How to Evaluate a Randomized Controlled Trial (RCT)?

Nora A. Kalagi, MSc

328 PHCL

Randomized clinical trial evaluation checklist

Study identification (*Include author, title, year of publication, journal title)*

Title and abstract				
Statements	**Yes**	**No**	**Not clear**	**Comments**
Identification as a randomised trial in the title				
Structured summary of trial design, methods, results, and conclusions				
Introduction				
Scientific background and explanation of rationale				
Specific objectives or hypotheses				
Methods				
Description of trial design (such as parallel, factorial)				
Eligibility criteria for participants				
Settings and locations where the data were collected				
The interventions for each group with sufficient details, including how and when they were actually administered				
Completely defined primary and secondary outcome measures, including how and when they were assessed				

Method used to generate the random allocation sequence				
Blindness after assignment to interventions				
Statistical methods used to compare groups for primary and secondary outcomes				
Results				
For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome				
For each group, losses and exclusions after randomisation, together with reasons				
A table showing baseline demographic and clinical characteristics for each group				
All important harms or unintended effects in each group				
Discussion				
Trial limitations, addressing sources of potential bias				
Other information				
Registration number and name of trial registry				
Sources of funding and other support (such as supply of drugs), role of funders				
References are satisfactory and updated				

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 26, 2009 VOL. 360 NO. 13

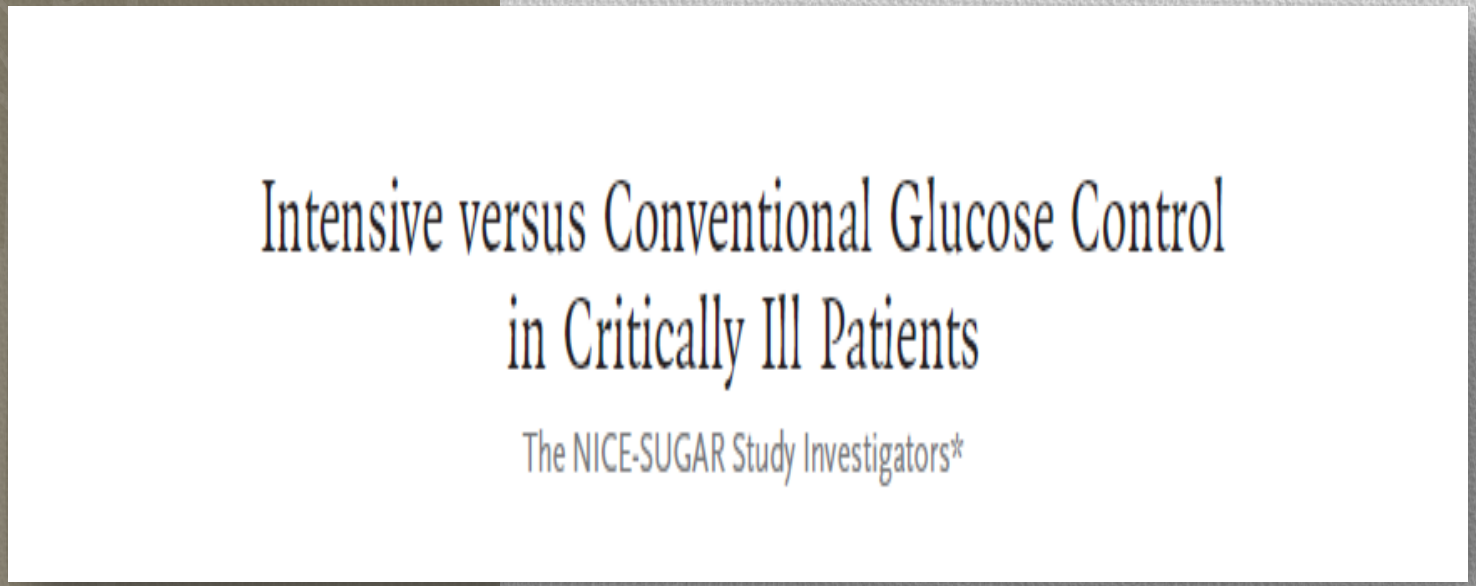
Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

Title and abstract

- **Identification as a randomized trial in the title ?**

NO



Title and abstract

- **Structured summary of trial design, methods, results, and conclusions?** **YES**

ABSTRACT

BACKGROUND

The optimal target range for blood glucose in critically ill patients remains unclear.

METHODS

Within 24 hours after admission to an intensive care unit (ICU), adults who were expected to require treatment in the ICU on 3 or more consecutive days were randomly assigned to undergo either intensive glucose control, with a target blood glucose range of 81 to 108 mg per deciliter (4.5 to 6.0 mmol per liter), or conventional glucose control, with a target of 180 mg or less per deciliter (10.0 mmol or less per liter). We defined the primary end point as death from any cause within 90 days after randomization.

RESULTS

Of the 6104 patients who underwent randomization, 3054 were assigned to undergo intensive control and 3050 to undergo conventional control; data with regard to the primary outcome at day 90 were available for 3010 and 3012 patients, respectively. The two groups had similar characteristics at baseline. A total of 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional-control group died (odds ratio for intensive control, 1.14; 95% confidence interval, 1.02 to 1.28; P=0.02). The treatment effect did not differ significantly between operative (surgical) patients and nonoperative (medical) patients (odds ratio for death in the intensive-control group, 1.31 and 1.07, respectively; P=0.10). Severe hypoglycemia (blood glucose level, ≤40 mg per deciliter [2.2 mmol per liter]) was reported in 206 of 3016 patients (6.8%) in the intensive-control group and 15 of 3014 (0.5%) in the conventional-control group (P<0.001). There was no significant difference between the two treatment groups in the median number of days in the ICU (P=0.84) or hospital (P=0.86) or the median number of days of mechanical ventilation (P=0.56) or renal-replacement therapy (P=0.39).

CONCLUSIONS

In this large, international, randomized trial, we found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter. (ClinicalTrials.gov number, NCT00220987.)

Introduction

- **Scientific background and explanation of rationale ?**

YES

The NEW ENGLAND JOURNAL of MEDICINE

HYPERGLYCEMIA IS COMMON IN ACUTELY ill patients, including those treated in intensive care units (ICUs).[1] The occurrence of hyperglycemia, in particular severe hyperglycemia, is associated with increased morbidity and mortality in a variety of groups of patients,[2-5] but trials examining the effects of tighter glucose control have had conflicting results.[6-13] Systematic reviews and meta-analyses have also led to differing conclusions.[14,15] Nevertheless, many professional organizations recommend tight glucose control for patients treated in ICUs.[16,17]

Barriers to widespread adoption of tight glucose control include the increased risk of severe hypoglycemia,[14] concerns about the external validity of some studies,[18,19] the difficulty in achieving normoglycemia in critically ill patients,[20,21] and the increased resources that would be required.[22] Because of these issues and uncertainty about the balance of risks and benefits, tight glucose control is used infrequently by some clinicians.[23,24] We designed the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial to test the hypothesis that intensive glucose control reduces mortality at 90 days.

tional-control target of 180 mg or less per deciliter (10.0 mmol or less per liter), based on practice surveys in Australia, New Zealand, and Canada.[23,25] Randomization was stratified according to type of admission (operative or nonoperative) and region (Australia and New Zealand or North America). Patients were randomly assigned to a treatment group by the clinicians treating them or by local study coordinators, with the use of a minimization algorithm[26] accessed through a secure Web site. The treatment assignments were concealed before randomization, but subsequently, clinical staff were aware of them.

Control of blood glucose was achieved with the use of an intravenous infusion of insulin in saline. In the group of patients assigned to undergo conventional glucose control, insulin was administered if the blood glucose level exceeded 180 mg per deciliter; insulin administration was reduced and then discontinued if the blood glucose level dropped below 144 mg per deciliter (8.0 mmol per liter). Blood glucose levels in each patient were managed as part of the normal duties of the clinical staff at the participating center. In both groups, this management was guided by treatment algorithms accessed through a secure Web site (for details of the treatment algorithm, see https://

Introduction

- **Specific objectives or hypotheses ?** **YES**

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Methodology

- **Description of trial design (such as parallel, factorial) ?**

YES

METHODS

STUDY DESIGN

We conducted a parallel-group, randomized, controlled trial involving adult medical and surgical patients admitted to the ICUs of 42 hospitals: 38 academic tertiary care hospitals and 4 community hospitals. Eligible patients were those expected to require treatment in the ICU on 3 or more consecutive days (see Appendix A in the Supplementary Appendix, available with the full text of this article at NEJM.org). A detailed description of the study was published previously.[25]

The study was approved by the ethics committees of the University of Sydney, the University of British Columbia, and each participating institution. Written informed consent, obtained before randomization, or delayed consent was obtained from each patient or from a legal surrogate.

Study participants were randomly assigned to glucose control with one of two target ranges: the intensive (i.e., tight) control target of 81 to 108 mg per deciliter (4.5 to 6.0 mmol per liter), based on that used in previous studies,[12,13] or a conven-

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discretion of the treating clinicians.

Assessments and Data Collection at Baseline

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Methodology

- **Eligibility criteria for participants?**

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Methodology

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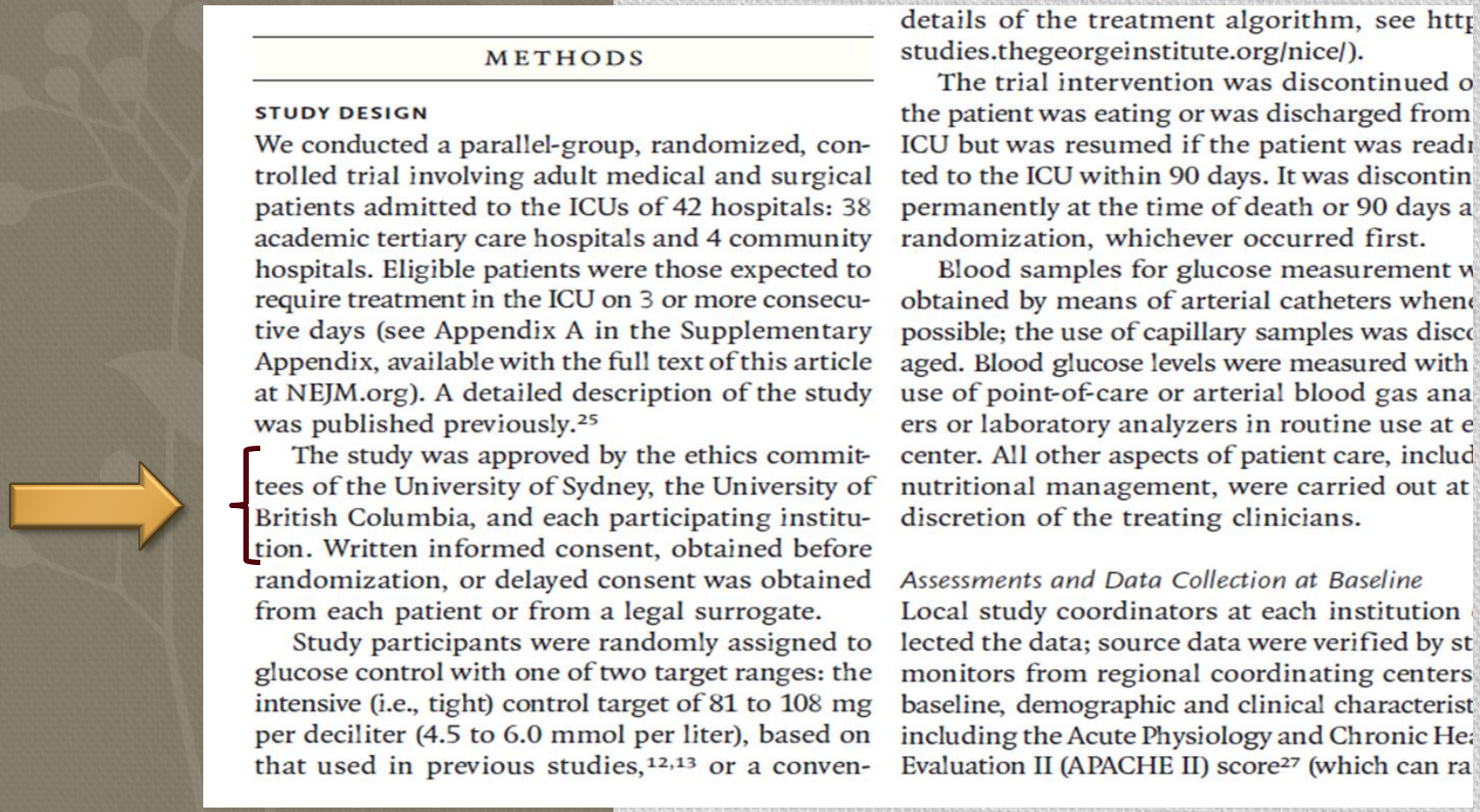

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Methodology

- **Completely defined primary and secondary outcome measures, including how and when they were assessed?**

YES

Outcome Measures

Outcome measures and statistical analyses were defined in a prespecified statistical-analysis plan.[30] The primary outcome measure was death from any cause within 90 days after randomization, in an analysis that was not adjusted for baseline characteristics. Secondary outcome measures were survival time during the first 90 days, cause-specific death (see Appendix C in the Supplementary Appendix for more information), and durations of mechanical ventilation, renal-replacement therapy, and stays in the ICU and hospital. Tertiary outcomes were death from any cause within 28 days after randomization, place of death (ICU, hospital ward, or other), incidence of new organ failure, positive blood culture, receipt of red-cell transfusion, and volume of the transfusion.

The primary outcome was also examined in six predefined pairs of subgroups: operative patients and nonoperative patients, patients with and those without diabetes, patients with and those without trauma, patients with and those without severe sepsis, patients treated and those not treated with corticosteroids, and patients whose APACHE II score was 25 or more and those whose score was less than 25.[30]

Serious Adverse Events

A blood glucose level of 40 mg per deciliter (2.2 mmol per liter) or less was considered a serious adverse event. When the blood glucose level was measured with a bedside point-of-care analyzer, we requested that the treating clinician obtain a blood sample for laboratory confirmation before treating the presumed hypoglycemia. The details of each event were reviewed by the two study man-

Methodology

- **Method used to generate the random allocation sequence ?**

YES

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- **Blindness after assignment to interventions ?**

NO

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Methodology

- **Statistical methods used to compare groups for primary and secondary outcomes?**

YES

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baseline. Other binary end points
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Continuous variables were compare
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test, and the results are presented as
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Results

- For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome?

- For each group, losses and exclusions after randomization, together with reasons?

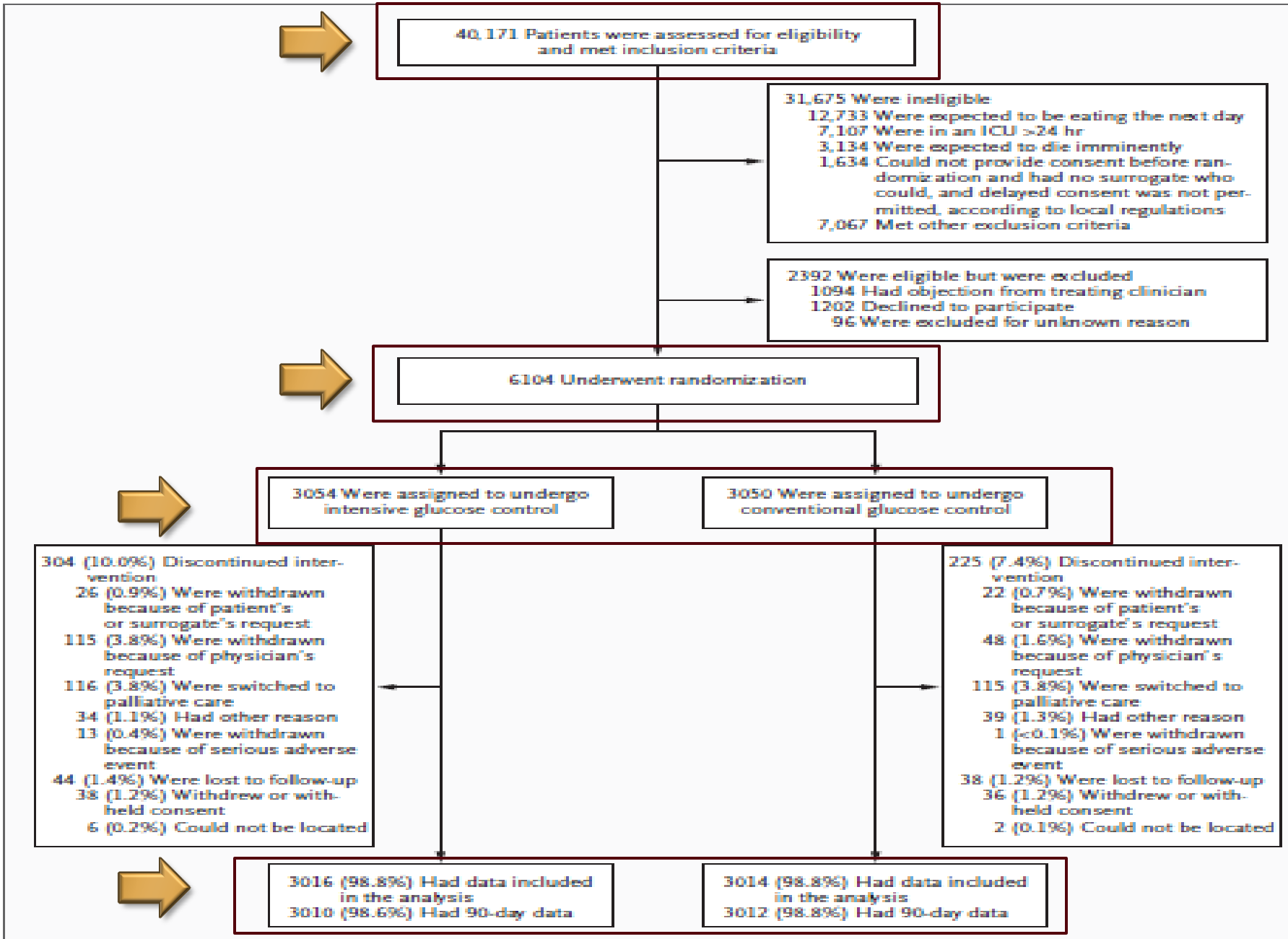
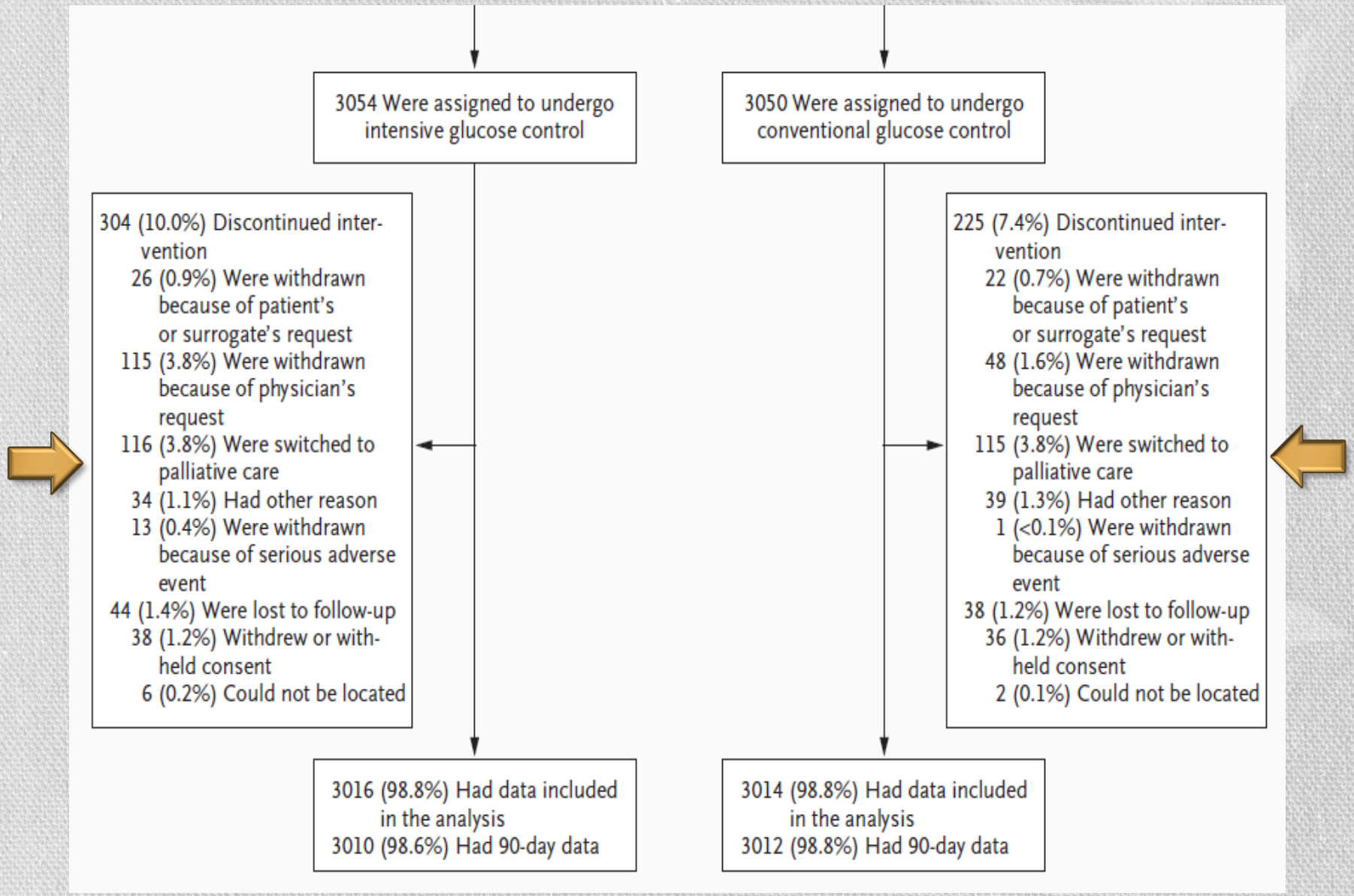


Figure 1. Assessment, Randomization, and Follow-up of the Study Patients.

A total of 14 of the expected 1132 monthly screening logs (1.2%) were not received at the coordinating center. ICU denotes intensive care unit.


3054 Were assigned to undergo intensive glucose control
3050 Were assigned to undergo conventional glucose control
304 (10.0%) Discontinued intervention
26 (0.9%) Were withdrawn because of patient's or surrogate's request
115 (3.8%) Were withdrawn because of physician's request
116 (3.8%) Were switched to palliative care
34 (1.1%) Had other reason
13 (0.4%) Were withdrawn because of serious adverse event
44 (1.4%) Were lost to follow-up
38 (1.2%) Withdrew or withheld consent
6 (0.2%) Could not be located
225 (7.4%) Discontinued intervention
22 (0.7%) Were withdrawn because of patient's or surrogate's request
48 (1.6%) Were withdrawn because of physician's request
115 (3.8%) Were switched to palliative care
39 (1.3%) Had other reason
1 (<0.1%) Were withdrawn because of serious adverse event
38 (1.2%) Were lost to follow-up
36 (1.2%) Withdrew or withheld consent
2 (0.1%) Could not be located
3016 (98.8%) Had data included in the analysis
3010 (98.6%) Had 90-day data
3014 (98.8%) Had data included in the analysis
3012 (98.8%) Had 90-day data

Results

- For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome?

- For each group, losses and exclusions after randomization, together with reasons?

YES

Results

- A table showing baseline demographic and clinical characteristics for each group?

- All important harms or unintended effects in each group?

Table 1. Baseline Characteristics of the Study Patients.*

Variable	Intensive Glucose Control	Conventional Glucose Control
Age — yr	60.4±17.2	59.9±17.1
Female sex — no./total no. (%)	1128/3016 (37.4)	1079/3014 (35.8)
Weight — kg	80.7±21.4	80.9±21.2
Body-mass index†	27.9±7.7	28.0±7.2
Interval from ICU admission to randomization — hr	13.4±7.6	13.4±7.7
Reason for ICU admission — no./total no. (%)		
Operative	1112/3015 (36.9)	1121/3014 (37.2)
Nonoperative	1903/3015 (63.1)	1893/3014 (62.8)
Location before ICU admission — no./total no. (%)		
Emergency department	718/3015 (23.8)	749/3014 (24.9)
Hospital floor (or ward)		
Without previous ICU admission	640/3015 (21.2)	618/3014 (20.5)
With previous ICU admission	42/3015 (1.4)	30/3014 (1.0)
Another ICU	125/3015 (4.1)	102/3014 (3.4)
Another hospital	445/3015 (14.8)	453/3014 (15.0)
Operating room		
After emergency surgery	682/3015 (22.6)	671/3014 (22.3)
After elective surgery	363/3015 (12.0)	391/3014 (13.0)
APACHE II score	21.1±7.91	21.1±8.3
Blood glucose level — mg/dl	146±52.3	144±49.1
Organ failure or dysfunction — no./total no. (%)		
Respiratory		
Dysfunction (SOFA score, 1–2)	1207/2993 (40.3)	1222/2990 (40.9)
Failure (SOFA score, 3–4)	1526/2993 (51.0)	1521/2990 (50.9)
Coagulatory		
Dysfunction (SOFA score, 1–2)	947/2987 (31.7)	874/2989 (29.2)
Failure (SOFA score, 3–4)	128/2987 (4.3)	137/2989 (4.6)
Hepatic		
Dysfunction (SOFA score, 1–2)	831/2807 (29.6)	834/2802 (29.8)
Failure (SOFA score, 3–4)	70/2807 (2.5)	50/2802 (1.8)
Cardiovascular		
Dysfunction (SOFA score, 1–2)	583/3011 (19.4)	614/3012 (20.4)
Failure (SOFA score, 3–4)	1726/3011 (57.3)	1695/3012 (56.3)
Renal		
Dysfunction (SOFA score, 1–2)	1042/2981 (35.0)	1071/2974 (36.0)
Failure (SOFA score, 3–4)	249/2981 (8.4)	228/2974 (7.7)

Table 3. Outcomes and Adverse Events.*

Outcome Measure	Intensive Glucose Control	Conventional Glucose Control	Odds Ratio or Absolute Difference (95% CI)†	Statistical Test	P Value
Death — no. of patients/total no. (%)				Logistic regression	
At day 90	829/3010 (27.5)	751/3012 (24.9)	1.14 (1.02 to 1.28)		0.02
At day 28	670/3010 (22.3)	627/3012 (20.8)	1.09 (0.96 to 1.23)		0.17
Potentially life-sustaining treatment limited or withheld before death — no. of patients/total no. (%)	746/816 (91.4)	669/741 (90.3)	1.15 (0.81 to 1.62)	Logistic regression	0.44
Limited because death was imminent	527/816 (64.6)	459/741 (61.9)	1.12 (0.91 to 1.38)		0.28
Withheld because not appropriate	219/816 (26.8)	210/741 (28.3)	0.93 (0.74 to 1.16)		0.51
CPR as terminal event — no. of patients/total no. (%)	70/816 (8.6)	72/741 (9.7)	0.87 (0.62 to 1.23)	Logistic regression	0.44
Days from randomization to limitation or withholding of potentially life-sustaining treatment — median (IQR)	6 (3 to 16)	6 (2 to 15)		t-test	0.42
Proximate cause of death — no. of patients/total no. (%)				Pearson's test	0.12
Cardiovascular-distributive shock	168/829 (20.3)	140/751 (18.6)			
Other cardiovascular	177/829 (21.4)	129/751 (17.2)			
Neurologic	180/829 (21.7)	194/751 (25.8)			
Respiratory	191/829 (23.0)	177/751 (23.6)			
Other	113/829 (13.6)	111/751 (14.8)			
Place of death — no. of patients/total no. (%)					
ICU	546/829 (65.9)	498/751 (66.3)			
Elsewhere in hospital	220/829 (26.5)	197/751 (26.2)			
Outside hospital, after discharge	63/829 (7.6)	56/751 (7.5)			
Severe hypoglycemia — no. of patients/total no. (%)	206/3016 (6.8)	15/3014 (0.5)	14.7 (9.0 to 25.9)	Logistic regression	<0.001
Days in ICU — median (IQR)	6 (2 to 11)	6 (2 to 11)	0	Log-rank test	0.84
Days in hospital — median (IQR)	17 (8 to 35)	17 (8 to 35)	0	Log-rank test	0.86
Mechanical ventilation — no. of patients/total no. (%)	2894/3014 (96.0)	2872/3014 (95.3)	0.7 (−0.3 to 1.76)	Pearson's test	0.17
Days of mechanical ventilation	6.6±6.6	6.6±6.5	0	Wilcoxon rank-sum test	0.56
Renal-replacement therapy — no. of patients/total no. (%)	465/3014 (15.4)	438/3014 (14.5)	0.9 (−0.9 to 2.7)	Pearson's test	0.34
Days of renal-replacement therapy	0.8±2.6	0.8±2.8	0	Wilcoxon rank-sum test	0.39
No. of new organ failures — no. of patients/total no. (%)‡				Pearson's test	0.11
0	1571/2682 (58.6)	1536/2679 (57.3)			
1	790/2682 (29.5)	837/2679 (31.2)			
2	263/2682 (9.8)	257/2679 (9.6)			
3	44/2682 (1.6)	46/2679 (1.7)			
4	11/2682 (0.4)	2/2679 (0.1)			
5	3/2682 (0.1)	1/2679 (<0.1)			

Results

- A table showing baseline demographic and clinical characteristics for each group?

- All important harms or unintended effects in each group?

YES

Discussion

- **Trial limitations, addressing sources of potential bias?**

YES

DISCUSSION

In this large, international, randomized trial involving adults in the ICU, we found that intensive glucose control, as compared with conventional glucose control, increased the absolute risk of death at 90 days by 2.6 percentage points; this represents a number needed to harm of 38. The difference in mortality remained significant after adjustment for potential confounders. Severe hypoglycemia was significantly more common with intensive glucose control.

In conducting our trial, we sought to ensure a high degree of internal and external validity by concealing treatment assignments before randomization, selecting a long-term outcome that is not subject to biased ascertainment, evaluating a number of clinically important outcomes, achieving

Figure 2. Data on Blood Glucose Level, According to Treat

Panel A shows mean blood glucose levels. Baseline data
the last blood glucose measurement obtained before ran
data are the average levels from the time of randomizatio
the day of randomization. The bars indicate the 95% conf
The dashed line indicates 108 mg per deciliter, the upper
range for intensive glucose control. Panel B shows the de
mean time-weighted blood glucose levels for individual p
dashed lines indicate the modes (most frequent values) i
control group (blue) and the conventional-control group
the upper threshold for severe hypoglycemia (black). To c
for blood glucose to millimoles per liter, multiply by 0.055

hypoglycemia was low in comparison with the rates in other trials.

Limitations of our trial include the use of a subjective criterion — expected length of stay in the ICU — for inclusion, the inability to make treating staff and study personnel unaware of the treatment-group assignments, and achievement of a glucose level modestly above the target range in a substantial proportion of patients in the intensive-control group. We did not collect specific data to address potential biologic mechanisms of the trial interventions or their costs. On the basis of the results in the predefined pairs of subgroups, we cannot exclude the possibility that intensive glucose control may benefit some patients.

Our findings differ from those of a recent meta-analysis showing that intensive glucose control did not significantly alter mortality among

with current evidence-based feeding guic
whereas a substantial proportion of the
included in the meta-analysis received
nantly parenteral nutrition.[14,34]

Our trial had greater statistical pov
previous trials, as well as a longer follow-u
than all but two trials in the meta-analys
our results may be due to a specific effe
treatment algorithm, may be most gene
to patients receiving predominantly ente
tion, or may reflect harm not apparent
with shorter follow-up and lower statistic

In our trial, more patients in the i
control group than in the conventiona
group were treated with corticosteroids,
excess deaths in the intensive-control gr
predominantly from cardiovascular caus
differences might suggest that reducing b
cose levels by the administration of ins

Other information

- **Registration number and name of trial registry?**

YES

Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

ABSTRACT

BACKGROUND

The optimal target range for blood glucose in critically ill patients remains unclear.

METHODS

Within 24 hours after admission to an intensive care unit (ICU), adults who were expected to require treatment in the ICU on 3 or more consecutive days were randomly assigned to undergo either intensive glucose control, with a target blood glucose range of 81 to 108 mg per deciliter (4.5 to 6.0 mmol per liter), or conventional glucose control, with a target of 180 mg or less per deciliter (10.0 mmol or less per liter). We defined the primary end point as death from any cause within 90 days after randomization.

RESULTS

Of the 6104 patients who underwent randomization, 3054 were assigned to undergo intensive control and 3050 to undergo conventional control; data with regard to the primary outcome at day 90 were available for 3010 and 3012 patients, respectively. The two groups had similar characteristics at baseline. A total of 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional-control group died (odds ratio for intensive control, 1.14; 95% confidence interval, 1.02 to 1.28; P=0.02). The treatment effect did not differ significantly between operative (surgical) patients and nonoperative (medical) patients (odds ratio for death in the intensive-control group, 1.31 and 1.07, respectively; P=0.10). Severe hypoglycemia (blood glucose level, ≤40 mg per deciliter [2.2 mmol per liter]) was reported in 206 of 3016 patients (6.8%) in the intensive-control group and 15 of 3014 (0.5%) in the conventional-control group (P<0.001). There was no significant difference between the two treatment groups in the median number of days in the ICU (P=0.84) or hospital (P=0.86) or the median number of days of mechanical ventilation (P=0.56) or renal-replacement therapy (P=0.39).

CONCLUSIONS

In this large, international, randomized trial, we found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter. (ClinicalTrials.gov number, NCT00220987.)

The NICE-SUGAR study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group, the George Institute for International Health (University of Sydney), the Canadian Critical Care Trials Group, and the Vancouver Coastal Health Research Institute (University of British Columbia). The NICE-SUGAR study writing committee (Simon Finfer, F.R.C.P., F.J.F.I.C.M., Dean R. Chittock, F.R.C.P.C., Steve Yu-Shuo Su, Ph.D., Deborah Blair, R.N., Denise Foster, R.N., Vinay Dhingra, F.R.C.P.C., Rinaldo Bellomo, F.J.F.I.C.M., Deborah Cook, M.D., Peter Dodek, M.D., William R. Henderson, F.R.C.P.C., Paul C. Hébert, M.D., Stephane Heritier, Ph.D., Daren K. Heyland, M.D., Colin McArthur, F.J.F.I.C.M., Ellen McDonald, R.N., Imogen Mitchell, F.R.C.P., F.J.F.I.C.M., John A. Myburgh, Ph.D., F.J.F.I.C.M., Robyn Norton, Ph.D., M.P.H., Julie Potter, R.N., M.H.Sc.(Ed.), Bruce G. Robinson, F.R.A.C.P., and Juan J. Ronco, F.R.C.P.C.) assumes full responsibility for the overall content and integrity of the article. Address reprint requests to Dr. Finfer at the George Institute for International Health, P.O. Box M201, Missenden Rd., Sydney NSW 2050, Australia, or at sfinfer@george.org.au.

*The Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study committees and investigators are listed in the Appendix.

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Other information

- **Sources of funding and other support (such as supply of drugs), role of funders?**

YES

the conventional-control group, among all patients and in six predefined pairs of subgroups. The size of the symbols indicates the relative numbers of deaths. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score can range from 0 to 71, with higher scores indicating more severe organ dysfunction.

al.,[12] intensive glucose control has been widely recommended[16,17] on the assumption that treatment aimed at normoglycemia will benefit patients. As noted in other fields of medicine,[37] a clinical trial targeting a perceived risk factor (in this case, hyperglycemia) is a test of a complex strategy that may have profound effects beyond its effect on the risk factor (here, the blood glucose level). Our findings suggest that a goal of normoglycemia for glucose control does not nec-

resulted in lower mortality than a target of 81 to 108 mg per deciliter. On the basis of our results, we do not recommend use of the lower target in critically ill adults.

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We dedicate this article to the memory of our colleagues and coinvestigators Angela Hamilton and Naresh Ramakrishnan, who did not live to see the results of the trial.

Other information

- **References are satisfactory and updated?**

YES

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