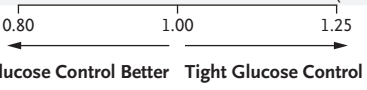
Figure 2. Blood-Glucose Control, Parenteral and Total Nutrition, and the Primary and Safety Outcomes.

Panel A shows the blood-glucose level at randomization and the morning blood-glucose levels from day 1 to day 14. To convert blood-glucose values to millimoles per liter, multiply by 0.05551. Panel B shows the dose of insulin. Panel C shows caloric intake of parenteral nutrition. Panel D shows total nutritional intake. In Panels A through D, data points reflect mean values and I bars represent the 95% confidence intervals. Panel E shows the cumulative proportion of patients who were discharged alive from the ICU in the two groups. The shaded area represents 95% confidence intervals. The widths of the 95% confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Panel F shows the probability of survival in the two groups. Two patients — one in the liberal glucose control group and one in the tight glucose control group — could not be contacted 90 days after randomization. The shaded area represents 95% confidence intervals.

nutrition. Further lowering of blood-glucose levels into the healthy fasting range with tight glucose control, guided by the LOGIC-Insulin computer algorithm to avoid iatrogenic severe hypoglycemia, did not affect the length of time that ICU care was needed or mortality. Secondary morbidity outcomes were also largely unaffected by tight glucose control, although the in-

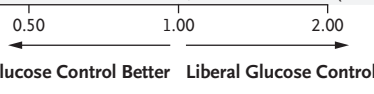
A Primary Outcome

Subgroup	Liberal Glucose Control	Tight Glucose Control	Hazard Ratio for Time to Discharge Alive from the ICU (95% CI)
	no. of patients		
History of diabetes			
Yes	955	933	0.98 (0.89–1.07)
No	3667	3675	1.00 (0.96–1.05)
Cardiac surgery or complications thereafter			
Yes	2084	2086	1.03 (0.96–1.09)
No	2538	2522	0.99 (0.93–1.04)
Major surgery or trauma, or complications thereafter			
Yes	3937	3942	0.99 (0.95–1.04)
No	685	666	1.02 (0.90–1.14)
Neurologic or neurosurgical diagnosis			
Yes	528	525	1.01 (0.89–1.14)
No	4094	4083	1.00 (0.96–1.05)
Sepsis			
Yes	1307	1313	1.00 (0.92–1.09)
No	3315	3295	1.00 (0.95–1.05)
Predicted ICU stay >1 wk			
Yes	1605	1625	1.00 (0.92–1.07)
No	3017	2983	1.01 (0.96–1.06)
All patients	4622	4608	1.00 (0.96–1.04)



B Safety Outcome

Subgroup	Liberal Glucose Control (N=4622)	Tight Glucose Control (N=4608)	Odds Ratio for Death at 90 Days (95% CI)
	no. of deaths/no. of patients with data available		
History of diabetes			
Yes	106/955	121/933	1.19 (0.90–1.58)
No	362/3666	365/3674	1.01 (0.86–1.17)
Cardiac surgery or complications thereafter			
Yes	97/2084	113/2085	1.17 (0.89–1.55)
No	371/2537	373/2522	1.01 (0.87–1.18)
Major surgery or trauma, or complications thereafter			
Yes	281/3936	315/3941	1.13 (0.96–1.34)
No	187/685	171/666	0.92 (0.72–1.17)
Neurologic or neurosurgical diagnosis			
Yes	66/528	47/525	0.69 (0.46–1.02)
No	402/4093	439/4082	1.11 (0.96–1.28)
Sepsis			
Yes	290/1307	295/1312	1.02 (0.85–1.22)
No	178/3314	191/3295	1.08 (0.88–1.34)
Predicted ICU stay >1 wk			
Yes	365/1605	381/1624	1.04 (0.88–1.23)
No	103/3016	105/2983	1.03 (0.78–1.36)
All patients	468/4621	486/4607	1.05 (0.92–1.20)



cidence of severe acute kidney injury, the new use of kidney-replacement therapy, and the incidence of cholestatic liver dysfunction appeared lower in the tight-control group than in the liberal-control group. These findings suggest that the use of early parenteral nutrition in

Figure 3 (facing page). Subgroup Analysis.
Panel A shows a forest plot of tight glucose control versus liberal glucose control in subgroups with respect to time to discharge alive from the ICU. Panel B shows a forest plot of tight glucose control versus liberal glucose control in subgroups with respect to death at 90 days. The widths of the 95% confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Interaction analysis revealed possible heterogeneity in treatment effect for patients with a neurologic or neurosurgical admission diagnosis.

previous studies was an important iatrogenic factor that increased hyperglycemia into a potentially toxic range.[22,23,36] These results add evidence to the recommendation to omit early parenteral nutrition for adult patients in the ICU because this omission reduces the need for blood-glucose control.

This randomized, controlled trial was performed in a heterogeneous patient population, which allowed assessment of the heterogeneity in treatment effect in large subgroups. Potential treatment heterogeneity was limited to patients who were admitted with a neurologic or neurosurgical diagnosis, among whom 90-day mortality appeared lower with tight glucose control than with liberal glucose control. A possible explanation is that the brain is particularly sensitive to harm from hyperglycemia, which may have been increased by glucocorticoid therapy, and to harm from hypoglycemia, which in this trial was effectively prevented by tight glucose control that was guided by a high-performance computer algorithm.[37-39] These findings contrast with those in previous randomized, controlled trials that investigated the effect of blood-glucose control in patients with stroke. Those trials showed smaller differences in blood-glucose levels between trial groups[40] and a substantially higher incidence of iatrogenic hypoglycemia.[32,40]

The limitations of the present trial include the inability to conceal the treatment assignments from the caregivers and the lack of correction for multiple comparisons for secondary outcomes. Unfortunately, the primary outcome may have been confounded by fluctuating discharge policies owing to a shortage of ICU beds, a major problem during the Covid-19 pandemic. Also, the clinical relevance of the lower incidence of kidney and liver dysfunction with tight glucose control and of the possible treatment heterogeneity in patients with a neurologic or neurosurgical admission diagnosis remains uncertain. The strengths of the trial include the very large sample size and excellent protocol adherence with use of a high-performance computer algorithm.

In critically ill patients who were not receiving early parenteral nutrition, hyperglycemia was less severe than that previously reported in patients receiving parenteral nutrition. Further lowering of blood-glucose levels into the normal fasting range, guided by a computer algorithm, avoided iatrogenic hypoglycemia without affecting the length of time that ICU care was needed or mortality.

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APPENDIX

The authors' full names and academic degrees are as follows: Jan Gunst, M.D., Ph.D., Yves Debaveye, M.D., Ph.D., Fabian Güiza, Ph.D., Jasperina Dubois, M.D., Astrid De Bruyn, M.D., Ph.D., Dieter Dauwe, M.D., Ph.D., Erwin De Troy, M.D., Michael P. Casaer, M.D., Ph.D., Greet De Vlieger, M.D., Ph.D., Renata Haghedooren, M.D., Bart Jacobs, M.D., Geert Meyfroidt, M.D., Ph.D., Catherine Ingels, M.D., Ph.D., Jan Muller, M.D., Dirk Vlasselaers, M.D., Ph.D., Lars Desmet, M.D., Liese Mebis, Ph.D., Pieter J. Wouters, M.Sc., Björn Stessel, M.D., Ph.D., Laurien Geebelen, M.Sc., Jeroen Vandenbrande, M.D., Michiel Brands, M.D., Ine Gruyters, M.D., Ester Geerts, M.D., Ilse De Pauw, M.D., Joris Vermassen, M.D., Harlinde Peperstraete, M.D., Eric Hoste, M.D., Ph.D., Jan J. De Waele, M.D., Ph.D., Ingrid Herck, M.D., Pieter Depuydt, M.D., Ph.D., Alexander Wilmer, M.D., Ph.D., Greet Hermans, M.D., Ph.D., Dominique D. Benoit, M.D., Ph.D., and Greet Van den Berghe, M.D., Ph.D.

The authors' affiliations are as follows: the Clinical Department of Intensive Care Medicine (J.G., Y.D., F.G., A.D.B., D.D., E.D.T., M.P.C., G.D.V., R.H., B.J., G.M., C.I., J.M., D.V., L.D., L.M., P.J.W., G.V.B.) and the Medical Intensive Care Unit (A.W., G.H.), University Hospitals of KU Leuven, Leuven, the Department of Anesthesiology and Intensive Care Medicine, Jessa Hospital, Hasselt (J.D., B.S., L.G., J. Vandenbrande, M.B., I.G., E.G., I.D.P.), and the Department of Intensive Care Medicine, Ghent University Hospital, Ghent (J. Vermassen, H.P., E.H., J.J.D.W., I.H., P.D., D.D.B.) — all in Belgium.

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