The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 9, 2014 VOL. 370 NO. 2

A Randomized Trial of Hyperglycemic Control in Pediatric Intensive Care

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ABSTRACT

BACKGROUND

Whether an insulin infusion should be used for tight control of hyperglycemia in critically ill children remains unclear.

METHODS

We randomly assigned children (≤16 years of age) who were admitted to the pediatric intensive care unit (ICU) and were expected to require mechanical ventilation and vasoactive drugs for at least 12 hours to either tight glycemic control, with a target blood glucose range of 72 to 126 mg per deciliter (4.0 to 7.0 mmol per liter), or conventional glycemic control, with a target level below 216 mg per deciliter (12.0 mmol per liter). The primary outcome was the number of days alive and free from mechanical ventilation at 30 days after randomization. The main prespecified subgroup analysis compared children who had undergone cardiac surgery with those who had not. We also assessed costs of hospital and community health services.

RESULTS

A total of 1369 patients at 13 centers in England underwent randomization: 694 to tight glycemic control and 675 to conventional glycemic control; 60% had undergone cardiac surgery. The mean between-group difference in the number of days alive and free from mechanical ventilation at 30 days was 0.36 days (95% confidence interval [CI], −0.42 to 1.14); the effects did not differ according to subgroup. Severe hypoglycemia (blood glucose, <36 mg per deciliter [2.0 mmol per liter]) occurred in a higher proportion of children in the tight-glycemic-control group than in the conventional-glycemic-control group (7.3% vs. 1.5%, P<0.001). Overall, the mean 12-month costs were lower in the tight-glycemic-control group than in the conventional-glycemic-control group. The mean 12-month costs were similar in the two groups in the cardiac-surgery subgroup, but in the subgroup that had not undergone cardiac surgery, the mean cost was significantly lower in the tight-glycemic-control group than in the conventional-glycemic-control group: −$13,120 (95% CI, −$24,682 to −$1,559).

CONCLUSIONS

This multicenter, randomized trial showed that tight glycemic control in critically ill children had no significant effect on major clinical outcomes, although the incidence of hypoglycemia was higher with tight glucose control than with conventional glucose control. (Funded by the National Institute for Health Research, Health Technology Assessment Program, U.K. National Health Service; CHiP Current Controlled Trials number, ISRCTN61735247.)

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This article was updated on January 9, 2014, at NEJM.org.

N Engl J Med 2014;370:107-18.
DOI: 10.1056/NEJMoa1302564

Hyperglycemia is a common complication in critical illness and is associated with adverse outcomes.[1-5] Single-center, randomized trials have shown that reduction of blood glucose to normal levels with the use of insulin reduces morbidity and mortality among adults in surgical intensive care units (ICUs),[6] with similar effects on morbidity but not on mortality among adults in nonsurgical ICUs.[7] However, two meta-analyses[8,9] have failed to show a benefit, and a large, international, multicenter trial showed that tight glycemic control increased mortality.[10]

Data on tight glucose control with the use of insulin in critically ill children have been lacking. One trial conducted in a single center, involving primarily patients who had undergone cardiac surgery,[11] did not include a full economic evaluation — a limitation that has also been seen in studies involving critically ill adults. The aim of the current trial, the Control of Hyperglycaemia in Paediatric Intensive Care (CHiP) trial, was to assess whether tight glycemic control with the use of an insulin infusion in children admitted to pediatric ICUs after cardiac surgery or for other reasons reduces mortality and morbidity and is cost-effective.

Methods

Study Oversight

We conducted a parallel-group, randomized, controlled trial involving children admitted to 13 pediatric ICUs in England. The trial was approved in 2007 by a National Health Service (NHS) multicenter research ethics committee. The protocol, which has been published previously,[12] is available, along with the statistical analysis plan, with the full text of this article at NEJM.org. All the authors were involved in designing the study and preparing the manuscript and vouch for the accuracy and completeness of this report, as well as the fidelity of this report to the study protocol. Written informed consent was obtained from each child's parent or legal surrogate. There was no commercial support for the trial.

Patients

Children were eligible if they were between 36 weeks of corrected gestational age and 16 years of age, if they had been admitted to a pediatric ICU, and if they had an arterial catheter in place and were receiving mechanical ventilation and vasoactive drugs after an injury or major surgery or for a critical illness, with an anticipated duration of treatment of at least 12 hours. Children were excluded if they had diabetes mellitus, if they had a confirmed or suspected inborn error of metabolism, if withdrawal of treatment was being considered, if they had been in a pediatric ICU for more than 5 days, or if they had already participated in the current trial.

Treatment

The randomization of patients to conventional glycemic control or tight glycemic control was performed by means of a central computerized system with the use of a minimization algorithm.[12] In the conventional-glycemic-control group, insulin in saline was infused intravenously when blood glucose levels exceeded 216 mg per deciliter (12.0 mmol per liter) in two consecutive blood samples obtained at least 30 minutes apart and was discontinued when blood glucose levels fell below 180 mg per deciliter (10.0 mmol per deciliter). In the tight-glycemic-control group, an intravenous infusion of insulin in saline was adjusted to maintain blood glucose levels in the range of 72 to 126 mg per deciliter (4.0 to 7.0 mmol per liter). In both groups, management was guided by treatment algorithms developed for the study.[12] All other aspects of patient care and nutrition were the responsibility of the treating clinicians.

Blood samples for glucose measurement were obtained from arterial catheters whenever possible. Blood glucose levels were measured with point-of-care blood gas analyzers or laboratory analyzers that were in routine use at each center. The analyzers were maintained according to NHS quality standards (www.cpa-uk.co.uk/dpmed.htm); all laboratories were registered with Clinical Pathology Accreditation (United Kingdom). During recruitment, the treatment assignments were blinded; however after randomization, the investigators were aware of the group assignments.

Patient Evaluation

Evaluation of Risk

Baseline demographic and clinical characteristics were recorded. For patients who had undergone cardiac surgery (cardiac-surgery subgroup), the score on the Risk Adjustment in Congenital Heart Surgery (RACHS-1, on which scores range from 1 to 6, with higher scores indicating greater

risk)[13] was assessed. For children who had been admitted to the pediatric ICU for other reasons (non–cardiac-surgery subgroup), the score on the Paediatric Index of Mortality 2 (PIM2, on which scores range from 0 to 100, with higher scores indicating a higher risk of death)[14] was assessed.

Outcome Measures

Outcome measures were defined and statistical analyses were prespecified in the statistical analysis plan.[12] The primary outcome was the number of days alive and free from mechanical ventilation at 30 days after randomization.[15] Secondary outcomes were assessed at two time points. At the time of discharge from the pediatric ICU (or at 30 days if the child was in the pediatric ICU for >30 days), we recorded the number of days in the pediatric ICU, vital status, duration of mechanical ventilation and of receipt of vasoactive drugs, status with respect to the need for renal-replacement therapy, incidence of bloodstream infection, use of antibiotics for more than 10 days, number of red-cell transfusions, Paediatric Logistic Organ Dysfunction (PELOD) score,[16,17] rate of readmission to the pediatric ICU, length of stay in the hospital, and costs. At 12 months after randomization, we assessed the length of stay in the pediatric ICU and hospital (including during readmissions), vital status, and costs of hospital and community health services. Data on readmissions to the original pediatric ICU were recorded on the case-report forms. Data on readmissions other than to the original ICU and use of primary and community health services were obtained from a questionnaire that was mailed to parents at 12 months. All costs are reported on the basis of 2010–2011 hospital charges.

Serious Adverse Events

Moderate hypoglycemia was defined as a blood glucose level of 36 to 45 mg per deciliter (2.0 to 2.5 mmol per liter). Severe hypoglycemia was defined as a blood glucose level lower than 36 mg per deciliter. The details of each hypoglycemic or other adverse event were reviewed by the clinical coordinating center and managed in compliance with the U.K. Medicines for Human Use (Clinical Trials) Regulations 2004.

STATISTICAL ANALYSIS

A difference of 2 days in the number of days free from mechanical ventilation at 30 days was considered to be clinically important. On the basis of data from the U.K. Paediatric Intensive Care Audit Network for 2003–2004,[18] a standard deviation of 7 days was assumed for both trial groups. We calculated that with a sample size of 1500, the study would have 80% power for an interaction test to detect a 2-day difference in the effect of the intervention between the cardiac-surgery subgroup and the non–cardiac-surgery subgroup, at a 5% level of significance.

Analyses were performed according to the intention-to-treat principle. For the primary outcome, linear regression models were used to estimate the mean between-group difference in the number of days free from mechanical ventilation at 30 days. For the secondary outcomes, appropriate generalized models were used. Odds ratios and mean differences are reported with 95% confidence intervals. Where there was evidence of nonnormality in the continuous outcome measures, nonparametric bootstrapping was used to estimate bias-corrected confidence intervals.[19]

Six subgroup analyses were prespecified for subgroups defined according to the following variables: admission to the pediatric ICU after cardiac surgery versus admission for other reasons, age (<1 year vs. 1 to 16 years), RACHS-1 score (1 through 4 vs. 5 and 6), PIM2 score for risk of death (<5%, 5 to <15%, and ≥15%), status with respect to traumatic brain injury, and "run-in" patients (i.e., the first 100 children who underwent randomization) versus patients who underwent randomization subsequently. Evidence of any differential effects of the intervention on the primary outcome, according to subgroup, was assessed with the use of likelihood ratio tests for the treatment-by-subgroup interaction terms. The effects in the various subgroups were estimated directly from the regression model with the interaction term included.

The difference in costs between tight glycemic control and conventional glycemic control were reported at 30 days and at 12 months, for the two groups overall and for the cardiac-surgery subgroup as compared with the non–cardiac-surgery subgroup. Missing data on cost at 12 months were handled with multiple imputation.[20-22] Imputation models included baseline covariates, the number of days mechanical ventilation was used, total length of stay in the hospital (including ICU), and costs at 30 days, as well as information on 12-month costs for children for whom

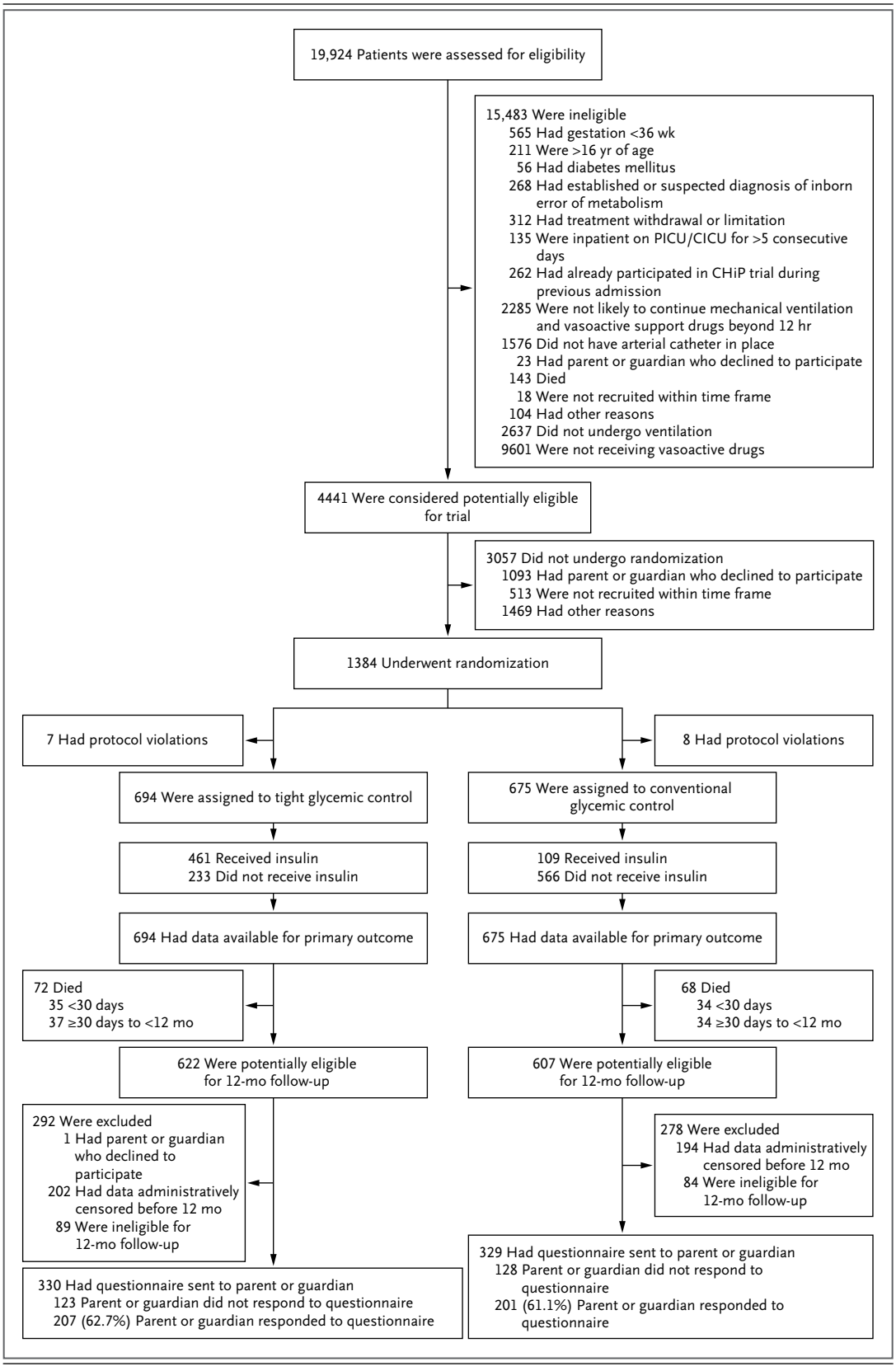


Figure 1 (facing page). Screening, Randomization, Assessment, and Follow-up.

Patients could have more than one reason for ineligibility for the study. Information on vital status up to 12 months was available for all patients, with the exception of 17 non-U.K. nationals, from the U.K. Office of National Statistics. Owing to funding constraints, the 12-month follow-up assessment was performed only for patients who underwent randomization up to October 30, 2010 (i.e., the follow-up was administratively censored). CHiP denotes Control of Hyperglycaemia in Paediatric Intensive Care, CICU cardiac intensive care unit, and PICU pediatric intensive care unit.

this end point was assessed. Sensitivity analyses were performed to assess the between-group differences in costs at 12 months according to assumptions about whether additional costs for insulin therapy and the monitoring of glycemic control were included, whether unit costs were taken from all pediatric ICUs in England (not just those in the CHiP trial), and whether costs were assumed to follow a gamma distribution rather than a normal distribution.

RESULTS

STUDY PARTICIPANTS

Participants were recruited between May 4, 2008, and August 31, 2011, at which time funding for recruitment ceased. A total of 19,924 children were screened at 13 sites, and 1369 eligible children were randomly assigned to a study group: 694 to tight glycemic control and 675 to conventional glycemic control (Fig. 1). The baseline characteristics of the groups were similar (Table 1, and Table S1 in the Supplementary Appendix, available at NEJM.org). A total of 60% of the children had been admitted to the pediatric ICU after having undergone cardiac surgery.

INSULIN ADMINISTRATION AND TREATMENT EFFECTS

More patients in the tight-glycemic-control group than in the conventional-glycemic-control group received insulin (461 of 694 patients [66.4%] vs. 109 of 675 patients [16.1%], P<0.001). Patients in the tight-glycemic-control group, as compared with those in the conventional-glycemic-control group, received more insulin while they were in the hospital (mean, 0.18 vs. 0.07 IU per kilogram of body weight per day) and for a longer duration (3.2 days vs. 1.7 days) and had lower mean daily blood glucose levels during the 10 days after randomization (Fig. 2, and Table S2 in the Supplementary Appendix). The mean caloric intake was similar in the two groups.

OUTCOMES

Status at 30 Days after Randomization

The mean between-group difference in the number of days alive and free from mechanical ventilation at 30 days was 0.36 days (95% confidence interval [CI], −0.42 to 1.14) (Table 2). Secondary outcomes were similar in the two groups at 30 days after randomization, although a lower proportion of patients in the tight-glycemic-control group received renal-replacement therapy (odds ratio, 0.63; 95% CI, 0.45 to 0.89). None of the interaction tests between the intervention and prespecified subgroups were significant: P=0.63 for the comparison of patients who had undergone cardiac surgery with those who had not (between-group difference, −0.37 days; 95% CI, −1.92 to 1.17); P=0.28 for the comparison of patients younger than 1 year of age with those 1 year of age or older (between-group difference, 0.88 days; 95% CI, −0.72 to 2.49); P=0.09 for the comparison of patients who had a RACHS-1 score of 1 through 4 with those who had a score of 5 and 6 (between-group difference, 2.78 days; 95% CI, −0.33 to 5.99); P=0.88 for the overall comparison of patients who had a PIM2 score of less than 5% with those who had a score of 5% to less than 15% and those who had a score of 15% or higher (between-group differences, 0.77 days; 95% CI, −4.19 to 2.65; and −1.74 days; 95% CI, −6.06 to 2.58); and P=0.66 for the comparison between run-in patients and non–run-in patients (between-group difference, 0.67 days; 95% CI, −2.33 to 3.66). Since there were only 13 cases of traumatic brain injury, no tests of interaction were performed for this subgroup.

Adverse Events and Serious Adverse Events

A total of 135 patients had at least one episode of hypoglycemia; 61 of these had one or more severe episodes (Table 2). Hypoglycemia occurred in 33 of the 799 patients (4.1%) who did not receive insulin and in 102 of the 570 patients (17.9%) who did receive insulin. The proportion of patients with hypoglycemia was greater in the tight-glycemic-control group than in the conventional-glycemic-control group (moderate hypoglycemia, 12.5% vs. 3.1%; P<0.001; and severe hypoglycemia, 7.3% vs. 1.5%; P<0.001). Of the 135 patients who had at least one episode of hy-

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Tight Glycemic Control (N=694)	Conventional Glycemic Control (N=675)
Age — no. (%)		
0 to <1 yr	432 (62.2)	421 (62.4)
1 to 16 yr	262 (37.8)	254 (37.6)
Reason for admission to pediatric ICU — no. (%)		
Cardiac surgery	421 (60.7)	416 (61.6)
Other reason	273 (39.3)	259 (38.4)
RACHS-1 score — no./total no. (%)†		
1 through 4	388/421 (92.2)	393/416 (94.5)
5 or 6	33/421 (7.8)	23/416 (5.5)
PIM2 score — no./total no. (%)‡		
<5%	74/273 (27.1)	67/259 (25.9)
5% to <15%	144/273 (52.7)	144/259 (55.6)
≥15%	55/273 (20.1)	48/259 (18.5)

* There were no significant differences (at P<0.05) between the two groups in any of the characteristics. All the categories of characteristics listed here were factors in a minimization algorithm that was used to balance the study-group assignments. ICU denotes intensive care unit.

† Scores on the Risk Adjustment in Congenital Heart Surgery (RACHS-1)[13] range from 1 to 6, with higher scores indicating greater risk. The RACHS-1 was assessed in the subgroup of patients who had undergone cardiac surgery.

‡ Scores on the Paediatric Index of Mortality (PIM2)[14] provide an estimate of the risk of death; scores range from 0 to 100, with higher scores indicating a higher estimated risk of death. The PIM2 was assessed in the subgroup of patients who had been admitted to the pediatric ICU for reasons other than cardiac surgery.

poglycemia, 8 (5.9%) had a seizure on the same day; all 8 were in the tight-glycemic-control group.

A total of 11.1% of the patients who had at least one hypoglycemic episode died, as compared with 4.4% of those who did not have any hypoglycemic episodes (P=0.001). In the subgroup of patients who had undergone cardiac surgery, 10.6% of the patients who had at least one hypoglycemic episode died, as compared with 2.1% of those who did not have any hypoglycemic episodes (P<0.001). In contrast, there was no excess mortality attributable to hypoglycemia in the subgroup that had not undergone cardiac surgery: 11.6% of patients with at least one hypoglycemic episode died, as compared with 8.2% of those who did not have any hypoglycemic episodes (P=0.35).

In both the cardiac-surgery and non–cardiac-surgery subgroups, hypoglycemia occurred in a greater proportion of patients in the tight-glycemic-control group than in the conventional-glycemic-control group. Among patients who had undergone cardiac surgery, moderate hypoglycemia occurred in 10.9% of the patients in the tight-glycemic-control group versus 1.4% in the conventional-glycemic-control group (P<0.001); severe hypoglycemia occurred in 5.5% versus 0.5% (P<0.001). Among patients who had not undergone cardiac surgery, moderate hypoglycemia occurred in 15.4% of the patients in the tight-glycemic-control group versus 5.8% in the conventional-glycemic-control group (P<0.001); severe hypoglycemia occurred in 10.3% versus 3.1% (P=0.001). Patients in the cardiac-surgery subgroup who received insulin were not at greater risk for hypoglycemia than were those in the non–cardiac-surgery subgroup who received insulin (16.4% and 20.3% with hypoglycemia in the two subgroups, respectively).

Costs at 30 Days and Hospitalization through 90 Days

The mean costs at 30 days after randomization were similar in the two study groups, both overall and in the cardiac-surgery subgroup. In the subgroup that had not undergone cardiac surgery, the mean costs were lower with tight glycemic control than with conventional glycemic control (Table S3 in the Supplementary Appendix).

The proportion of patients still in the hospital at each time point after randomization was similar in the two study groups, both overall (P=0.48 by the log-rank test for the comparison at 90 days) and in the cardiac-surgery subgroup (P=0.17) (Fig. 3). In the subgroup that had not undergone cardiac surgery, fewer patients in the tight-glycemic-control group than in the conventional-glycemic-control group remained in the hospital at 30 days, 60 days, and 90 days after randomization (P=0.006 for the 90-day comparison) (Fig. 3).

DEATHS, HOSPITALIZATIONS, AND COSTS AT 12 MONTHS

The number of deaths at 12 months was similar in the two groups (73 in the tight-glycemic-control group and 71 in the conventional-glycemic-control group; hazard ratio with tight glycemic control, 1.00; 95% CI, 0.72 to 1.39; P=0.99 by the log-rank test). The corresponding subgroup hazard ratios were 1.02 (95% CI, 0.61 to 1.68) in the

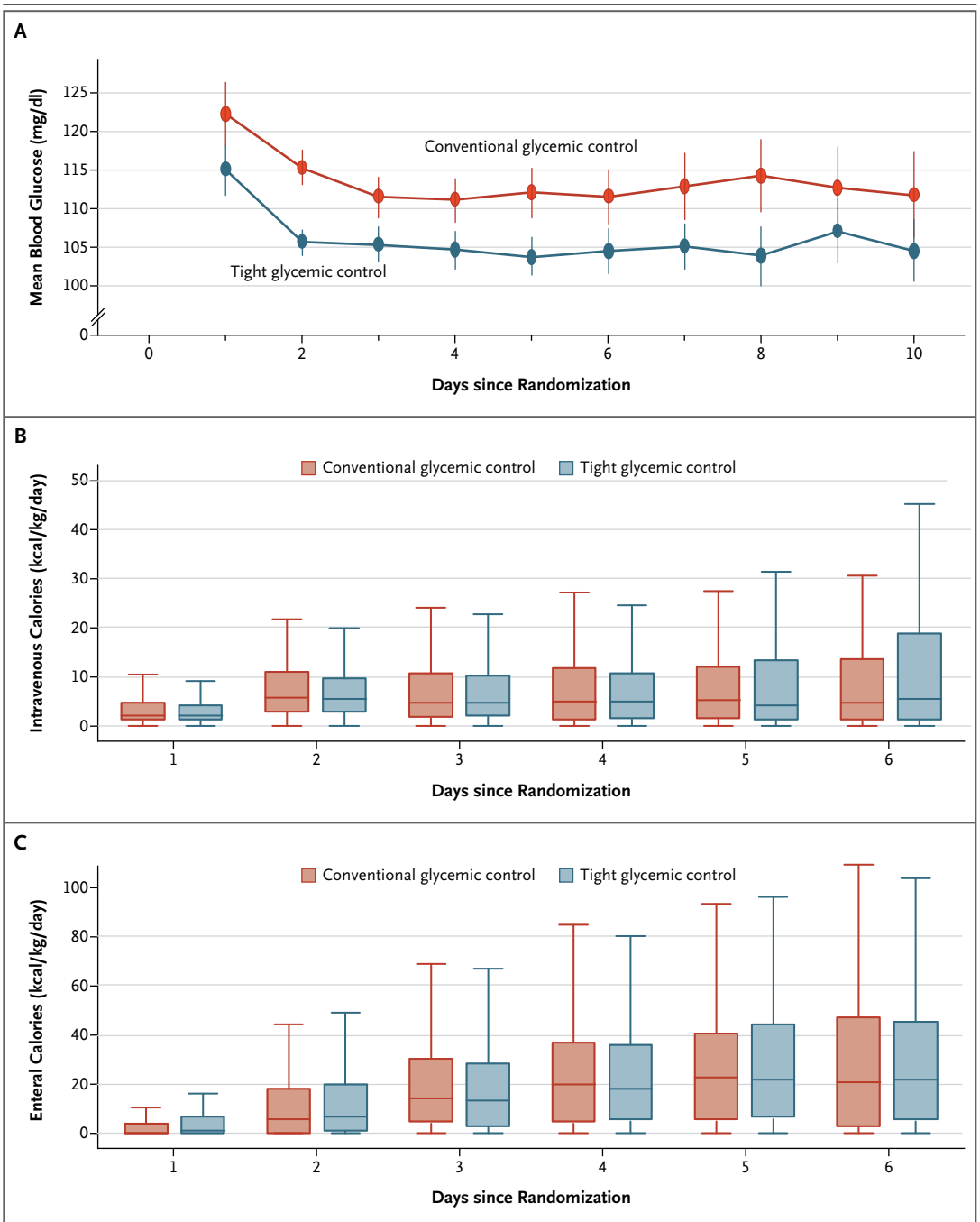


Figure 2. Blood Glucose Level and Caloric Intake, According to Treatment Group.

Panel A shows the mean blood glucose levels for the first 10 days after randomization, with vertical bars indicating 95% confidence intervals. To convert the values for glucose to millimoles per liter, multiply by 0.05551. Day 1 data are the average levels from the time of randomization to the end of the day of randomization. The target range of blood glucose levels with tight glycemic control was 72 to 126 mg per deciliter. The target blood glucose level with conventional glycemic control was less than 216 mg per deciliter. The daily intake of calories intravenously and enterally is shown in Panels B and C, respectively. The horizontal lines within the boxes indicate medians, the upper and lower ends of the boxes indicate the 75th and 25th percentiles, respectively, and the whiskers indicate the ranges.

Table 2. Clinical Outcomes and Adverse Events.*

Outcome	Tight Glycemic Control (N=694)	Conventional Glycemic Control (N=675)	Mean Difference (95% CI)	Odds Ratio with Tight Glycemic Control (95% CI)
Primary outcome: no. of days alive and free from mechanical ventilation at 30 days	23.6±0.3	23.2±0.3	0.36 (–0.42 to 1.14)	
Secondary outcomes				
Death within 30 days after trial entry — no. of patients/total no. (%)	35/693 (5.1)	34/674 (5.0)		1.00 (0.62 to 1.63)
No. of days in pediatric ICU	6.5±0.2	7.0±0.2	–0.47 (–1.12 to 0.15)	
No. of days in hospital	16.4±0.3	16.7±0.4	–0.33 (–1.24 to 0.62)	
No. of days receiving mechanical ventilation	5.3±0.2	5.6±0.2	–0.31 (–0.87 to 0.25)	
PELOD score†	9.8±0.2	9.8±0.2	–0.31 (–0.87 to 0.25)	
Median no. of days receiving vasoactive drugs (IQR)	3 (2–6)	4 (2–6)	–0.20 (–0.64 to 0.25)	
Renal-replacement therapy — no. of patients (%)‡	62 (8.9)	91 (13.5)		0.63 (0.45 to 0.89)
Bloodstream infection — no. of patients (%)§	38 (5.5)	43 (6.4)		0.85 (0.54 to 1.34)
Use of antibiotics >10 days — no. of patients (%)	62 (8.9)	74 (11.0)		0.80 (0.56 to 1.14)
No. of red-cell transfusions	1.0±0.1	1.1±0.1	–0.11 (–0.43 to 0.18)	
≥1 Moderate or severe hypoglycemic episode — no. of patients (%)¶	110 (15.9)	25 (3.7)		4.90 (3.13 to 7.67)
Moderate hypoglycemic episodes				
Total no.	127	30		
≥1 Episode — no. of patients (%)	87 (12.5)	21 (3.1)		4.46 (2.73 to 7.28)
No. of episodes/patient	0.20±0.03	0.04±0.01	0.14 (0.09 to 0.20)	
Severe hypoglycemic episode				
Total no.	70	11		
≥1 Episode — no. of patients (%)	51 (7.3)	10 (1.5)		5.27 (2.65 to 10.48)
No. of episodes/patient	0.10±0.02	0.02±0.01	0.08 (0.05 to 0.12)	
Seizure requiring medication — no. of patients (%)	23 (3.3)	15 (2.2)	1.15 (0.77 to 2.98)	

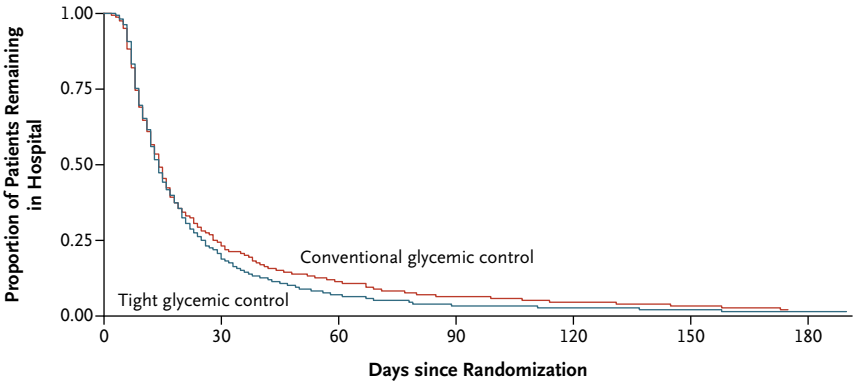
* Plus–minus values are means ±SE. IQR denotes interquartile range.
† Scores on the Paediatric Logistic Organ Dysfunction (PELOD) assessment range from 0 to 71, with higher scores indicating more severe organ dysfunction.
‡ Renal-replacement therapy was defined as peritoneal dialysis or hemofiltration.
§ A bloodstream infection was defined as a positive blood culture in association with two or more features of systemic inflammation[23] or any blood culture that was positive for fungus.
¶ Moderate hypoglycemia was defined as a blood glucose level of 36 to 45 mg per deciliter (2.0 to 2.5 mmol per liter), and severe hypoglycemia as a blood glucose level of less than 36 mg per deciliter. Patients may have had both a moderate episode and a severe episode.

cardiac-surgery subgroup and 0.98 (95% CI, 0.63 to 1.51) in the non–cardiac-surgery subgroup. The time from randomization to death was also similar in the two study groups — overall, in the subgroup that had undergone cardiac surgery, and in the subgroup that had not undergone cardiac surgery (Fig. S1 in the Supplementary Appendix).

In the cardiac-surgery subgroup, the average length of stay in the hospital up to 12 months after randomization was 20 days in each of the two study groups (Table S4 in the Supplementary Appendix). In the subgroup that had not undergone cardiac surgery, the corresponding length of stay was, on average, 13.5 days shorter with tight glycemic control than with conventional glycemic control (Table S4 in the Supplementary Appendix).

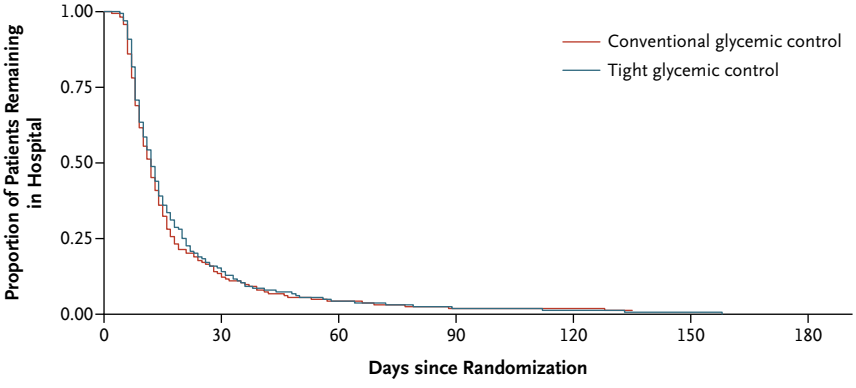
Overall, the mean 12-month costs were lower in the tight-glycemic-control group than in the

A All Patients



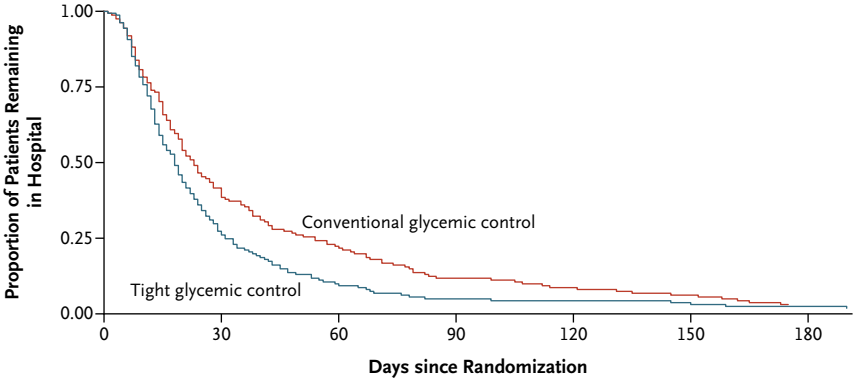
No. at Risk							
Conventional glycemic control	675	162	76	40	29	21	12
Tight glycemic control	694	139	46	22	17	12	8

B Patients Admitted to PICU after Cardiac Surgery



No. at Risk							
Conventional glycemic control	416	55	19	9	7	5	5
Tight glycemic control	421	65	19	9	6	2	1

C Patients Admitted to PICU for Other Reasons



No. at Risk							
Conventional glycemic control	259	107	57	31	22	16	7
Tight glycemic control	273	74	27	13	11	10	7

Figure 3. Proportion of Patients Remaining in the Hospital, from the Time of the Index Admission to 180 Days after Randomization, According to Treatment Group.

conventional-glycemic-control group (difference in cost per patient, −$4,815; 95% CI, −10,298 to 668) (Table S2 in the Supplementary Appendix). In the subgroup that had undergone cardiac surgery, the costs were similar in the two study groups, but in the subgroup that had not undergone cardiac surgery, the mean costs were lower in the tight-glycemic-control group than in the conventional-glycemic-control group, with a difference in cost of −$13,120 (95% CI, −24,682 to −1,559). Sensitivity analyses showed that the results were robust with respect to the prespecified assumptions.

DISCUSSION

In this multicenter, randomized trial involving critically ill children in pediatric ICUs, tight glycemic control did not increase the number of days that children were alive and free from mechanical ventilation at 30 days. However, the secondary outcomes reveal a complex relationship of potential benefits and harms. Although tight glycemic control was associated with a smaller proportion of patients receiving renal-replacement therapy than was conventional glycemic control, it resulted in more episodes of hypoglycemia. In addition, as compared with conventional glycemic control, tight glycemic control was associated with a shorter length of stay in the hospital and lower total health care costs at 12 months; the lower costs appear to be driven by results in the subgroup that had not undergone cardiac surgery.

Our trial involving a pediatric cohort sought to ensure a high degree of internal and external validity by concealing the treatment assignment during recruitment, by including a range of pediatric ICUs delivering protocols that fit within routine clinical practice ("pragmatic" design), by evaluating both clinical and economic factors with follow-up at 12 months, and by following a prespecified analysis plan.[12] The inability to conceal the group assignments after randomization was a limitation of the study. In addition, although the primary end point in the study (freedom from mechanical ventilation at 30 days) was selected on the basis of the best evidence at the time,[15,18] our time-to-event analysis indicates that for patients who have not undergone cardiac surgery, future trials could assess ventilator-free days at later time points. Our trial highlights the importance of designing pediatric ICU trials with longer-term clinical and economic end points, (e.g., hospital stay and costs at 12 months), especially among patients who have not undergone cardiac surgery.

The current study differs from previous studies of tight glycemic control in children in several ways.[11,24] First, Vlasselaers et al.[11] reported the results of a single-center, "early adopter" study involving predominantly patients who had undergone cardiac surgery, and Agus et al.[24] reported the results of a 2-center study involving children who had undergone cardiac surgery, whereas our study recruited children from 13 pediatric ICUs and included both patients who had undergone cardiac surgery and those who had been admitted to the pediatric ICU for other reasons. It is possible that clinical outcomes have improved over time; for example, the rate of secondary infection was lower in the study by Agus et al., in 2012, than in the study by Vlasselaers et al., in 2009 (5% vs. 33%). Second, Vlasselaers et al. used a lower range for tight glycemic control than we used in our study, and our insulin dosing was closer to the lower dosing reported by Agus et al. Vlasselaers et al. reported a benefit of tight glycemic control, whereas Agus et al. did not — with the findings of Agus et al. consistent with findings in the cardiac-surgery subgroup in our study. Finally, our study examined potential differences in the effect of tight glycemic control in patients who had undergone cardiac surgery as compared with patients who had not. We speculate that since the outcomes of cardiac surgery are currently very good, there is little potential for improvement with respect to patients who have undergone cardiac surgery, but in patients who have not undergone cardiac surgery, stress hyperglycemia may be truly detrimental[5,25,26]; hence, tight glycemic control is important.

Hypoglycemia is a major complication of tight glycemic control.[27] A post hoc analysis of the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study indicated that hypoglycemia was associated with increased mortality.[28] In contrast, follow-up of children in the study by Vlasselaers et al. at 4 years showed that neither hypoglycemia nor tight glycemic control resulted in significantly worse neurodevelopmental se-

quelae than did conventional glycemic control.[29,30] Our finding of increased mortality associated with hypoglycemia in the cardiac-surgery subgroup is consistent with the findings of the NICE-SUGAR study and should be considered as further evidence to support the use of conventional management of blood glucose levels in patients who have undergone cardiac surgery.[27] However, the absence of this association in patients who had not undergone cardiac surgery, together with the absence of an association with neurodevelopmental sequelae of hypoglycemia,[29] makes the economic analysis more relevant; the reduction in 12-month costs cannot be explained by earlier increased mortality. Tight glycemic control, as compared with conventional glycemic control, can lead to an average reduction of $13,000 per patient in 12-month costs for children who have not undergone cardiac surgery. In the NHS, implementing tight glycemic control for this subgroup could yield annual savings of approximately $16 million in pediatric ICUs in the United Kingdom. However, this overall benefit must be balanced against the risk of hypoglycemia. Agus et al. reported a very low rate of severe (but not moderate) hypoglycemia, almost certainly owing to their use of continuous glucose monitoring.[24]

In conclusion, our study shows that in a population of critically ill children, tight glycemic control (72 to 126 mg per deciliter) did not have a significant effect on major clinical outcomes among children admitted to a pediatric ICU after cardiac surgery. Among children admitted to a pediatric ICU for other reasons, however, tight glycemic control, as compared with conventional glycemic control, led to a shorter length of stay in the hospital and lower health care costs in the 12 months after randomization. As with any trial, further studies would be required to assess whether these findings apply to routine clinical practice in other settings.[27]

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Health Research, Health Technology Assessment Program (NIHR-HTA).

Supported by a grant from the NIHR-HTA, a research institute of the U.K. National Health Service.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the parents and guardians of the children who participated in the study.

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