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A Randomized Trial of Hyperglycemic Control in Pediatric Intensive Care

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ABSTRACT

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*A complete list of investigators in the Control of Hyperglycaemia in Paediatric Intensive Care (CHiP) trial is provided in the Supplementary Appendix, available at NEJM.org.

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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 (7.3% vs. 1.5%, P<0.001). Overall, 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. (Fundied by the National Institute for Health Research, Health Technology Assessment Program, U.K. National Health Service; CHiP Current Controlled Trials number, ISRCTN61735247.)
Hyperglycemia is a common complication in critical illness and is associated with adverse outcomes. 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), with similar effects on morbidity but not on mortality among adults in nonsurgical ICUs. However, two meta-analyses have failed to show a benefit, and a large, international, multicenter trial showed that tight glycemic control increased mortality.

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, 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, 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. 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. 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/dpmmed.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
Dysfunction (PELOD) score, of red-cell transfusions, Paediatric Logistic Organ
use of antibiotics for more than 10 days, number
ment therapy, incidence of bloodstream infection,
status with respect to the need for renal-replace-
ical ventilation and of receipt of vasoactive drugs,
pediatric ICU, vital status, duration of mechani-
>30 days), we recorded the number of days in the
at 30 days if the child was in the pediatric ICU for
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 mechani-
cal ventilation and of receipt of vasoactive drugs,
status with respect to the need for renal-replace-
ment therapy, incidence of bloodstream infection,
use of antibiotics for more than 10 days, number
of red-cell transfusions, Paediatric Logistic Organ
Dysfunction (PELOD) score, rate of readmis-
tion to the pediatric ICU, length of stay in the
hospital, and costs. At 12 months after random-
ization, we assessed the length of stay in the
pediatric ICU and hospital (including during re-
admissions), vital status, and costs of hospital
and community health services. Data on readmis-
tions to the original pediatric ICU were recorded
on the case-report forms. Data on readmissions
other than to the original ICU and use of pri-
mary and community health services were ob-
tained from a questionnaire that was mailed
to parents at 12 months. All costs are reported on
the basis of 2010–2011 hospital charges.

**Outcome Measures**

Outcome measures were defined and statistical
analyses were prespecified in the statistical analy-
sis plan. The primary outcome was the number
of days alive and free from mechanical ventila-
tion at 30 days after randomization. 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 mechani-
cal ventilation and of receipt of vasoactive drugs,
status with respect to the need for renal-replace-
ment therapy, incidence of bloodstream infection,
use of antibiotics for more than 10 days, number
of red-cell transfusions, Paediatric Logistic Organ
Dysfunction (PELOD) score, rate of readmis-
tion to the pediatric ICU, length of stay in the
hospital, and costs at 30 days, as well as infor-
mation on 12-month costs for children for whom

**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 de-
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

**Statistical Analysis**

A difference of 2 days in the number of days free
from mechanical ventilation at 30 days was con-
sidered to be clinically important. On the basis of
data from the U.K. Paediatric Intensive Care Audit
Network for 2003–2004, 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 sub-
group 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 out-
come, linear regression models were used to esti-
mate the mean between-group difference in the
number of days free from mechanical ventilation
at 30 days. For the secondary outcomes, appro-
priate generalized models were used. Odds ra-
tios and mean differences are reported with 95%
confidence intervals. Where there was evidence
of nonnormality in the continuous outcome mea-
sures, nonparametric bootstrapping was used to
estimate bias-corrected confidence intervals.

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 under-
went randomization) versus patients who under-
went randomization subsequently. Evidence of any
differential effects of the intervention on the pri-
mary outcome, according to subgroup, was as-
sessed 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 inter-
action term included.

The difference in costs between tight glyce-
mic 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-sur-
gery subgroup. Missing data on cost at 12 months
were handled with multiple imputation. Im-
putation models included baseline covariates,
the number of days mechanical ventilation was
used, total length of stay in the hospital (includ-
ing ICU), and costs at 30 days, as well as infor-
mation on 12-month costs for children for whom
19,924 Patients were assessed for eligibility

15,483 Were ineligible
565 Had gestation <36 wk
211 Were >16 yr of age
56 Had diabetes mellitus
268 Had established or suspected diagnosis of inborn
error of metabolism
312 Had treatment withdrawal or limitation
133 Were inpatient on PICU/CICU for >5 consecutive
days
262 Had already participated in CHIP trial during
previous admission
2285 Were not likely to continue mechanical ventilation
and vasoactive support drugs beyond 12 hr
1576 Did not have arterial catheter in place
23 Had parent or guardian who declined to participate
143 Died
18 Were not recruited within time frame
104 Had other reasons
2637 Did not undergo ventilation and vasoactive drugs

4441 Were considered potentially eligible for trial

3057 Did not undergo randomization
1093 Had parent or guardian who declined to participate
513 Were not recruited within time frame
1469 Had other reasons

1384 Underwent randomization

7 Had protocol violations
694 Were assigned to tight glycemic control
461 Received insulin
233 Did not receive insulin
694 Had data available for primary outcome
72 Died
35 <30 days
37 ≥30 days to <12 mo
622 Were potentially eligible for 12-mo follow-up

8 Had protocol violations
675 Were assigned to conventional glycemic control
109 Received insulin
566 Did not receive insulin
675 Had data available for primary outcome
68 Died
34 <30 days
34 ≥30 days to <12 mo
607 Were potentially eligible for 12-mo follow-up

330 Had questionnaire sent to parent or guardian
123 Parent or guardian did not respond to questionnaire
207 (62.7%) Parent or guardian responded to questionnaire

292 Were excluded
1 Had parent or guardian who declined to participate
202 Had data administratively censored before 12 mo
80 Were ineligible for 12-mo follow-up

278 Were excluded
194 Had data administratively censored before 12 mo
84 Were ineligible for 12-mo follow-up
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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 4 through 6 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-
There were no significant differences (at P<0.05) between the two groups in‡ Scores on the Paediatric Index of Mortality (PIM2)† Scores on the Risk Adjustment in Congenital Heart Surgery (RACHS-1) assignments. ICU denotes intensive care unit.

tent was used to balance the study-group assignments. ICU denotes intensive care unit.

glycemic 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

### Table 1. Baseline Characteristics of the Study Patients.*

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

* 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) 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) 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.
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.
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

<table>
<thead>
<tr>
<th>Table 2. Clinical Outcomes and Adverse Events.*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Primary outcome: no. of days alive and free from mechanical ventilation at 30 days</td>
</tr>
<tr>
<td>Secondary outcomes</td>
</tr>
<tr>
<td>Death within 30 days after trial entry — no. of patients/total no. (%)</td>
</tr>
<tr>
<td>No. of days in pediatric ICU</td>
</tr>
<tr>
<td>No. of days in hospital</td>
</tr>
<tr>
<td>No. of days receiving mechanical ventilation</td>
</tr>
<tr>
<td>PELOD score†</td>
</tr>
<tr>
<td>Median no. of days receiving vasoactive drugs (IQR)</td>
</tr>
<tr>
<td>Renal-replacement therapy — no. of patients (%)‡</td>
</tr>
<tr>
<td>Bloodstream infection — no. of patients (%)§</td>
</tr>
<tr>
<td>Use of antibiotics &gt;10 days — no. of patients (%)</td>
</tr>
<tr>
<td>No. of red-cell transfusions</td>
</tr>
<tr>
<td>≥1 Moderate or severe hypoglycemic episode — no. of patients (%)¶</td>
</tr>
<tr>
<td>Moderate hypoglycemic episodes</td>
</tr>
<tr>
<td>Total no.</td>
</tr>
<tr>
<td>≥1 Episode — no. of patients (%)</td>
</tr>
<tr>
<td>No. of episodes/patient</td>
</tr>
<tr>
<td>Severe hypoglycemic episode</td>
</tr>
<tr>
<td>Total no.</td>
</tr>
<tr>
<td>≥1 Episode — no. of patients (%)</td>
</tr>
<tr>
<td>No. of episodes/patient</td>
</tr>
<tr>
<td>Seizure requiring medication — no. of patients (%)</td>
</tr>
</tbody>
</table>

* 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 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.
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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.

A All Patients

B Patients Admitted to PICU after Cardiac Surgery

C Patients Admitted to PICU for Other Reasons

No. at Risk
Conventional glycemic control
Tight glycemic control

Conventional glycemic control
Tight glycemic control

Proportion/uni0020of/uni0020Patients/uni0020Remaining
in/uni0020Hospital

Proportion/uni0020of/uni0020Patients/uni0020Remaining
in/uni0020Hospital

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. 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, 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. First, Vlasselaers et al. reported the results of a single-center, “early adopter” study involving predominantly patients who had undergone cardiac surgery, and Agus et al. 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., compared with the study by Vlasselaers et al., in 2009 (5% vs. 33%). Second, 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 and, hence, tight glycemic control is important.

Hypoglycemia is a major complication of tight glycemic control. 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. 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-
Our finding of increased mortality associated with hyperglycemia 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. 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, 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.

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.

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Brown Pelican in Breeding Colors


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