

# 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\*

### 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,  $\leq 40$  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 Dhinra, 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](mailto: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.

This article (10.1056/NEJMoa0810625) was published at [NEJM.org](http://www.nejm.org) on March 24, 2009.

N Engl J Med 2009;360:1283-97.  
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**H**YPERGLYCEMIA IS COMMON IN ACUTELY ill patients, including those treated in intensive care units (ICUs).<sup>1</sup> The occurrence of hyperglycemia, in particular severe hyperglycemia, is associated with increased morbidity and mortality in a variety of groups of patients,<sup>2-5</sup> but trials examining the effects of tighter glucose control have had conflicting results.<sup>6-13</sup> Systematic reviews and meta-analyses have also led to differing conclusions.<sup>14,15</sup> Nevertheless, many professional organizations recommend tight glucose control for patients treated in ICUs.<sup>16,17</sup>

Barriers to widespread adoption of tight glucose control include the increased risk of severe hypoglycemia,<sup>14</sup> concerns about the external validity of some studies,<sup>18,19</sup> the difficulty in achieving normoglycemia in critically ill patients,<sup>20,21</sup> and the increased resources that would be required.<sup>22</sup> Because of these issues and uncertainty about the balance of risks and benefits, tight glucose control is used infrequently by some clinicians.<sup>23,24</sup> 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.

## 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.<sup>25</sup>

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,<sup>12,13</sup> or a conven-

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.<sup>23,25</sup> 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<sup>26</sup> 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://studies.thegeorgeinstitute.org/nice/>).

The trial intervention was discontinued once the patient was eating or was discharged from the ICU but was resumed if the patient was readmitted to the ICU within 90 days. It was discontinued permanently at the time of death or 90 days after randomization, whichever occurred first.

Blood samples for glucose measurement were obtained by means of arterial catheters whenever possible; the use of capillary samples was discouraged. Blood glucose levels were measured with the use of point-of-care or arterial blood gas analyzers or laboratory analyzers in routine use at each center. All other aspects of patient care, including nutritional management, were carried out at the discretion of the treating clinicians.

### Assessments and Data Collection at Baseline

Local study coordinators at each institution collected the data; source data were verified by study monitors from regional coordinating centers. At baseline, demographic and clinical characteristics, including the Acute Physiology and Chronic Health Evaluation II (APACHE II) score<sup>27</sup> (which can range

from 0 to 71, with higher scores indicating more severe illness) and the diagnostic criteria for severe sepsis,<sup>28</sup> were collected. Admissions to the ICU directly from the operating or recovery room were classified as operative admissions. Patients were classified as having diabetes on the basis of their medical history and were classified as having trauma if the ICU admission occurred within 48 hours after admission to the hospital for trauma. Previous treatment with corticosteroids was defined as treatment with systemic corticosteroids for 72 hours or more immediately before randomization.

From the time of randomization to the time of discharge from the ICU or 90 days after randomization (whichever came first), we recorded all blood glucose measurements, insulin administration, red-cell administration, blood cultures that were positive for pathogenic organisms, type and volume of all enteral and parenteral nutrition and additional intravenous glucose administered, and corticosteroid administration. Also recorded were the cardiovascular, respiratory, renal, hepatic, and hematologic components of the Sequential Organ Failure Assessment (SOFA, for which scores can range from 0 to 4 for each organ system, with higher scores indicating more severe dysfunction)<sup>29</sup> and the use of mechanical ventilation and renal-replacement therapy.

#### *Outcome Measures*

Outcome measures and statistical analyses were defined in a prespecified statistical-analysis plan.<sup>30</sup> 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.<sup>30</sup>

#### *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 management committees and submitted to the research ethics committees of all participating centers and to the independent data and safety monitoring committee.

#### **STATISTICAL ANALYSIS**

The study was originally designed to enroll 4000 patients. On the basis of data reported by Van den Berghe et al. in 2006,<sup>13</sup> the sample size was increased to 6100, thereby providing a statistical power of 90% to detect an absolute difference in mortality between the two groups of 3.8 percentage points, assuming a baseline mortality of 30% at a two-sided alpha level of less than 0.05. All data were analyzed according to the intention-to-treat principle, with no imputation for missing values. The primary analysis for death at 90 days was performed with the use of an unadjusted chi-square test. A secondary analysis based on logistic regression was also conducted, with the strata used for randomization (type of admission and geographic region) as covariates, as well as age, location before ICU admission, APACHE II score, and use or nonuse of mechanical ventilation at baseline. Other binary end points were analyzed by means of a chi-square test or Fisher's exact test. Continuous variables were compared with the use of unpaired t-tests, Welch's tests, or Wilcoxon rank-sum tests. All odds ratios and their corresponding 95% confidence intervals were calculated according to the profile-likelihood method. The time from randomization to death in the two treatment groups was compared with the use of the log-rank test, and the results are presented as Kaplan-Meier curves. Hazard ratios were obtained from Cox models. The time-weighted blood glucose level (with weighting based on the time difference be-

tween two consecutive measurements applied to the average of the two consecutive measurements) was computed for all patients for whom data were available.

Subgroup analyses for the primary outcome were based on an unadjusted test of interaction in a logistic model. Estimated distributions of individual patients' average time-weighted blood glucose levels, according to treatment group, were obtained by fitting generalized lambda distributions with the use of the method of maximum likelihood.<sup>31,32</sup> All analyses were conducted with the use of S-PLUS software (version 8.0) and R software (version 2.7.0), and the results were verified independently with SAS software (version 9.1). The data were analyzed by the Statistical Services Division of the George Institute for International Health (University of Sydney).

Two preplanned interim analyses were performed by an independent statistician when 1500 and 4000 of the 6100 patients (25% and 66%, respectively) reached the 90th day of follow-up. The analyses were reviewed by the independent data and safety monitoring committee, which was charged with recommending that the trial be stopped if there was evidence beyond a reasonable doubt of a difference in the rate of death from any cause between the two treatment groups. Since a difference of 3 SE was used as a guideline to recommend early stopping, the final mortality analysis was conducted with an alpha of 0.048.

## RESULTS

### STUDY PARTICIPANTS

Participants were recruited and had follow-up during the period from December 2004 through November 2008; 6104 were randomly assigned to one of the two treatment groups: 3054 to intensive glucose control and 3050 to conventional glucose control (Fig. 1). Where delayed consent was permitted, every patient or a legal surrogate was approached for consent. Delayed consent to the use of study-related data was withheld, or previously obtained consent was withdrawn, for 38 of the 3054 patients (1.2%) assigned to intensive control and 36 of the 3050 patients (1.2%) assigned to conventional control; thus, study data were available for 3016 and 3014 patients, respectively. At 90 days, an additional six patients (0.2%) in the intensive-control group and two (0.1%) in the conventional-control group were lost to follow-up. Of the 6030 patients

for whom study data were available, 5275 (87.5%) were recruited in Australia or New Zealand.

The baseline characteristics of the treatment groups were similar (Table 1). The mean ( $\pm$ SD) age was 60.4 $\pm$ 17.2 and 59.9 $\pm$ 17.1 years in the intensive-control group and the conventional-control group, respectively; the percentage of male patients, 62.6% and 64.2%; the mean APACHE II score, 21.1 $\pm$ 7.9 and 21.1 $\pm$ 8.3; and the percentage of operative admissions, 36.9% and 37.2%.

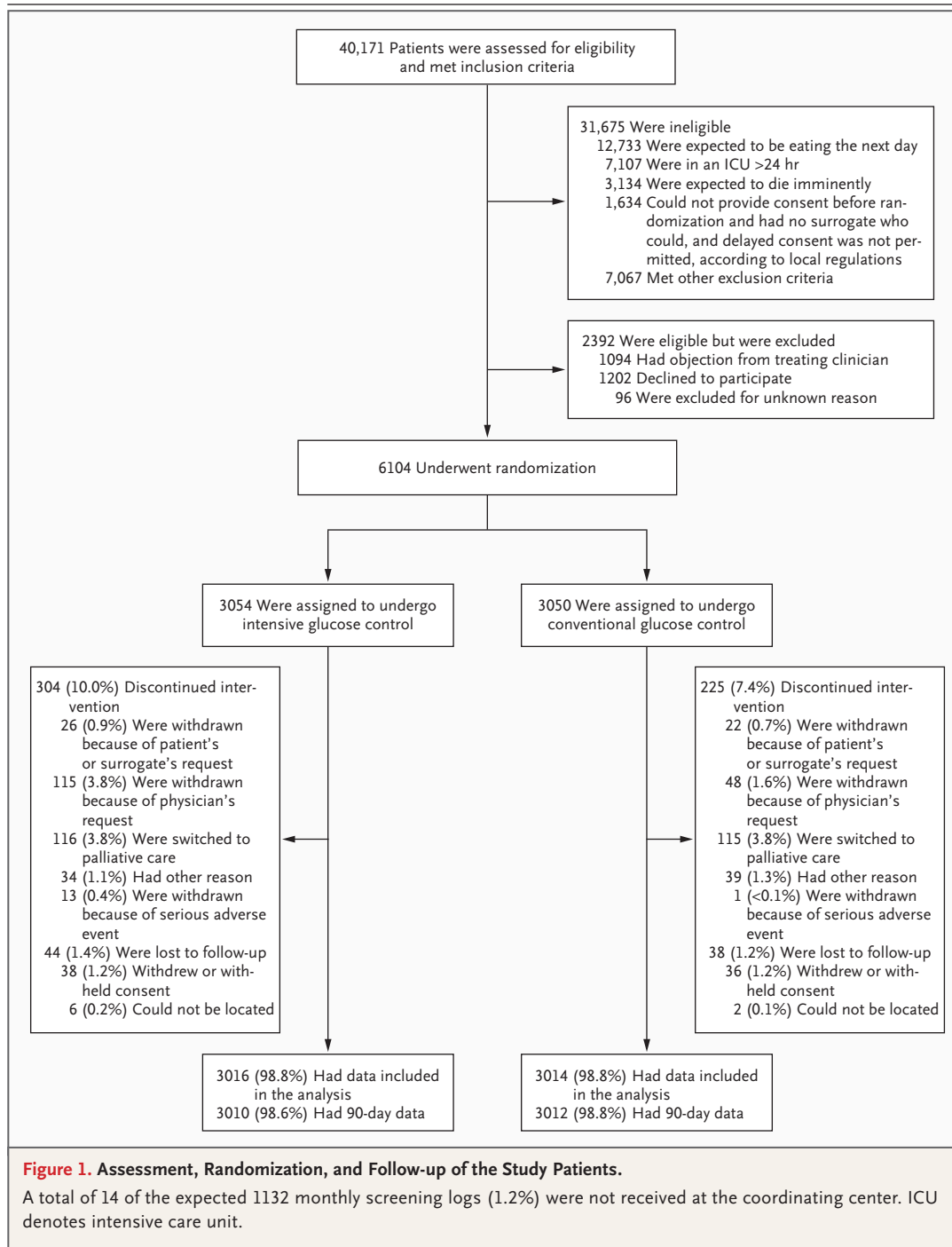
The assigned study treatment, intensive or conventional blood glucose management according to the study-treatment algorithm, was administered to 5997 of 6030 patients (99.5%); 2998 of 3016 (99.4%) in the intensive-control group and 2999 of 3014 (99.5%) in the conventional-control group. The median duration of study treatment was 4.2 days (interquartile range, 1.9 to 8.7) in the intensive-control group and 4.3 days (interquartile range, 2.0 to 9.0) in the conventional-control group ( $P=0.69$ ).

Study treatment was discontinued prematurely in 304 of 3054 patients (10.0%) in the intensive-control group and 225 of 3050 patients (7.4%) in the conventional-control group. Reasons for discontinuation were withdrawal because of a request by the patient or surrogate (26 patients [0.9%] assigned to intensive control and 22 patients [0.7%] assigned to conventional control) or by the treating physician (115 patients [3.8%] and 48 patients [1.6%], respectively), because of serious adverse events (13 patients [0.4%] and 1 patient [ $<0.1\%$ ], respectively), because of a change in the focus of treatment to palliative care (116 patients [3.8%] and 115 patients [3.8%], respectively), and miscellaneous reasons (34 patients [1.1%] and 39 patients [1.3%], respectively).

At the completion of the trial, data on vital status 90 days after randomization were unavailable for 82 of 6014 patients (1.4%), 44 in the intensive-control group and 38 in the conventional-control group. For 74 of these patients, the vital-status data were missing because consent had been withheld or withdrawn (Fig. 1).

### INSULIN ADMINISTRATION AND TREATMENT EFFECTS

Patients undergoing intensive glucose control were more likely than those undergoing conventional control to have received insulin (2931 of 3014 patients [97.2%] vs. 2080 of 3014 [69.0%],  $P<0.001$ ), and they received a larger mean insulin dose



(50.2±38.1 units per day, vs. 16.9±29.0 with conventional control; P<0.001) (Table 2). The mean time-weighted blood glucose level was significantly lower in the intensive-control group than in the conventional-control group (115±18 vs. 144±23 mg per deciliter [6.4±1.0 vs. 8.0±1.3 mmol per liter],

P<0.001). Additional measures of glycemic control are shown in Table 2 and Figures 2A and 2B.

**NUTRITION AND CONCOMITANT TREATMENT**

During the first 14 days after randomization, the mean daily amount of nonprotein calories admin-

istered was  $891\pm 490$  kcal in the intensive-control group and  $872\pm 500$  kcal in the conventional-control group ( $P=0.14$ ). Of this amount,  $624\pm 496$  kcal (70.0%) and  $623\pm 496$  kcal (71.4%), respectively, were given as enteral nutrition;  $173\pm 359$  kcal (19.4%) and  $162\pm 345$  kcal (18.6%) as parenteral nutrition; and  $93.4\pm 88.8$  kcal (10.5%) and  $87.2\pm 93.5$  kcal (10.0%) as intravenous glucose (Table 2, and Appendix B in the Supplementary Appendix).

After randomization, more patients in the intensive-control group than in the conventional-control group were treated with corticosteroids (1042 of 3010 [34.6%] vs. 955 of 3009 [31.7%],  $P=0.02$ ). The median time from randomization to

**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 1. (Continued.)**

| Variable   | Intensive Glucose Control | Conventional Glucose Control |
|--|---------------------------|------------------------------|
| Mechanical ventilation — no./total no. (%)                           | 2825/3014 (93.7)          | 2793/3014 (92.7)             |
| Renal-replacement therapy — no./total no. (%)                        | 179/3014 (5.9)            | 165/3014 (5.5)               |
| History of diabetes mellitus — no./total no. (%)                     | 615/3015 (20.4)           | 596/3014 (19.8)              |
| Type I diabetes  | 50/615 (8.1)              | 42/596 (7.0)                 |
| Type II diabetes   | 565/615 (91.9)            | 554/596 (93.0)               |
| Previous treatment with insulin                                      | 183/615 (29.8)            | 163/596 (27.3)               |
| Previous treatment with systemic corticosteroids — no./total no. (%) | 393/3014 (13.0)           | 378/3014 (12.5)              |
| Subgroup classification — no./total no. (%)                          |                           |                              |
| Severe sepsis at randomization                                       | 676/3014 (22.4)           | 626/3014 (20.8)              |
| Trauma   | 422/3014 (14.0)           | 466/3014 (15.5)              |
| APACHE II score $\geq$ 25  | 929/3013 (30.8)           | 945/3012 (31.4)              |

\* Plus–minus values are means  $\pm$ SD. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores can range from 0 to 71, with higher scores indicating more severe illness, and Sequential Organ Failure Assessment (SOFA) scores can range from 0 to 4 for each organ system, with higher scores indicating more severe organ dysfunction. Severe sepsis was defined according to the consensus-conference criteria of the American College of Chest Physicians–Society of Critical Care Medicine.<sup>28</sup> To convert the values for blood glucose to millimoles per liter, multiply by 0.05551. ICU denotes intensive care unit.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

commencement of corticosteroid treatment was 0 days (interquartile range, 0 to 1) in both groups ( $P=0.34$ ). The most common indication for corticosteroid administration in both groups was the treatment of septic shock, occurring in 376 of the 1042 patients in the intensive-control group (36.1%) who received corticosteroids, as compared with 328 of the 955 patients in the conventional-control group (34.3%) (absolute difference, 1.7 percentage points; 95% confidence interval [CI],  $-2.5$  to 5.9;  $P=0.42$ ) (Table 2).

#### OUTCOMES

Ninety days after randomization, 829 of 3010 patients (27.5%) in the intensive-control group had died, as compared with 751 of 3012 patients (24.9%) in the conventional-control group (Table 3). The absolute difference in mortality was 2.6 percentage points (95% CI, 0.4 to 4.8), and the odds ratio for death with intensive control was 1.14 (95% CI, 1.02 to 1.28;  $P=0.02$ ). The difference in mortality between the two treatment groups was still significant after adjustment for the predefined baseline risk factors (adjusted odds ratio, 1.14; 95% CI, 1.01 to 1.29;  $P=0.04$ ). The median survival time was lower in the intensive-control group than in the conventional-control group (hazard ratio, 1.11; 95% CI, 1.01 to 1.23;  $P=0.03$ ) (Fig. 3A).

Overall, the distributions of proximate causes of death were similar in the two groups ( $P=0.12$ )

(Table 3). However, deaths from cardiovascular causes were more common in the intensive-control group (345 of 829 patients [41.6%]) than in the conventional-control group (269 of 751 patients [35.8%]) (absolute difference, 5.8 percentage points;  $P=0.02$ ). In the intensive-control group and the conventional-control group, the majority of deaths occurred in the ICU (546 of 829 patients [65.9%] and 498 of 751 patients [66.3%], respectively) or in the hospital after discharge from the ICU (220 of 829 patients [26.5%] and 197 of 751 patients [26.2%], respectively). The remaining deaths (63 of 829 patients [7.6%] undergoing intensive control and 56 of 751 patients [7.5%] undergoing conventional control) occurred after hospital discharge. In both groups, potentially life-sustaining treatments were withheld or withdrawn in more than 90% of the patients who died (see Appendix D in the Supplementary Appendix).

During the 90-day study period, there was no significant difference between the two groups in the median length of stay in the ICU or hospital (Table 3). At 90 days, 7 of the 3016 patients (0.2%) in the intensive-control group and 6 of the 3014 patients (0.2%) in the conventional-control group were still in the ICU ( $P=0.78$ ), and 174 patients (5.8%) and 166 patients (5.5%), respectively, were still in the hospital ( $P=0.66$ ).

The number of patients in whom new single or multiple organ failures developed were simi-

**Table 2. Blood Glucose Management and Levels, Calorie Administration, and Corticosteroid Treatment, According to Treatment Group.\***

| Variable   | Total No. of Patients with Data | Intensive Glucose Control | Conventional Glucose Control | Absolute Difference (95% CI)<br><i>percentage points</i> | Statistical Test | P Value |
|--|---------------------------------|---------------------------|------------------------------|--|------------------|---------|
| Treated with insulin — no./total no. (%)   | 6028                            | 2931/3014 (97.2)          | 2080/3014 (69.0)             | 28.2 (26.5 to 30.0)                                      | Pearson's test   | <0.001  |
| Insulin dose — units/day   | 6028                            | 50.2±38.1                 | 16.9±29.0                    | 33.3 (31.6 to 35.0)                                      | Welch's test     | <0.001  |
| Days on treatment algorithm — median (interquartile range)                             | 5991                            | 4.2 (1.9 to 8.7)          | 4.3 (2.0 to 9.0)             | -0.2   | t-test           | 0.69    |
| Morning blood glucose — mg/dl  |                                 |                           |                              |  |                  |         |
| From randomization to cessation of study treatment                                     | 6001                            | 118±25                    | 145±26                       | -27 (-28 to -25)   | Welch's test     | <0.001  |
| From randomization to ICU discharge  | 5987                            | 118±25                    | 145±26                       | -27 (-28 to -25)   | Welch's test     | <0.001  |
| Time-weighted blood glucose — mg/dl  |                                 |                           |                              |  |                  |         |
| From randomization to cessation of study treatment                                     | 6014                            | 115±18                    | 144±23                       | -29 (-30 to -28)   | Welch's test     | <0.001  |
| From randomization to ICU discharge  | 6000                            | 115±19                    | 144±23                       | -29 (-30 to -28)   | Welch's test     | <0.001  |
| Nonprotein calories administered on days 1–14 — kcal/day                               |                                 |                           |                              |  |                  |         |
| By enteral route   |                                 | 624±496                   | 623±496                      | 2 (-24 to 27)  | Welch's test     | 0.89    |
| By parenteral route  |                                 | 173±359                   | 162±345                      | 11 (-7 to 29)  | Welch's test     | 0.22    |
| As intravenous glucose   |                                 | 93.4±88.8                 | 87.2±93.5                    | 6.3 (1.6 to 10.9)  | t-test           | 0.008   |
| Total  |                                 | 891±490                   | 872±500                      | 19 (-6 to 44)  | t-test           | 0.14    |
| Corticosteroid treatment — no./total no. (%)   | 6022                            | 1042/3013 (34.6)          | 955/3009 (31.7)              | 2.9 (0.5 to 5.2)   | Pearson's test   | 0.02    |
| Interval from randomization to corticosteroid treatment — median (interquartile range) | 1996                            | 0 (0 to 1)                | 0 (0 to 1)                   | 0  | t-test           | 0.34    |
| Indication for corticosteroids — no./total no. (%)†                                    | 1997                            |                           |                              |  | Pearson's test   |         |
| Replacement for previous corticosteroid treatment                                      |                                 | 168/1042 (16.1)           | 168/955 (17.6)               | -1.5 (-4.8 to 1.8)                                       |                  | 0.38    |
| Septic shock   |                                 | 376/1042 (36.1)           | 328/955 (34.3)               | 1.7 (-2.5 to 5.9)  |                  | 0.42    |
| Fibroproliferative ARDS  |                                 | 26/1042 (2.5)             | 17/955 (1.8)                 | 0.7 (-0.6 to 2.0)  |                  | 0.27    |
| Immunosuppression for prevention or treatment of organ rejection                       |                                 | 40/1042 (3.8)             | 41/955 (4.3)                 | -0.5 (-2.2 to 1.3)                                       |                  | 0.61    |
| Immunosuppression for treatment of inflammatory disease                                |                                 | 73/1042 (7.0)             | 61/955 (6.4)                 | 0.6 (-1.6 to 2.8)  |                  | 0.58    |
| Cerebral edema after neurosurgery  |                                 | 46/1042 (4.4)             | 43/955 (4.5)                 | -0.1 (-1.9 to 1.7)                                       |                  | 0.92    |
| Acute exacerbation of COPD   |                                 | 98/1042 (9.4)             | 90/955 (9.4)                 | -0.02 (-2.6 to 2.6)                                      |                  | 0.99    |
| Acute asthma   |                                 | 39/1042 (3.7)             | 32/955 (3.4)                 | 0.4 (-1.2 to 2.0)  |                  | 0.64    |
| Other  |                                 | 256/1042 (24.6)           | 237/955 (24.8)               | -0.3 (-4.0 to 3.5)                                       |                  | 0.90    |

\* Plus-minus values are means ±SD. To convert the values for blood glucose to millimoles per liter, multiply by 0.05551. ARDS denotes acute respiratory distress syndrome, and COPD chronic obstructive pulmonary disease.

† The sum of the number of indications for corticosteroids is greater than the number of patients with data (the number of patients treated), since some patients had more than one indication.

lar with intensive and conventional glucose control ( $P=0.11$ ) (Table 3). There was no significant difference between the two groups in the numbers of days of mechanical ventilation and renal-replacement therapy or in the rates of positive blood cultures and red-cell transfusion (Table 3).

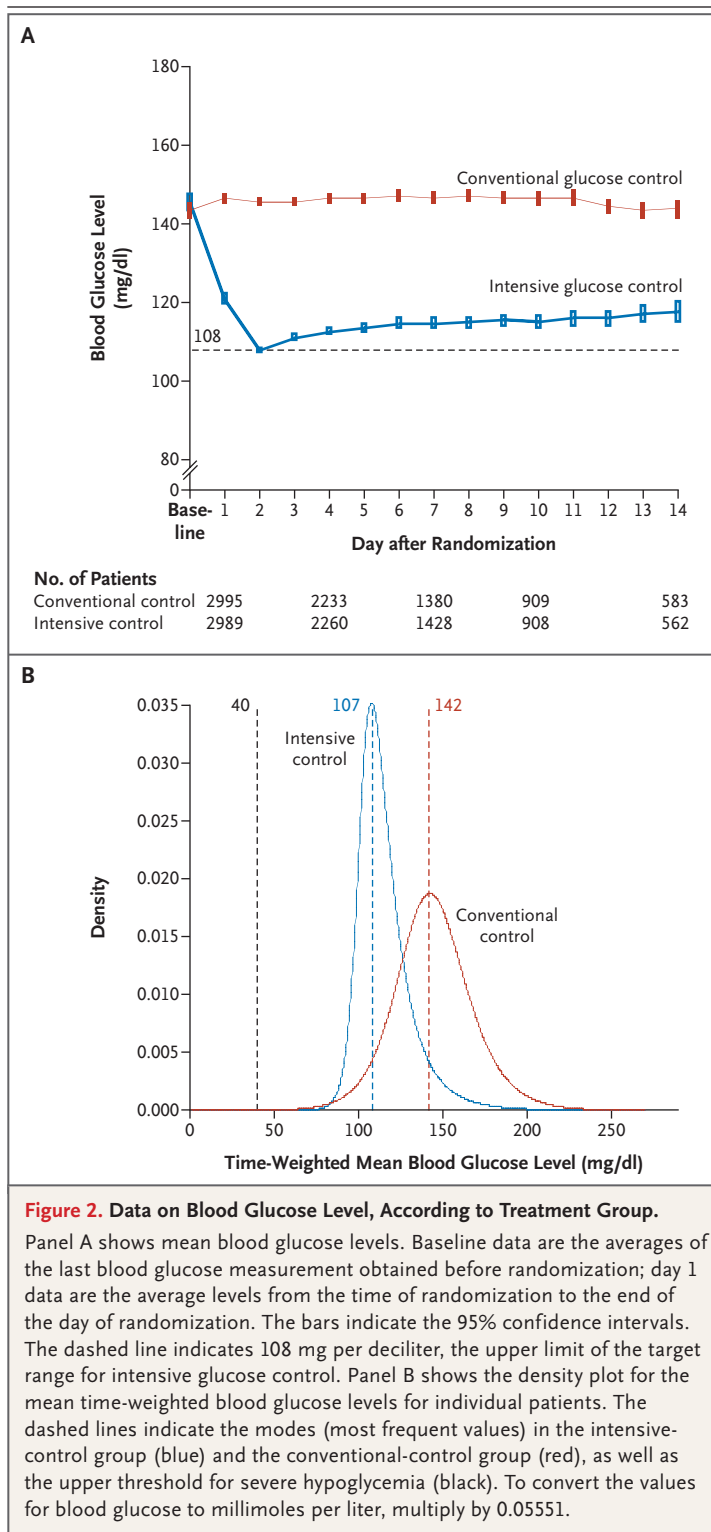
With respect to 90-day mortality, subgroup analyses suggested no significant difference in the treatment effect for the comparisons of operative and nonoperative patients ( $P=0.10$ ), patients with and those without diabetes ( $P=0.60$ ), patients with and those without severe sepsis ( $P=0.93$ ), and patients with an APACHE II score of 25 or more and those with a score of less than 25 ( $P=0.84$ ) (Fig. 3B). Tests for interaction indicated a possible trend toward subgroup-specific treatment effects for patients with trauma as compared with those without trauma ( $P=0.07$ ) and for patients receiving corticosteroids at baseline as compared with those not receiving corticosteroids ( $P=0.06$ ).

Severe hypoglycemia (defined as a blood glucose level  $\leq 40$  mg per deciliter [2.2 mmol per liter]) was recorded in 206 of 3016 patients (6.8%) undergoing intensive glucose control, as compared with 15 of 3014 patients (0.5%) undergoing conventional control (odds ratio, 14.7; 95% CI, 9.0 to 25.9;  $P<0.001$ ). The recorded number of episodes of severe hypoglycemia was 272 in the intensive-control group, as compared with 16 in the conventional-control group; 173 of all 288 episodes (60.1%) were confirmed by a laboratory measurement, 112 (38.9%) were unconfirmed bedside readings, and 3 (1.0%) were of unknown confirmation status. No long-term sequelae of severe hypoglycemia were reported.

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 random-



**Figure 2. Data on Blood Glucose Level, According to Treatment Group.** Panel A shows mean blood glucose levels. Baseline data are the averages of the last blood glucose measurement obtained before randomization; day 1 data are the average levels from the time of randomization to the end of the day of randomization. The bars indicate the 95% confidence intervals. The dashed line indicates 108 mg per deciliter, the upper limit of the target range for intensive glucose control. Panel B shows the density plot for the mean time-weighted blood glucose levels for individual patients. The dashed lines indicate the modes (most frequent values) in the intensive-control group (blue) and the conventional-control group (red), as well as the upper threshold for severe hypoglycemia (black). To convert the values for blood glucose to millimoles per liter, multiply by 0.05551.

ization, selecting a long-term outcome that is not subject to biased ascertainment, evaluating a number of clinically important outcomes, achieving

| <b>Table 3. Outcomes and Adverse Events.*</b>  |                                  |                                     |  |                         |                |
|--|----------------------------------|-------------------------------------|--|-------------------------|----------------|
| <b>Outcome Measure</b>   | <b>Intensive Glucose Control</b> | <b>Conventional Glucose Control</b> | <b>Odds Ratio or Absolute Difference (95% CI)†</b> | <b>Statistical Test</b> | <b>P Value</b> |
| Death — no. of patients/total no. (%)  |                                  |                                     |  |                         |                |
| At day 90  | 829/3010 (27.5)                  | 751/3012 (24.9)                     | 1.14 (1.02 to 1.28)                                | Logistic regression     | 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. (%)       |                                  |                                     |  |                         |                |
| Limited because death was imminent   | 527/816 (64.6)                   | 459/741 (61.9)                      | 1.12 (0.91 to 1.38)                                | Logistic regression     | 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. (%)   |                                  |                                     |  |                         |                |
| Cardiovascular-distributive shock  | 168/829 (20.3)                   | 140/751 (18.6)                      |  | Pearson's test          | 0.12           |
| 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. (%)  |                                  |                                     |  |                         |                |
| 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. (%)‡   |                                  |                                     |  |                         |                |
| 0  | 1571/2682 (58.6)                 | 1536/2679 (57.3)                    |  | Pearson's test          | 0.11           |
| 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)                       |  |                         |                |

Table 3. (Continued.)

| Outcome Measure   | Intensive Glucose Control | Conventional Glucose Control | Odds Ratio or Absolute Difference (95% CI) <sup>†</sup> | Statistical Test       | P Value |
|---|---------------------------|------------------------------|---|------------------------|---------|
| Temporary sequelae of severe hypoglycemia — no. of patients/total no. (%)       |                           |                              |   |                        |         |
| Neurologic  | 1/206 (0.5)               | 1/15 (6.7)                   |   |                        |         |
| Cardiovascular  | 6/206 (2.9)               | 1/15 (6.7)                   |   |                        |         |
| Other   | 6/206 (2.9)               | 0                            |   |                        |         |
| Blood culture positive for pathogenic organisms — no. of patients/total no. (%) | 387/3014 (12.8)           | 372/3011 (12.4)              |   | Pearson's test         | 0.57    |
| Transfusion of packed red cells — no. of patients/total no. (%)                 | 1268/3013 (42.1)          | 1246/3014 (41.3)             |   | Pearson's test         | 0.56    |
| Volume of packed cells transfused — ml  | 122±144                   | 126±193                      |   | Wilcoxon rank-sum test | 0.82    |

\* Plus-minus values are means ±SD. CPR denotes cardiopulmonary resuscitation, ICU intensive care unit, and IQR interquartile range.

<sup>†</sup> Absolute differences (percentage points) are given for median days in the ICU or hospital, percentage of patients undergoing mechanical ventilation or renal-replacement therapy, and median days of mechanical ventilation or renal-replacement therapy; for all other measures, odds ratios are given.

<sup>‡</sup> Organ failure was defined as a Sequential Organ Failure Assessment (SOFA) score of 3 or 4 for any individual organ system.

nearly complete follow-up, and following a pre-defined statistical-analysis plan.<sup>30</sup> The management of blood glucose levels was standardized — nearly all patients received their assigned treatment, the mean blood glucose levels differed significantly between the two treatment groups during the 90-day study period, and the rate of severe 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.

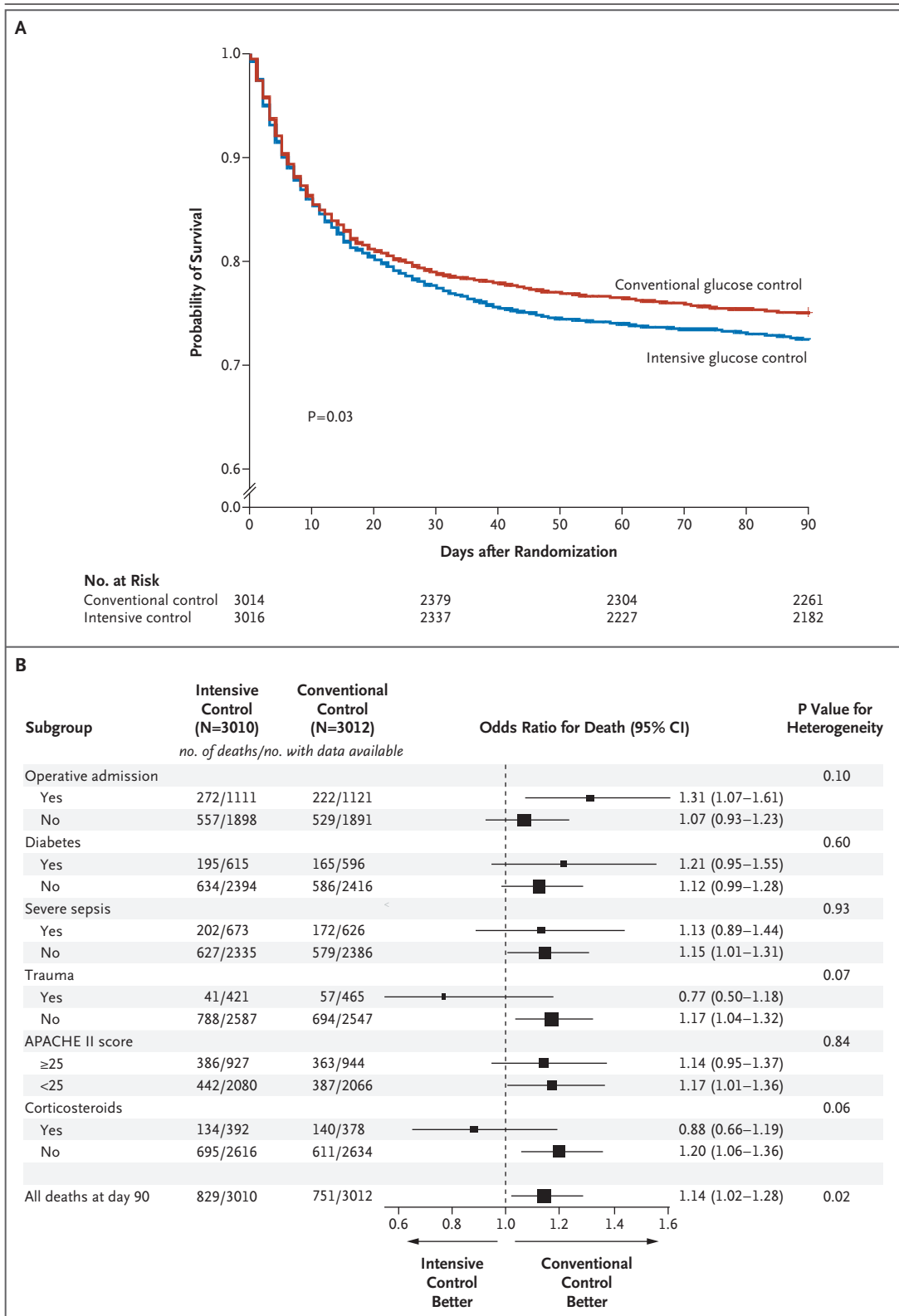
Our findings differ from those of a recent meta-analysis showing that intensive glucose control did not significantly alter mortality among critically ill adults.<sup>14</sup> In keeping with the trials included in the meta-analysis, patients in our trial who were assigned to intensive glucose control, as compared with those assigned to conventional control, had lower blood glucose levels, received

more insulin, and had more episodes of severe hypoglycemia.<sup>14</sup> A unique feature of our trial was the standardized, complex management of blood glucose made possible at multiple centers through a computerized treatment algorithm accessible on centralized servers. In addition, our patients received predominantly enteral nutrition, consonant with current evidence-based feeding guidelines,<sup>33</sup> whereas a substantial proportion of the patients included in the meta-analysis received predominantly parenteral nutrition.<sup>14,34</sup>

Our trial had greater statistical power than previous trials, as well as a longer follow-up period than all but two trials in the meta-analysis. Thus, our results may be due to a specific effect of our treatment algorithm, may be most generalizable to patients receiving predominantly enteral nutrition, or may reflect harm not apparent in trials with shorter follow-up and lower statistical power.

In our trial, more patients in the intensive-control group than in the conventional-control group were treated with corticosteroids, and the excess deaths in the intensive-control group were predominantly from cardiovascular causes. These differences might suggest that reducing blood glucose levels by the administration of insulin has adverse effects on the cardiovascular system.<sup>35,36</sup> However, our trial was not designed to examine such mechanisms; further research is needed to understand the increased mortality in our trial.

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**Figure 3 (facing page). Probability of Survival and Odds Ratios for Death, According to Treatment Group.**

Panel A shows Kaplan–Meier estimates for the probability of survival, which at 90 days was greater in the conventional-control group than in the intensive-control group (hazard ratio, 1.11; 95% confidence interval, 1.01 to 1.23;  $P=0.03$ ). Panel B shows the odds ratios (and 95% confidence intervals) for death from any cause in the intensive-control group as compared with 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.,<sup>12</sup> intensive glucose control has been widely recommended<sup>16,17</sup> on the assumption that treatment aimed at normoglycemia will benefit patients. As noted in other fields of medicine,<sup>37</sup> 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-

essarily benefit critically ill patients and may be harmful. Whether the harm we observed resulted from the reduced blood glucose level, increased administration of insulin, occurrence of hypoglycemia, methodologic factors specific to our trial, or other factors is unclear.

In conclusion, our trial showed that a blood glucose target of less than 180 mg per deciliter 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.

Supported by grants from the Australian National Health and Medical Research Council, the Health Research Council of New Zealand, and the Canadian Institutes for Health Research.

Dr. Finfer reports receiving reimbursement for travel to present research results at scientific meetings from Eli Lilly, Cardinal Health, and CSL Bioplasma and for serving on steering committees for studies sponsored by Eli Lilly and Eisai (paid to the George Institute for International Health); he also reports that the George Institute for International Health, an independent, not-for-profit institute affiliated with the University of Sydney, has received research funding from Servier, Novartis, Eisai, Merck Sharp & Dohme, Pfizer Australia, Fresenius Kabi Deutschland, and Sanofi-Aventis. No other potential conflict of interest relevant to this article was reported.

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.

**APPENDIX**

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