Objective: The implementation of intensive insulin therapy in the intensive care unit is accompanied by an increase in hypoglycemia. We studied the relation between hypoglycemia on intensive care unit mortality, because the evidence on this subject is conflicting.

Design: Retrospective database cohort study.

Setting: An 18-bed medical/surgical intensive care unit in a teaching hospital (Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, The Netherlands).

Patients: A total of 5961 patients admitted to from 2004 to 2007 were analyzed. Readmissions and patients with a withholding care policy or with hypoglycemia on the first glucose measurement were excluded. Patients were treated with a computerized insulin algorithm (target glucose range, 72–126 mg/dL).

Interventions: None.

Measurements and Main Results: All first episodes of hypoglycemia (glucose \(<45\) mg/dL) were derived from 154,015 glucose values. Using Poisson regression, the incidence rates for intensive care unit death and incidence rate ratio comparing exposure and nonexposure to hypoglycemia were calculated. Patients were considered to be exposed to hypoglycemia from the event until the end of intensive care unit admittance. We corrected for severity of disease using the daily Sequential Organ Failure Assessment score. Age, sex, cardiothoracic surgery, sepsis, and diabetes mellitus were also included as possible confounders. Two hundred eighty-eight (4.8%) patients experienced at least one episode of hypoglycemia. Median age was 68 yrs (range, 58–75 yrs), 66% were male, and 6.4% died in the intensive care unit. The incidence rate of death in patients exposed to hypoglycemia was 40 per 1000 intensive care unit days compared with 17 per 1000 intensive care unit days in patients without exposure. The adjusted incidence rate ratio for intensive care unit death was 2.1 (95% confidence interval, 1.6–2.8; \(p < .001\)).

Conclusions: Hypoglycemia is related to intensive care unit mortality, also when adjusted for a daily adjudicated measure of disease severity, indicating the possibility of a causal relationship. (Crit Care Med 2010; 38:1430–1434)

Key Words: hypoglycemia; intensive care unit; intensive insulin therapy; severity of disease; ICU mortality

Learning Objectives
After participating in this activity, the participant should be better able to:
1. Interpret blood glucose levels to properly identify hypoglycemia.
2. Evaluate the effect of glucose protocols on incidence of hypoglycemia.
3. Evaluate the effect of hypoglycemia on intensive care unit mortality.

Unless otherwise noted below, each faculty or staff’s spouse/life partner (if any) has nothing to disclose.

The authors have disclosed that they have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity.

All faculty and staff in a position to control the content of this CME activity have disclosed that they have no financial relationship with, or financial interests in, any commercial companies pertaining to this educational activity.

Visit the Critical Care Medicine Web site (www.ccmjournal.org) for information on obtaining continuing medical education credit.
INTRODUCTION

After completing this CME activity, readers should be able to assess hypoglycemia and evaluate the effect of glucose control protocols on hypoglycemia and the effect of hypoglycemia on mortality.

Hyperglycemia in the intensive care unit (ICU) is common, also in patients without known diabetes, and is related to poor outcome (1). The implementation of strict glucose control with intensive insulin therapy in the ICU, targeting for a fasting morning glucose of 80–110 mg/dL (to convert to mmol/L, multiply by 0.0555) was proven to be beneficial with regard to mortality in the two “Leuven” trials if ICU treatment exceeded 5 and 3 days, respectively (2, 3). Two large multicenter randomized controlled trials were carried out to confirm these results but were terminated prematurely because of high rates of severe hypoglycemia or because the target glucose range was not reached (4, 5). The recently published Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial showed that mortality was increased when the investigators aimed for a blood glucose 81–108 mg/dL in the intensive insulin therapy group as compared to ≤180 mg/dL in the control group (27.5% vs. 24.9%, p = 0.02) (6). Several explanations have already been proposed to explain the conflicting results regarding strict glucose control, including the increased risk of (severe) hypoglycemia that accompanies intensive insulin therapy (7–9). A meta-analysis including the NICE-SUGAR data indicated that intensive insulin therapy was associated with a sixfold increased risk for hypoglycemic events (95% confidence interval [CI], 4.5–8.0). However, the causal relation with mortality in the ICU remains unclear. Several studies have specifically investigated outcomes after hypoglycemia in the ICU and yielded conflicting results (4, 10–13). Because it is possible that hypoglycemia is a risk marker for severe illness or dying, rather than a risk factor for mortality, it is important to correct for severity of disease. All previous studies used the Acute Physiology and Chronic Health Evaluation (APACHE) II score to this purpose, a validated score designed to predict mortality in the first 24 hrs of ICU admittance. To discriminate between hypoglycemia as a risk marker and a risk factor, we reasoned the optimal correction is for severity of disease on the day of the hypoglycemic event. Therefore, in this study, we investigated the relation between hypoglycemia in the ICU and mortality corrected for a measure of severity of disease taken on the day of the hypoglycemic event.

MATERIALS AND METHODS

Design and Setting. We performed a cohort study in an 18-bed mixed surgical/medical ICU in a teaching hospital (Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, The Netherlands). The nurse-to-patient ratio was on average 1:2 and all beds were equipped with a clinical information system. Informed consent was not required according to Dutch Ethical Review Board regulations, because it concerned analysis of anonymized data.

Glucose Regulation Protocol. The glucose regulation algorithm (target range, 72–126 mg/dL) was fully computerized and connected to the clinical information system. The software suggested an insulin infusion rate based on the current glucose value, the rate of glucose change over the previous five measurements, previous insulin drip rates, and given insulin boluses. The software also provided the timing of the next glucose measurement, which could vary between 15 mins and 4 hrs. In case of a glucose measurement <63 mg/dL, the insulin pump was stopped and 20 mL of 30% glucose administered. Glucose was measured 15 mins thereafter and if euglycemia was reached, the insulin pump was restarted at 50% of the previous infusion rate. If still <63 mg/dL, glucose was administered again and the insulin pump was not restarted for at least 2 hrs. In case of a glucose measurement between 63 and 81 mg/dL, the insulin pump infusion rate was decreased with the percentage of decrease between the current and the last glucose value. Within 24 hrs after admission, enteral feeding was started, targeting for 2000 kcal/24 hrs within 48 hrs or 1500 kcal/24 hrs within 24 hrs. In case of gastric retention, a feeding tube was inserted in the duodenum. When normal eating was resumed, the glucose regulation protocol was stopped. The protocol was implemented in 2001 (14).

Hypoglycemia. Glucose was measured from blood samples obtained from an arterial catheter using the Accu-check (Roche/Hitachi, Basel, Switzerland). We obtained all measurements from the clinical information system. Hypoglycemia was defined as one or more glucose measurements ≤45 mg/dL. This is using the same cutoff value we used earlier for the SOFA tertile (15) and the NICE-SUGAR investigators (≤40 mg/dL) (6, 13).

Because the cutoff value for (severe) hypoglycemia in the ICU in different studies ranges from 40–81 mg/dL, we also assessed the risk for ICU death associated with different cutoff values for hypoglycemia: <25, 35, 55, 65, 75, 85, 95, and 105 mg/dL.

Data Collection. All data were extracted from the clinical information system. Patients admitted between January 2004 and January 1, 2008, were included. No changes in the glucose regulation protocol were applied in this period. Readmissions, patients with a withholding care policy and patients who had hypoglycemia at admission were excluded. We collected information on the medical history, demographic variables, and admission diagnosis. For each day of ICU admittance, we calculated the Sequential Organ Failure Assessment (SOFA) score as a measure of severity of disease on that particular day (16). If the SOFA score was not available on the day of ICU discharge, we imputed the SOFA score of the preceding day.

Statistical Analyses. Results are presented as median with interquartile range. We calculated the incidence rate of ICU death per 1000 ICU days for patients with- and without hypoglycemia and calculated the crude incidence rate ratio (IRR), thereby assuming a more or less constant hazard for ICU death. Every calendar day of ICU admittance was counted as 1 day of ICU admittance. When a patient experienced hypoglycemia, we considered the patient to be exposed all subsequent days of the ICU admittance. To correct for severity of disease per day, we divided the daily SOFA scores into tertiles and compared mortality in the exposed with the nonexposed within each SOFA tertile. We created tertiles to maintain sufficient power for multivariate analyses. Using Poisson regression, we adjusted the IRR for the altering SOFA tertile. We also included the interaction between SOFA tertile and ICU admission days in the model (SOFA tertile × ICU admission days), because the predictive value of the SOFA score differs when patients are admitted longer. Furthermore, we adjusted for admission diagnosis of sepsis according to the APACHE II diagnostic criteria, because this can cause hypoglycemia and is also related to ICU mortality (17). Diabetes mellitus is known to predispose patients to hypoglycemia in the ICU (17); however, it might affect outcome positively (18) and was therefore included in the analyses. Cardiothoracic surgery was also included as a potential confounder, because mortality among cardiothoracic patients is generally lower and they differ with respect to several demographic and physiological characteristics (19).

Finally, the analyses were adjusted for age and sex. The same analysis was performed for different cutoff values for hypoglycemia. All statistical analyses were performed in SPSS 16.0 (SPSS Inc, Chicago, IL).

RESULTS

From 6725 admissions, 5961 patients were eligible for analyses after excluding 656 readmissions and patients with a withholding care policy (n = 86) or glucose ≤45 mg/dL according to their first
In total, we collected 20,737 SOFA scores (1152 missing scores [5.6%]), mainly SOFA scores on the discharge day, of which the tertiles ranged from 0 to 4, 5 to 6, and >6.

**ICU Mortality and Hypoglycemia.** The incidence ratio of ICU death was 19 per 1000 ICU days. The overall incidence ratio for ICU death after experiencing a hypoglycemic event was 40 per 1000 ICU days as compared to 17 per 1000 ICU days without a hypoglycemic episode, crude IRR 2.3 (95% CI 1.8–3.1; p < .001). The incidence ratios after experiencing hypoglycemia were higher across all SOFA score ranges (Fig. 1). After adjusting for age, sex, admission for cardiothoracic surgery, sepsis, SOFA score, ICU days, and the interaction between SOFA score and ICU days, the adjusted IRR was to 2.1 (95% CI, 1.6–2.8; p < .001). The crude incidence ratio for patients experiencing only one episode of hypoglycemia was 36 per 1000 ICU days as compared to 42 per 1000 ICU days for patients with more than one episode (IRR, 1.2; 95% CI, 0.7–2.0; p = .58). When the APACHE II score was used to correct for severity of disease, instead of the daily SOFA score, the IRR for ICU death was 1.6 (95% CI, 1.2–2.1).

Figure 2 shows the adjusted IRRs for the different cutoff values for hypoglycemia in the ICU. There was an increased risk for ICU death up to the cutoff value of 85 mg/dL (IRR, 1.4; 95% CI, 1.1–1.8; p = .006). With cutoff values >85 mg/dL, no effect on IRR for ICU death was found (IRR, 1.1; 95% CI, 0.9–1.4; p = .44).

**DISCUSSION**

In this cohort study, we showed that hypoglycemia (≤45 mg/dL) in the ICU is accompanied by an increase in ICU death 2.1 (95% CI, 1.6–2.8; p < .001) after adjusting for the daily SOFA score over time.

In a previous nested case–control study, we did not find an association between hypoglycemia and in-hospital death (hazard ratio, 1.03; 95% CI, 0.68–1.56) in a relatively small sample of 156 hypoglycemic events (13). Arabi and coworkers (12) also found no significant relation between hypoglycemia and ICU mortality. In contrast with these findings, Kinsley et al (11) found in a small retrospective case–control-designed study that hypoglycemia (<40 mg/dL) was associated with an increased mortality risk (odds ratio, 2.28; 95% CI, 1.41–3.70) in a population that was only partly treated with intensive insulin therapy. Also, Bagshaw et al (10) showed in a large multicenter ICU cohort (n = 66,184) that the odds ratio for ICU mortality after exposure to a glucose value <81 mg/dL was 1.41 (95% CI, 1.31–1.54). However, this study was limited to the first 24 hrs of ICU admission and a relatively small number of glucose values per patient (approximately two) were collected.

All previous studies used the APACHE II score to correct for disease severity (20).

We excluded patients with severe hypoglycemia as the first glucose measurement (n = 22). The patient characteristics are displayed in Tables 1 and 2. In total, 154,015 glucose values were collected, a median of 11 values per day per patient (interquartile range, 6–14). Median age was 68 yrs (interquartile range, 58–75); 66% of the population was male, and 6.4% of the patients died in the ICU. Patients were in target range a median of 42% of the time (interquartile range, 17–56) and 288 (4.8%) of patients encountered one or more episodes of hypoglycemia (≤45 mg/dL) and of these, 113 patients experienced more than one episode.
ment. This was because these patients were not under strict glucose control before the event and spontaneous hypoglycemia can be a marker of severe disease (21–23).

A strength of the current study is that we attempted to adjust for severity of disease as a changing variable over time instead of using the APACHE II score. Although APACHE II is validated to predict mortality, it is determined at ICU admission and does not take any changes thereafter into account. The SOFA score is a measure of disease severity that it is updated daily during admittance and therefore seems to provide a better distinction between hypoglycemia as a risk factor or risk marker. The use of the SOFA score is limited by the interaction with time spent in the ICU and different predictive power of identical SOFA scores depending on the failing organ systems that contribute to the score (24). However, in the current study, it was the best available predictive score that could be assessed on a daily basis and it is validated to discriminate between ICU survivors and nonsurvivors (16, 24). Furthermore, we have attempted to correct for the interaction with time spent in the ICU by including this in the model. After experiencing a hypoglycemic event, we considered patients to be exposed the remaining days of the ICU admittance, because from a pathophysiological viewpoint, hypoglycemia may cause damage that is, at least during the ICU stay, likely to be sustained.

Hypoglycemia may contribute to ICU mortality by inducing neuroglycopenia with neuronal cell loss and hypoglycemic coma, especially after hyperglycemic reperfusion (13, 25, 26). Furthermore, hypoglycemia might provoke ischemia in pre-existing vascular disease in patients with diabetes (27) and it has also been shown to induce platelet activation and inflammation in an experimental setting (28–30). Hypoglycemia could thus contribute to ICU mortality by aggravating overall illness.

Another strength of this study is that adequate glycemic control was achieved while the hypoglycemia rate was low compared with other studies (31). Our study is limited by its single-center origin. However, there was a high quality of data collection, because all clinical information and laboratory values were directly or even automatically stored in the computerized clinical information system.

The additional analyses we performed investigating different cutoff values for hypoglycemia showed that up to 85 mg/dL, hypoglycemia was associated with a significant increased risk for ICU death. This is in concordance with the study of Bagshaw and colleagues, who found an increased mortality risk when defining hypoglycemia as <81 mg/dL. The recently published NICE-SUGAR study was the start of a debate about the optimal blood glucose range in the ICU (6) and a higher, perhaps safer, range than the tight range of the Leuven studies is proposed (2). The present and previous studies thus suggest that hypoglycemia might be harmful when aiming for strict glycemic control, targeting for a range between 72 and 126 mg/dL (5).

Future investigations looking at strict glycemic control in the ICU should consider the possibility that even glucose values <85 mg/dL are harmful. Higher target ranges for glucose control will diminish the incidence hypoglycemia and seem justified.

CONCLUSIONS

Hypoglycemia is related to ICU mortality, also when adjusted for a daily adjudicated measure of disease severity. Although residual confounding can never be ruled out, a causal relationship between hypoglycemia and ICU mortality is a likely possibility.

After completing this CME activity, readers should be better able to assess hypoglycemia and evaluate the effect of
glucose control protocols on hypoglycemia and the effect of hypoglycemia on mortality.

REFERENCES