ORIGINAL ARTICLE

Hypoglycemia and Risk of Death in Critically Ill Patients

The NICE-SUGAR Study Investigators*

ABSTRACT

BACKGROUND

Whether hypoglycemia leads to death in critically ill patients is unclear.

METHODS

We examined the associations between moderate and severe hypoglycemia (blood glucose, 41 to 70 mg per deciliter [2.3 to 3.9 mmol per liter] and ≤40 mg per deciliter [2.2 mmol per liter], respectively) and death among 6026 critically ill patients in intensive care units (ICUs). Patients were randomly assigned to intensive or conventional glucose control. We used Cox regression analysis with adjustment for treatment assignment and for baseline and postrandomization covariates.

RESULTS

Follow-up data were available for 6026 patients: 2714 (45.0%) had moderate hypoglycemia, 2237 of whom (82.4%) were in the intensive-control group (i.e., 74.2% of the 3013 patients in the group), and 223 patients (3.7%) had severe hypoglycemia, 208 of whom (93.3%) were in the intensive-control group (i.e., 6.9% of the patients in this group). Of the 3089 patients who did not have hypoglycemia, 726 (23.5%) died, as compared with 774 of the 2714 with moderate hypoglycemia (28.5%) and 79 of the 223 with severe hypoglycemia (35.4%). The adjusted hazard ratios for death among patients with moderate or severe hypoglycemia, as compared with those without hypoglycemia, were 1.41 (95% confidence interval [CI], 1.21 to 1.62; P<0.001) and 2.10 (95% CI, 1.59 to 2.77; P<0.001), respectively. The association with death was increased among patients who had moderate hypoglycemia on more than 1 day (>1 day vs. 1 day, P=0.01), those who died from distributive (vasodilated) shock (P<0.001), and those who had severe hypoglycemia in the absence of insulin treatment (hazard ratio, 3.84; 95% CI, 2.37 to 6.23; P<0.001).

CONCLUSIONS

In critically ill patients, intensive glucose control leads to moderate and severe hypoglycemia, both of which are associated with an increased risk of death. The association exhibits a dose–response relationship and is strongest for death from distributive shock. However, these data cannot prove a causal relationship. (Funded by the Australian National Health and Medical Research Council and others; NICE-SUGAR ClinicalTrials.gov number, NCT00220987.)

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Hyperglycemia occurs commonly in patients treated in intensive care units (ICUs),[1] and more severe hyperglycemia is associated with higher morbidity and mortality.[2-6] A number of trials have compared outcomes in ICU patients who were randomly assigned to a higher or lower blood glucose target.[7-14] Initial trials suggested that intensive glucose control could reduce mortality among patients treated in a surgical ICU and reduce morbidity among patients treated in a medical ICU.[13,14] Subsequent trials have not confirmed these findings.[7-12] We previously reported the primary results of a large study, the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, in which patients assigned to intensive glucose control had an increased risk of death,[10] but the mechanism leading to increased mortality has not been explained.

Patients assigned to intensive glucose control have an increased incidence of severe hypoglycemia,[8-14] which is independently associated with increased mortality.[8,11,14] In observational studies, both moderate and severe hypoglycemia have been independently associated with increased mortality.[15-17] To better understand the results of the NICE-SUGAR study, we analyzed the trial database to explore the relation between moderate and severe hypoglycemia and the risk of death.

METHODS

STUDY OVERSIGHT

The present study is a post hoc analysis of the NICE-SUGAR study database; the protocol and statistical analysis plan for the study have been published previously.[18,19] Written informed consent to participate in the study was obtained before randomization, or delayed consent was obtained, from each patient or a legal surrogate.

Independently of the funding agencies, the members of the writing committee designed the study, analyzed the data, wrote the manuscript, and made the decision to submit the manuscript for publication. The members of the writing committee vouch for the accuracy and completeness of the reported data and for the fidelity of the study to the protocol.

STUDY PARTICIPANTS

The NICE-SUGAR study was a multicenter, randomized, controlled trial that recruited 6104 adults in ICUs in 42 hospitals between 2004 and 2008. The main results and a detailed description of the study protocol have been published previously.[10,18] In brief, eligible participants were patients who were expected to be in the ICU for 3 or more days. Patients who were considered to be at increased risk for hypoglycemia or who had previously had hypoglycemia without full neurologic recovery were excluded. Participants were randomly assigned to intensive blood 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 per deciliter (10.0 mmol per liter) or less. The assigned intervention was continued until the patient was eating, was discharged from the ICU, or died. The primary outcome measure was death within 90 days after randomization.

Data on demographic and clinical characteristics of the patients were collected at baseline. From randomization until discharge from the ICU or death or until 90 days had elapsed since randomization — whichever came first — we recorded all blood glucose measurements; the administration of insulin, enteral and parenteral nutrition, intravenous glucose, and glucocorticoids; daily Sequential Organ Failure Assessment scores (ranging from 0 to 4 for each of five organ systems, with higher scores indicating more severe organ dysfunction)[20]; and the use of mechanical ventilation and renal-replacement therapy.

Severe hypoglycemia was defined as a recorded blood glucose value of 40 mg per deciliter (2.2 mmol per liter) or less, and moderate hypoglycemia as a value between 41 and 70 mg per deciliter (2.3 to 3.9 mmol per liter).[21,22] We recorded whether the patient was being treated with an insulin infusion when the first episode of moderate or severe hypoglycemia occurred.

STATISTICAL ANALYSIS

Full details of the statistical analysis are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. Risk factors for moderate or severe hypoglycemia were examined with the use of univariate and multivariate logistic regression; factors with a P value of less than 0.20 in the univariate analysis were included in the multivariate analysis. Differences in postrandomization factors and events between the patients who had moderate or severe hypoglycemia and those who did not have hypoglyce-

mia were examined with the use of generalized linear models adjusted for treatment assignment.

We then estimated the association between moderate or severe hypoglycemia and mortality, using Cox regression. For each of the main regression analyses, we estimated three hazard ratios: the hazard ratio stratified according to treatment assignment (intensive or conventional glucose control), the hazard ratio stratified according to treatment assignment and adjusted for baseline characteristics, and the hazard ratio adjusted for treatment assignment, baseline characteristics, and time-dependent factors that occurred after randomization and that may influence the probability of death.

In addition, we examined the relationship between moderate or severe hypoglycemia and mortality according to the number of days on which hypoglycemic episodes were recorded and whether patients were being treated with insulin at the time of the first episode. To determine whether the relation between hypoglycemia and mortality varied according to patient population, we estimated hazard ratios in subgroups of patients defined according to predetermined baseline characteristics, using the likelihood-ratio test to test for heterogeneity. We also examined the association of hypoglycemia with cause-specific mortality, with adjustment for the same variables as those in the main analysis.[23] Because we did not know whether hypoglycemia occurred in these patients outside the ICU, we conducted a sensitivity analysis in which we censored follow-up data at the date of discharge from the ICU. All analyses were conducted with the use of Stata software, version 10.1 (StataCorp).

RESULTS

STUDY PARTICIPANTS

We enrolled 6104 patients and obtained complete follow-up data to 28 days and 90 days for 6026 patients (98.7%) and 6022 patients (98.7%), respectively. Data at 28 days were available for 3013 patients assigned to intensive glucose control and 3013 patients assigned to conventional glucose control.

RATES AND TIMING OF HYPOGLYCEMIA

Of 6026 patients, 2714 (45.0%) had moderate hypoglycemia, including 2237 of the 3013 patients (74.2%) in the intensive-control group and 477 of the 3013 (15.8%) in the conventional-control group. The 223 patients (3.7%) with severe hypoglycemia included 208 of the 3013 in the intensive-control group (6.9%) and 15 of the 3013 in the conventional-control group (0.5%). The median time from randomization to hypoglycemia was 1 day (interquartile range, 0 to 2) among the patients with moderate hypoglycemia and 4 days (interquartile range, 2 to 9) among those with severe hypoglycemia.

RISK FACTORS FOR HYPOGLYCEMIA

The clinical characteristics of the patients with moderate or severe hypoglycemia are listed in Table S1 in the Supplementary Appendix; independent risk factors for moderate or severe hypoglycemia are shown in Table 1. Full details of the univariate and multivariate analysis are provided in Table S2 in the Supplementary Appendix.

CLINICAL COURSE AND HYPOGLYCEMIA

The 2717 patients who stayed in the ICU for 7 days or longer were more likely than the 3296 who stayed for a shorter period to have moderate or severe hypoglycemia (1424 patients [52.4%] vs. 1280 [38.8%] among those with moderate hypoglycemia, $P<0.001$; and 162 [6.0%] vs. 60 [1.8%] among those with severe hypoglycemia, $P<0.001$). However, mortality was similar in the two groups (694 deaths [25.5%] and 885 deaths [26.9%], respectively; $P=0.26$).

Analyses adjusted for treatment assignment that compared patients who had moderate hypoglycemia with those who did not have hypoglycemia and compared patients who had severe hypoglycemia with those who did not have severe hypoglycemia showed that patients with moderate or severe hypoglycemia had a longer stay in the ICU and in the hospital. In addition, they spent longer having their blood glucose concentration controlled according to the study protocol (which was a reflection of prolonged critical illness rather than the time taken to reach the target blood glucose level), received more units of insulin per day, were more likely to receive parenteral nutrition and received more nutrition, had a lower mean blood glucose concentration, had more blood glucose measurements per day, and had a higher standard deviation for blood glucose (Table S3 in the Supplementary Appendix).

Table 1. Results of Multivariate Analysis for Factors at Baseline That Were Independent Risk Factors for Subsequent Moderate or Severe Hypoglycemia.*

Variable	Moderate Hypoglycemia		Severe Hypoglycemia	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Age, per 1-yr increase	1.00 (1.00–1.01)	0.04	1.00 (0.99–1.01)	0.6
APACHE II score, per 1-point increase†	1.01 (1.00–1.02)	0.01	1.01 (0.99–1.03)	0.5
BMI, per 1-point increase‡	0.97 (0.96–0.98)	<0.001	0.96 (0.94–0.99)	0.003
Blood glucose, per increase of 1 mg/dl§	—		1.00 (0.99–1.00)	0.009
Sex				
Female	1.00		1.00	
Male	0.78 (0.67–0.90)	0.001	0.88 (0.66–1.17)	0.4
Postoperative status				
No	1.00		1.00	
Yes	0.82 (0.71–0.96)	0.01	0.78 (0.56–1.07)	0.1
Severe sepsis				
No	1.00		1.00	
Yes	1.28 (1.08–1.53)	0.006	0.92 (0.66–1.29)	0.6
Trauma				
No	1.00		1.00	
Yes	1.28 (1.03–1.59)	0.02	0.77 (0.46–1.28)	0.3
Diabetes¶				
No	1.00			
Yes	1.24 (1.01–1.52)	0.04		
Prior insulin treatment				
No	1.00		1.00	
Yes	1.61 (1.14–2.28)	0.007	1.46 (0.85–2.52)	0.2
Prior glucocorticoid treatment				
No	1.00		1.00	
Yes	1.09 (0.88–1.34)	0.4	1.51 (1.05–2.18)	0.03
Cardiovascular failure‖				
No	1.00		1.00	
Yes	1.24 (1.07–1.44)	0.005	1.41 (1.04–1.92)	0.03
Treatment group				
Conventional glucose control	1.00		1.00	
Intensive glucose control	24.19 (20.98–27.88)	<0.001	16.39 (9.32–28.81)	<0.001

* Moderate hypoglycemia was defined as a blood glucose value of 70 mg per deciliter (3.9 mmol per liter) or less, and severe hypoglycemia as a blood glucose value of 40 mg per deciliter (2.2 mmol per liter) or less. In this analysis, patients with severe hypoglycemia (all of whom had moderate hypoglycemia also, as defined) were included in the group for comparison with those with no hypoglycemia. The factors included in the multivariate analysis were those with P values of less than 0.20 in the univariate analysis.

† Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating an increased risk of death.

‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

§ To convert value for glucose to millimoles per liter, multiply by 0.05551. The baseline blood glucose value was not included in the multivariate analysis for moderate hypoglycemia because of the P value in the univariate analysis (P=0.32).

¶ Diabetes at baseline was not included in the multivariate analysis for severe hypoglycemia because of the P value in the univariate analysis (P=0.22).

‖ Cardiovascular failure was defined as a score of 3 or 4 on the cardiovascular section of the Sequential Organ Failure Assessment (on a scale ranging from 0 to 4 for each of five organ systems, with higher scores indicating more severe organ dysfunction).

Subgroup	Deaths	Population	Median Time from Randomization to Hypoglycemia (IQR)	Median Time from Hypoglycemia to Death (IQR)	Hazard Ratio (95% CI)	P Value
	no.		*days*			
No hypoglycemia	726	3089			1.00	
Moderate hypoglycemia	774	2714	1 (0–2)	7 (2–21)		
Stratified by treatment					1.81 (1.59–2.07)	<0.001
Stratified by treatment and adjusted for baseline characteristics					1.60 (1.39–1.85)	<0.001
Stratified by treatment and adjusted for baseline and postrandomization characteristics					1.41 (1.21–1.62)	<0.001
Severe hypoglycemia	79	223	4 (2–9)	8 (3–15)		
Stratified by treatment					3.21 (2.49–4.15)	<0.001
Stratified by treatment and adjusted for baseline characteristics					2.64 (2.01–3.47)	<0.001
Stratified by treatment and adjusted for baseline and postrandomization characteristics					2.10 (1.59–2.77)	<0.001

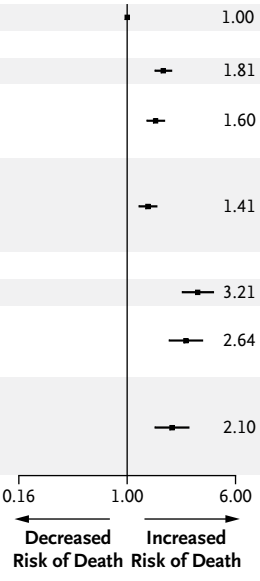

Figure 1. Hazard Ratio for Death According to Occurrence of Moderate or Severe Hypoglycemia.

Moderate hypoglycemia was defined as a blood glucose value of 41 to 70 mg per deciliter (2.3 to 3.9 mmol per liter), and severe hypoglycemia as a blood glucose value of 40 mg per deciliter (2.2 mmol per liter) or less.

ASSOCIATION OF HYPOGLYCEMIA WITH DEATH

During follow-up, 1579 of the 6026 patients (26.2%) died, including 726 of the 3089 patients (23.5%) who did not have hypoglycemia, 774 of the 2714 (28.5%) who had moderate hypoglycemia, and 79 of the 223 (35.4%) who had severe hypoglycemia (Fig. 1). The median time from the first episode of hypoglycemia to death was 7 days (interquartile range, 2 to 21) among patients with moderate hypoglycemia and 8 days (interquartile range, 3 to 15) among those with severe hypoglycemia.

The hazard ratio for death with adjustment for treatment assignment was significantly increased among patients with moderate or severe hypoglycemia, as compared with those without hypoglycemia (moderate hypoglycemia, 1.81; 95% confidence interval [CI], 1.59 to 2.07; P<0.001; severe hypoglycemia, 3.21; 95% CI, 2.49 to 4.15; P<0.001). The hazard ratio remained significantly increased after adjustment for baseline characteristics (moderate hypoglycemia, 1.60; 95% CI, 1.39 to 1.85; P<0.001; severe hypoglycemia, 2.64; 95% CI, 2.01 to 3.47; P<0.001) and after adjustment for both baseline characteristics and postrandomization factors (moderate hypoglycemia, 1.41; 95% CI, 1.21 to 1.62; P<0.001; severe hypoglycemia, 2.10; 95% CI, 1.59 to 2.77; P<0.001; P=0.001 for heterogeneity between moderate and severe hypoglycemia) (Fig. 1).

The relationship between moderate or severe hypoglycemia and death, with adjustment for baseline characteristics and postrandomization factors, did not differ significantly between patients assigned to intensive glucose control and those assigned to conventional glucose control (P=0.22) (Fig. 2A), and the hazard ratio remained consistent when follow-up data were censored at the date of discharge from the ICU (moderate hypoglycemia, 1.33; 95% CI, 1.11 to 1.59; P=0.002; severe hypoglycemia, 1.90; 95% CI, 1.36 to 2.65; P<0.001) (Fig. S1 in the Supplementary Appendix). The relationship between hypoglycemia and death was similar among patients with and those without a diagnosis of diabetes (P=0.42) (Fig. 2B), but it was stronger among postoperative patients (those who had been admitted to the ICU directly

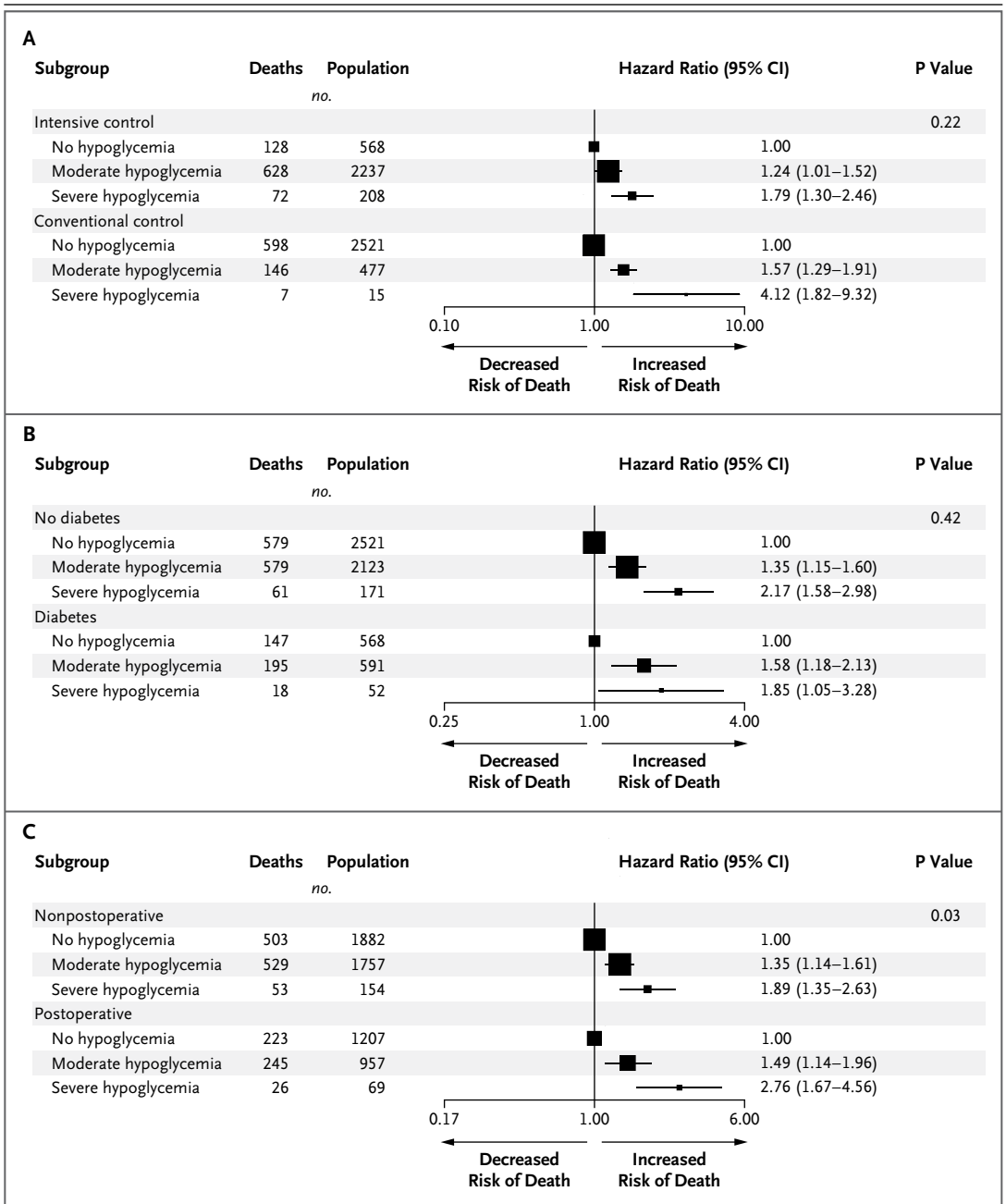

Figure 2. Hazard Ratio for Death According to Treatment Assignment and Status with Respect to Diabetes and Postoperative Status at Baseline.

The relationship between moderate or severe hypoglycemia and death did not differ significantly between patients assigned to intensive glucose control and those assigned to conventional glucose control (Panel A). The relationship was similar among patients with and those without a diagnosis of diabetes (Panel B), but it was stronger among postoperative patients (those admitted to the ICU directly from the operating room or recovery room) than among nonpostoperative patients (Panel C). The size of the squares is proportional to the number of deaths.

from the operating room or the recovery room) than among nonpostoperative patients (P=0.03) (Fig. 2C).

The relationship was also stronger among patients who had moderate hypoglycemia on more than 1 day, as compared with those who had mod-

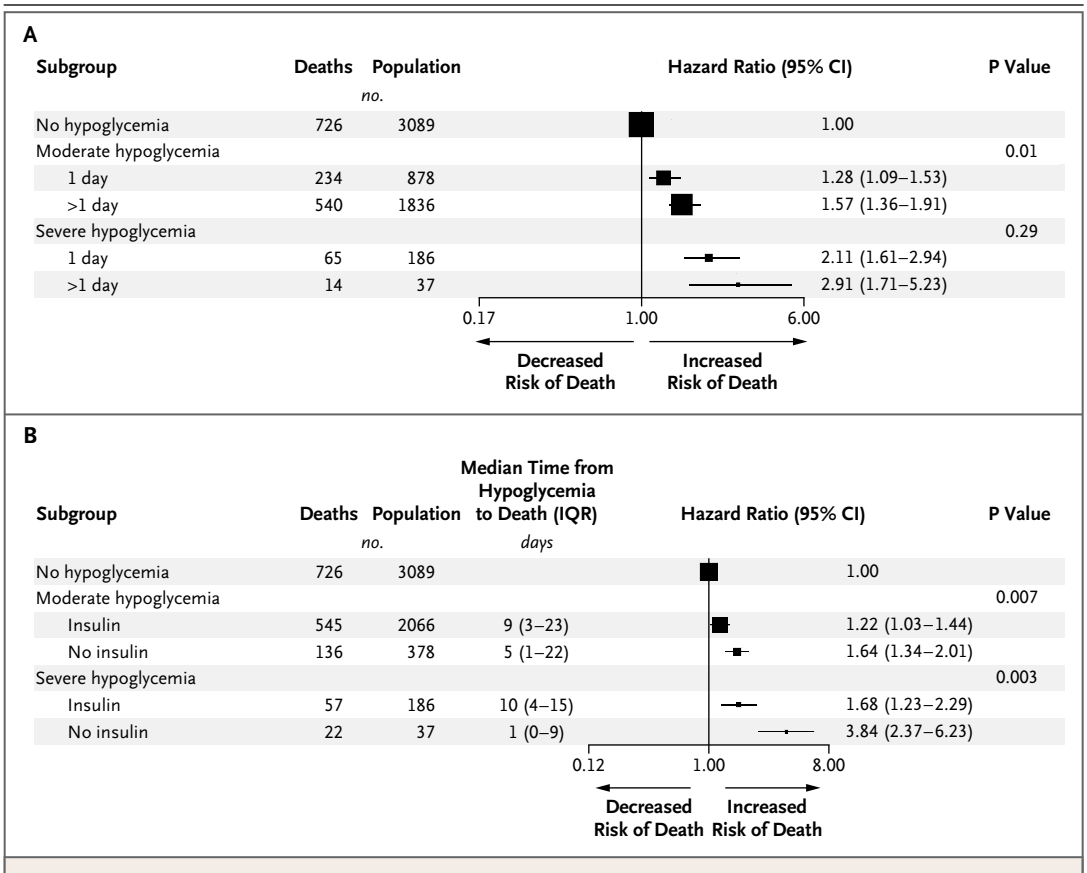

Figure 3. Hazard Ratio for Death According to the Occurrence of Hypoglycemia on 1 Day or More Than 1 Day and Receipt or Nonreceipt of Insulin Therapy at the Time of the First Hypoglycemic Episode.

The risk of death was increased among patients who had moderate hypoglycemia on more than 1 day, as compared with just 1 day (Panel A), and among patients who were not receiving insulin when hypoglycemia first occurred, as compared with those who were receiving insulin (Panel B). The interval from the first episode of hypoglycemia to death was shorter among patients who were not being treated with insulin when hypoglycemia first occurred ($P=0.004$ and $P<0.001$ for moderate and severe hypoglycemia, respectively). The size of the squares is proportional to the number of deaths.

erate hypoglycemia on only 1 day ($P=0.01$) (Fig. 3A), and among patients who were not being treated with insulin when hypoglycemia first occurred, as compared with those who were ($P=0.007$ and $P=0.003$ for moderate and severe hypoglycemia, respectively) (Fig. 3B). The interval from the first episode of hypoglycemia to death was shorter among patients who were not being treated with insulin when hypoglycemia first occurred, as compared with those who were receiving insulin at that time ($P=0.004$ and $P<0.001$ for moderate and severe hypoglycemia, respectively) (Fig. 3B).

INFLUENCE OF POSTRANDOMIZATION FACTORS

The hazard ratio for death was consistently elevated among patients with moderate or severe hypoglycemia, as compared with those who did not have hypoglycemia, regardless of receipt or nonreceipt of parenteral nutrition ($P=0.21$) and the average amount of nonprotein kilocalories per day (<1000 vs. ≥1000, $P=0.43$). The hazard ratios for death after moderate or severe hypoglycemia were also elevated regardless of the standard deviation for the blood glucose concentration (<27 mg per deciliter [1.5 mmol per liter] vs. ≥27 mg per deciliter, $P=0.81$) and the average daily dose of insulin administered in the ICU (<30 IU vs. ≥30 IU, $P=0.34$) (Fig. S2 in the Supplementary Appendix).

CAUSE-SPECIFIC MORTALITY

As compared with patients who did not have hypoglycemia, patients with moderate hypoglycemia and those with severe hypoglycemia had a

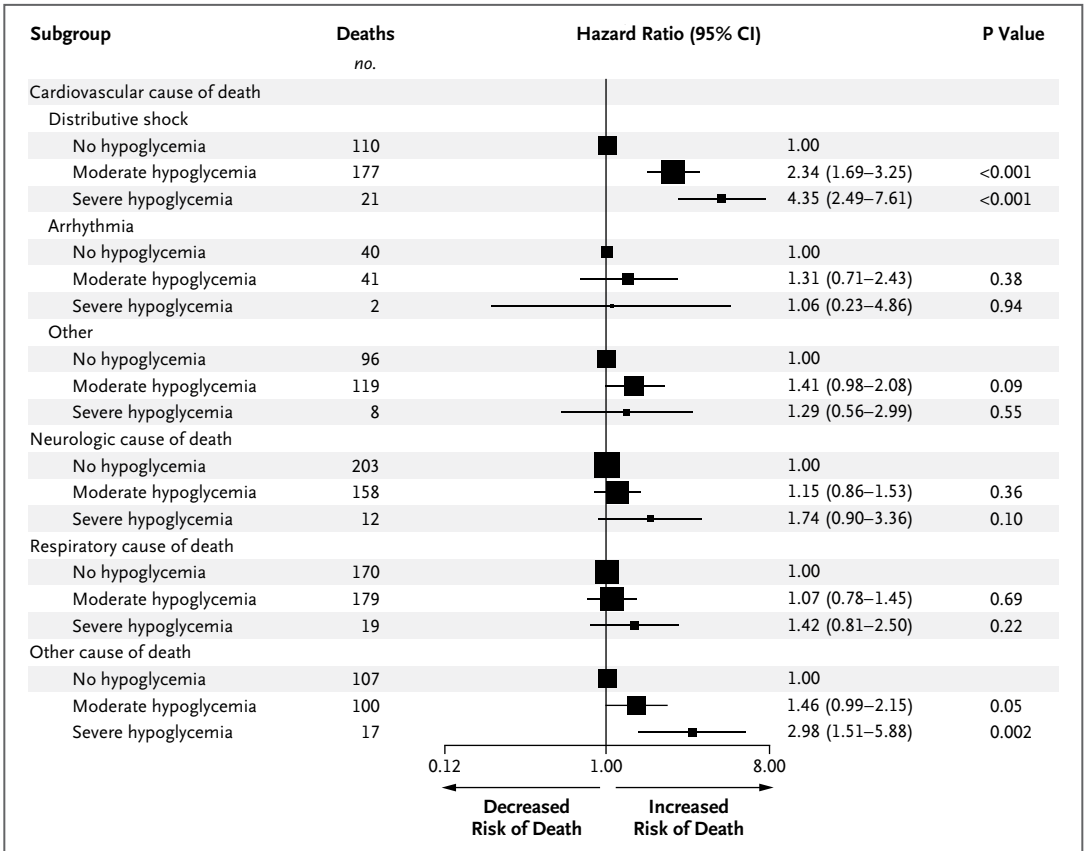

Figure 4. Hazard Ratio for Death from Specific Causes According to the Occurrence of Moderate or Severe Hypoglycemia.

The hazard ratio for death from distributive (vasodilated) shock was significantly higher for patients with moderate or severe hypoglycemia than for those who did not have hypoglycemia. Patients with severe hypoglycemia also had an increased hazard ratio for death from miscellaneous causes. The size of the squares is proportional to the number of deaths.

significantly increased hazard ratio for death from distributive (vasodilated) shock ($P<0.001$ for both comparisons). Patients who had severe hypoglycemia also had an increased hazard ratio for death from causes other than cardiovascular, neurologic, or respiratory causes ($P=0.002$) (Fig. 4).

DISCUSSION

In the NICE-SUGAR study, moderate and severe hypoglycemia occurred frequently and was predominantly observed in patients assigned to intensive glucose control. The risk factors for hypoglycemia were similar to those identified in previous studies.[24,25] Although hypoglycemia was significantly more common among patients assigned to intensive versus conventional glucose control, the association of hypoglycemia with death was similar in the two groups. Adjustment for potential baseline and postrandomization confounders attenuated the risks, but the associations remained significant. These findings are supported by data from smaller, randomized, controlled trials and from observational studies.[8,11,14-17]

In our study, the association between hypoglycemia and death was strong. However, our study design cannot prove causality. Characteristics that may help establish a causal relationship between death and exposure to potential harm include the strength of the association, its consistency, its specificity (i.e., whether the association is stronger for death from a specific cause), its temporal pattern, the presence of a dose–response relationship, the plausibility of the association, and whether manipulating similar factors improves the outcome.[26] Our data allow us to comment on some of these characteristics.

Even after adjustment for events occurring after the first episode of hypoglycemia, moderate hypoglycemia was associated with an increase in the risk of death of 40%, and severe hypoglycemia with a doubling of the risk. The associations were consistent across the subgroups of patients we examined.

For both moderate and severe hypoglycemia, the association was strongest for death from distributive shock. In addition, the association was stronger among patients with severe hypoglycemia than among those with moderate hypoglycemia, and was stronger among those with moderate hypoglycemia that occurred on more than 1 day than among those with moderate hypoglycemia on only 1 day.

A causal relationship is plausible because hypoglycemia may increase mortality by means of impairment of autonomic function, alteration of blood flow and composition, white-cell activation, vasoconstriction, and the release of inflammatory mediators and cytokines.[27-29] These mechanisms are consistent with our finding that the hazard ratio for death from distributive shock was significantly increased among both patients with moderate hypoglycemia and those with severe hypoglycemia. Severe hypoglycemia may also be associated with a prolonged QT interval,[30,31] which confers a predisposition to potentially fatal cardiac arrhythmias, but we did not find a significant association between hypoglycemia and death from arrhythmias in our study.

An alternative explanation is that hypoglycemia occurs as a result of disease processes that confer a predisposition to death and that hypoglycemia thus represents a marker, rather than a cause, of an increased risk of death. Our finding that the hazard ratios were attenuated after adjustment for baseline characteristics and postrandomization factors suggests that substantial confounding was present. Furthermore, the hazard ratio for death was significantly greater, and the time to death shorter, among patients who had severe or moderate hypoglycemia and were not being treated with insulin, as compared with those who were receiving insulin. These findings are similar to those reported by Kosiborod et al. for patients hospitalized with acute myocardial infarction.[32] Thus, spontaneous hypoglycemia appears to identify patients at particularly high risk for death, and in such circumstances hypoglycemia is probably a marker of severe underlying disease processes.

Another possibility is that patients who stay longer in the ICU are more likely to die, and because they are in the ICU longer, they are also more likely to have hypoglycemia. Although we found that hypoglycemia was more common among patients who stayed in the ICU for 7 or more days than among those who stayed for fewer than 7 days, the mortality in this group was not increased, so our data do not support this hypothesis.

Our study has certain limitations. We prospectively collected blood glucose measurements obtained in the ICU, but sampling was intermittent and included measurements made on point-of-care glucose meters, which may overestimate blood glucose concentration.[33,34] As a result, it is possible that a small number of patients had undetected hypoglycemia. We did not collect data on hypoglycemia that occurred after discharge from the ICU, although we still found a significant relationship between hypoglycemia and death when we censored follow-up data at the time of discharge from the ICU. We did not collect biologic samples from our patients, so we can only speculate on the mechanisms linking hypoglycemia to an increased risk of death.

The strengths of our study are its size and its prospective nature. Although the percentage of patients who had severe hypoglycemia was low in comparison with the proportions in other trials of intensive glucose control, the size of the cohort and the large number of events ensure a precise examination of the association between hypoglycemia and death. Prospective and comprehensive data collection provided the opportunity to adjust our analyses for potentially confounding factors.

Our findings confirm that among critically ill patients, moderate and severe hypoglycemia are both strongly associated with an increased risk of death and that the risk is greater among patients who have severe hypoglycemia and among those who have moderate hypoglycemia on more than 1 day. Although our data exhibit some characteristics suggesting a causal relationship, they cannot prove such a relationship. In some patients, particularly those in whom hypoglycemia occurs in the absence of insulin therapy, hypoglycemia appears to be a marker of impending death rather than a cause of subsequent death. However, it would seem prudent to ensure that strategies for managing the blood glucose concentration in critically ill patients focus not only

on the control of hyperglycemia but also on avoidance of both moderate and severe hypoglycemia. According to the current recommendation of the American Diabetes Association,[35] a target blood glucose concentration of 144 to 180 mg per deciliter (8.0 to 10.0 mmol per liter) is likely to reduce the risk of hypoglycemia in critically ill patients.

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

APPENDIX

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