Blood glucose control and monitoring in the critically ill
van Hooijdonk, R.T.M.

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Chapter 7

Associations Between Dynamics of the Blood Glucose Level after Hypoglycemia and Intensive Care Unit Mortality: A Retrospective Multicenter Study

Roosmarijn T.M. van Hooijdonk, Jan M. Binnekade, Ameen Abu–Hanna, Floris van Braam Houckgeest, Lieuwe S. Hofstra, Janneke Horn, Michael A. Kuiper, Nicole P. Juffermans, Huub L.A. van den Oever, Johannes P. van der Sluijs, Peter E. Spronk, Marcus J. Schultz for the Tight Glucose Control Group

Submitted
Abstract

Introduction
Dynamics of the blood glucose level after hypoglycemia could be associated with outcome in critically ill patients. In particular a transition from hypoglycemia to hyperglycemia is considered harmful. We investigated associations between changes in the blood glucose level within eight hours after hypoglycemia and intensive care unit (ICU) mortality in patients under moderately strict to strict glucose control.

Methods
This is a retrospective analysis in patients who developed hypoglycemia (blood glucose level below 70 mg/dL) in a pooled cohort from seven ICUs in the Netherlands over six years. Readmitted patients, and patients in whom no follow-up blood glucose measurement were performed within eight hour following hypoglycemia were excluded from this analysis. We compared ICU mortality in quartiles of the peak blood glucose level (the peak glucose), defined as the highest blood glucose level, the delta of blood glucose levels (the delta glucose), defined as the difference between minimum and maximum blood glucose level, and the standard deviation of blood glucose levels (the SD glucose), all calculated from blood glucose levels obtained within the first eight hours after occurrence of hypoglycemia, and determined the independent association with ICU mortality.

Results
Out of 19,505 patients, 4,512 patients developed at least one episode of hypoglycemia. There was a U–shaped association in non–elective admitted patients between changes in blood glucose levels following hypoglycemia and ICU mortality, with a higher mortality in the lowest and the highest quartiles of the peak glucose, the delta glucose and the SD glucose; in electively admitted patients, mortality was highest in the lowest quartiles of the peak glucose and the SD glucose. In multivariate analyses, an independent association with ICU mortality was only found for the lowest quartile of the delta glucose and the lowest quartile of the SD glucose.

Conclusions
In patients under moderately strict to strict glucose control poor recovery from hypoglycemia, but not a transition from hypoglycemia to hyperglycemia, has an independently association with increased ICU mortality.
Introduction
As critically ill patients frequently have an impaired physiological response to hypoglycemia with counter-regulatory hormones, they may be more vulnerable to long-lasting hypoglycemia [1, 2]. In addition, warning signals of hypoglycemia, such as palpitations, tremor, drowsiness, confusion and hunger are easily missed or misinterpreted in critically ill patients, and sedatives can suppress these symptoms [2], preventing caregivers from a timely correction of the blood glucose level. Notably, occurrence of hypoglycemia increases with more intensive use of insulin [3–10], which could offset the beneficial effect of strict glycemic control in critically ill patients [8–10].

Hypoglycemia can cause severe harm, including cerebral damage, epileptic insults, and even permanent coma. Therefore it is generally considered to correct hypoglycemia as soon as possible [11]. However, a transition of hypoglycemia to hyperglycemia could also be harmful, as this is associated with an hampered endothelial function, increased oxidative stress and inflammation in non-critically ill diabetes patients [12], and increased superoxide production and neuronal death in rats [13]. Nevertheless, in fear of harmful effects of hypoglycemia, intensive care unit (ICU) nurses usually respond to hypoglycemia with abrupt stopping insulin infusion and administering of (sometimes large) boluses of dextrose [14].

It is highly uncertain what is more harmful in ICU patients under glycemic control with insulin: poor recovery from hypoglycemia or a transition form hypoglycemia to hyperglycemia. Based on studies in animals and non-critically ill patients we hypothesized that in particular the transition from hypoglycemia to hyperglycemia is independently associated with ICU mortality of critically ill patients. We tested this hypothesis in large cohorts of ICU patients developing hypoglycemia under moderately strict or strict glucose control with insulin.

Materials and Methods
Study design and ethical approval
This is a retrospective analysis of pooled cohorts from seven hospitals in the Netherlands from January 2007 till December 2012. Six teaching hospitals participating in a national project of implementation of strict glucose control (see ‘study settings and local guidelines for blood glucose control’ and data supplement table 1) [15] and one university hospital provided blood glucose and outcome data for this analysis. The Institutional Review Board of the Academic Medical Center, Amsterdam, The Netherlands, approved the study protocol and waived the need for ethical approval and individual patient consent to collect and analyze data from registries that exclude patient-identifying information.

Study settings and local guidelines for blood glucose control
All ICUs were mixed medical–surgical ICUs with their patients under the direct care of a team consisting of board–certified ICU nurses and ICU physicians. The nurse to patient ratio was always equal or higher than 1:2.

In the six hospitals involved in the national implementation project (Gelre Hospital, Apeldoorn; Medical Center Haaglanden, The Hague; Tergooi Hospital, Hilversum; Deventer Hospital, Deventer; Scheper Hospital, Emmen; and Medical Center Leeuwarden, Leeuwarden, The Netherlands), blood glucose control followed
the 2004 Surviving Sepsis Campaign Guidelines, aiming for blood glucose levels < 150 mg/dL [16] before implementation of strict glycemic control. For this, ICU nurses administered insulin either intravenously or subcutaneously, following blood glucose measurements at the bedside or in the central laboratory using either capillary or arterial blood samples. Recommendations in the local guidelines were rather loosely defined, including loose suggestions on timing of follow-up of blood glucose measurements. The local guidelines did not recommend on how to correct hypoglycemia. Recovery from hypoglycemia, though, was often established by abrupt stops in insulin infusion and the administration of large intravenous boluses of dextrose. See also data supplement (Table S1).

Then the ICU nurses of three of these six hospitals (Gelre Hospital, Medical Center Haaglanden and Tergooi Hospital) developed and implemented an evidence-based guideline for strict glucose control, aiming for blood glucose levels between 80 and 110 mg/dL. The new guideline knew two important differences with the local guidelines in use before start of the project: the new guideline had strict recommendations on timing of blood glucose measurements, with at least one measurement every four hours; and patients were allowed to gradually recover from hypoglycemia, explicitly avoiding abrupt stops of insulin infusion as well as avoiding administration of dextrose [15]. The three other ICUs (Deventer Hospital, Schepet Hospital and Medical Center Leeuwarden) did not change their local guidelines and continued targeting blood glucose levels below 150 mg/dL.

In the ICU in the university hospital (Academic Medical Center), the local guideline for blood glucose control did not change during the study period included in the present analysis. ICU nurses titrated insulin aiming at blood glucose levels between 90 and 144 mg/dL. For this, continuous insulin infusion was started when the blood glucose level exceeded 144 mg/dL, and adjustments were made following a flow chart. The flow chart provided advices regarding timing of follow-up blood glucose measurement, which could vary from 30 minutes until 4 hours. Blood glucose levels were measured in blood samples obtained via an arterial catheter using local blood gas analyzers. Insulin infusion was stopped, and a bolus of glucose was usually given when the blood glucose level dropped below 61 mg/dL.

Inclusion and exclusion criteria
Readmitted patients and patients < 18 years old were excluded from the present analysis. Patients were included when developing hypoglycemia, defined as a blood glucose level below 70 mg/dL [17–19]. Patients in whom hypoglycemia occurred but in whom no follow-up blood glucose measurement within eight hours were performed were also excluded from the analysis.

Data collection
Blood glucose measurement data were retrieved from the hospitals’ clinical information systems and linked to patient data. Prospectively collected admission diagnosis, demographic data, Acute Physiology and Chronic Health Evaluation (APACHE) II scores and Simplified Acute Physiology Scores (SAPS) II, and outcome data were extracted from the Dutch National Intensive Care Evaluation (NICE) registry [20].

Endpoint and definitions
The endpoint was ICU mortality, defined as death in the ICU. We used a cut-off of 70 mg/dL for hypoglycemia, because two previous studies showed that a blood glucose
level below 70 mg/dL was associated with increased mortality, an association that was independent of local guidelines for blood glucose control [18, 19]. A period of eight hours after hypoglycemia was chosen, for two reasons: first, we expected all corrections, including possible transitions from hypoglycemia to hyperglycemia, to be captured within this timeframe; second, sufficient numbers of blood glucose levels are needed to calculate the metrics of blood glucose variability used in the present analysis; the number of blood glucose measurements, including the index measurement was expected to be three or more within eight hours.

**Categorization of blood glucose levels following hypoglycemia**

We categorized blood glucose levels following hypoglycemia using quartiles of the peak blood glucose level (the peak glucose), the delta of blood glucose levels (the delta glucose) and the standard deviation of blood glucose levels (the SD glucose), all calculated from blood glucose levels obtained within eight hours after the first blood glucose measurements revealing hypoglycemia. Peak glucose was defined as the highest blood glucose level within that time frame; delta glucose was defined as the difference between the lowest and highest blood glucose level within that time frame; and SD glucose was defined as the standard deviation of all blood glucose levels within that time frame [17, 21].

**Analysis plan**

First, we determined ICU mortality in the groups of quartiles of the peak glucose, the delta glucose and the SD glucose, and in electively admitted patients versus non–elective patients.

Then, we performed three separate multivariate logistic regression models examining the independent associations between the three metrics for blood glucose variability and ICU mortality. The quartiles with the lowest ICU mortality were used as reference categories. Continuous covariates were fitted using restricted cubic splines. We defined a covariate as a confounder when it changed the Odds ratio for one of the quartiles by at least 10% when entered into each model [22]. As such, the APACHE II score, elective versus non–elective admission, the median blood glucose level during stay in ICU, the lowest blood glucose level in the hypoglycemic period, duration of hypoglycemia in minutes and one versus more than one hypoglycemic episode were considered significant confounders. As all these covariates showed no collinearity (the Pearson correlation coefficients were all under 0.5), they were all included in multivariate analysis. Other covariates tested for confounding but not changing the Odds ratio by at least 10%, and thus not included in multivariate analysis, included, the local guideline for blood glucose control (see Table S1), and the standard deviation of the mean blood glucose level calculated from blood glucose levels obtained during the entire stay in ICU.

We performed several post–hoc analyses. First, we repeated the complete analysis using a cut–off of 60 mg/dL, instead of 70 mg/dL, for hypoglycemia. Second, to provide more insight, we summarized ICU mortality and metrics of blood glucose control per local blood glucose guideline (as presented in Table S1), and we summarized APACHE II score and admission type per quartile of the peak glucose, the delta glucose and the SD glucose.

**Statistical analysis**

Data were reported as means with their standard deviations, medians with their
interquartile ranges, or percentages, where appropriate. Data were compared using the Student’s \( t \)-test, the Mann–Whitney \( U \) test or the Chi–Square test. Blood glucose metrics calculated from blood glucose levels obtained within eight hours after hypoglycemia and blood glucose metrics calculated from blood glucose levels obtained during the entire stay in ICU were summarized for the total cohort and compared for patients who died or survived the ICU. Analyses were performed using R (version: 3.1.1; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was considered to be at a \( P \)–value < 0.05. When appropriate, statistical uncertainty was expressed by the 95% confidence levels.

## Results

### Patients

The seven cohorts consisted of 19,505 patients, of which 4,512 patients (23%) were included in the present analysis (figure 1). Demographic data and commonly used metrics of blood glucose control are presented in tables 1 and 2. Patients who died in the ICU were older, sicker according to the disease severity scores in the first 24 hours of stay in ICU, and were more frequently after emergency surgery. Length of stay in the ICU was shorter in patients who died in the ICU.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Died in ICU ( N = 966 )</th>
<th>Survived ICU ( N = 3,546 )</th>
<th>( P )–value</th>
<th>All patients ( N = 4,512 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years, median [IQR]</td>
<td>70 [59–78]</td>
<td>67 [56–75]</td>
<td>&lt;0.001</td>
<td>67 [56–76]</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>563 (58)</td>
<td>2063 (58)</td>
<td>0.983</td>
<td>2626 (58)</td>
</tr>
<tr>
<td>Non–elective admission, no (%)</td>
<td>874 (91)</td>
<td>2629 (75)</td>
<td>&lt;0.001</td>
<td>3503 (78)</td>
</tr>
<tr>
<td>APACHE II scores, median [IQR], 12 missing</td>
<td>28 [22–34]</td>
<td>20 [15–26]</td>
<td>&lt;0.001</td>
<td>22 [16–28]</td>
</tr>
<tr>
<td>ICU LOS – days, median [IQR]</td>
<td>4.8 [2.1–11.8]</td>
<td>5.6 [2.7–10.9]</td>
<td>N.A.</td>
<td>5.4 [2.5–11.1]</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; BMI, body–mass index; APACHE, Acute Physiology and chronic Health Evaluation; SAPS, Simplified Acute Physiology Score LOS, length of stay; ICU, intensive care unit; NA, not applicable

### Table 2. Glucose metrics calculated from blood glucose levels obtained during over the entire stay in ICU

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Died in ICU ( N = 966 )</th>
<th>Survived ICU ( N = 3,546 )</th>
<th>( P )–value</th>
<th>All patients ( N = 4,512 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median blood glucose level – mg/dL, median [IQR]</td>
<td>115 [101–133]</td>
<td>115 [105–133]</td>
<td>0.014</td>
<td>115 [105–133]</td>
</tr>
<tr>
<td>Minimum blood glucose level – mg/dL, median [IQR]</td>
<td>50 [40–59]</td>
<td>56 [45–63]</td>
<td>&lt;0.001</td>
<td>54 [43–61]</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range
There were some typical differences in blood glucose metrics calculated over the entire stay in ICU between patients who died in the ICU and patient who survived: time interval between measurements was shorter, the median blood glucose level was slightly but significantly lower, and the metrics for blood glucose variability and the highest and lowest blood glucose levels suggested more fluctuations of the blood glucose level in patients who died.

Median time between ICU admission and the first hypoglycemic event was 26 [11–60] hours; median time between the last hypoglycemic event and death in patients who died in the ICU was 24 [9–66] hours. ICU mortality was independent of the number of hypoglycemic episodes (20.4% in 2,232 patients with one single hypoglycemic event versus 22.4% in 2,280 patients with more than one hypoglycemic event, \( P = 0.105 \)).

Median time between the blood glucose measurement showing hypoglycemia and the first follow–up measurement was 79 [52–128] minutes; the median number of blood glucose measurements and the median time between those measurements within the eight–hour time frame following hypoglycemia was 4 [3–6] and 114 [83–158] minutes, versus 3 [2–4] per eight hours and 130 [111–179] minutes between blood glucose measurements outside this time frame.

**Metrics of blood glucose variability within the eight hours following hypoglycemia**

The peak glucose, the delta glucose and the SD glucose are presented in table 3. All three metrics were lower in patients who were treated with the new guideline for blood glucose control, in line with its recommendation to have a patient gradually recover from hypoglycemia, explicitly avoiding abrupt stops of insulin infusion as well
as avoiding administration of dextrose.

ICU mortality in quartiles of peak glucose, delta glucose and SD glucose are shown in figure 2. Visual inspection suggested a U–shaped relationship between the peak glucose, the delta glucose and the SD glucose and ICU mortality, with the highest mortality in the lowest and highest quartiles. In non–electively admitted patients a U–shaped relationship was suggested between all three metrics and ICU mortality; in electively admitted patients, a U–shaped relationship was only suggested for the SD glucose. APACHE II scores and admission types are summarized per quartile of peak glucose, delta glucose and SD glucose in Table S2.

Table 3. Peak glucose, delta glucose and SD glucose calculated from blood glucose measurements obtained within 8 hours after occurrence of hypoglycemia

<table>
<thead>
<tr>
<th>Blood glucose target of the guideline for blood glucose control in use</th>
<th>80–110 mg/dL</th>
<th>90–144 mg/dL</th>
<th>&lt; 150 mg/dL</th>
<th>P–value</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1,184</td>
<td>N = 1,570</td>
<td>N = 1,758</td>
<td></td>
<td></td>
<td>N = 4,512</td>
</tr>
</tbody>
</table>


Abbreviations: IQR, interquartile range; SD, standard deviation

Univariate and multivariate analysis

In the univariate analysis, only the lowest quartile of the peak glucose, the delta glucose and the SD glucose were associated with increased ICU mortality compared to the reference categories (figure 3).

In the multivariate analysis of the peak glucose, when including the APACHE II score and elective versus non–elective admission as confounder, the lowest quartile remained to be associated with ICU mortality. However, when including the APACHE II score, elective versus non–elective admission, the median blood glucose level calculated from blood glucose levels obtained during the entire stay in ICU, duration of hypoglycemia and one versus more than one hypoglycemic episode, this association disappeared. Using a similar approach in multivariate analyses of the delta glucose and the SD glucose, the lowest quartiles of the delta glucose and the SD glucose remained to show a significant association with ICU mortality (figure 3).

Post–hoc analyses

The post–hoc analysis using 60 mg/dL as a cut–off for hypoglycemia showed similar associations as with the analysis using a cut–off of 70 mg/dL (results are shown in the data supplement, Tables S3, S4, and S5 and Figure S1 and S2). The post–hoc analysis for the three different blood glucose guidelines in use showed similar associations which each guideline (Table S6 and Figure S3).

Discussion

We examined the relationship between dynamics of the blood glucose level in the first eight hours after hypoglycemia and ICU mortality in a large cohort of ICU
Figure 2. Intensive care unit (ICU) mortality per quartile of peak glucose (A and D), per quartile of delta glucose for all patients (B and E) and per quartile of SD glucose (C and F); upper graphs (A to C) show mortality for all patients, lower graphs (D to F) show mortality of elective (open bars) and non–elective patients (closed bars). Ranges of the quartiles of the peak glucose, delta glucose and SD glucose are presented in table 2.

The later remains speculative, though, since we did not study corrections of hypoglycemia, but changes in the blood glucose level after hypoglycemia, which is not necessarily the same. Indeed, we analyzed association between dynamics of the blood glucose level and ICU mortality, and not association between the
Figure 3. Odds ratios in the univariate (squares), in the multivariate model including baseline confounders (open circles) and in the multivariate model including all confounders (closed circles) per quartile of the peak glucose (reference: second quartile), delta glucose (reference: second quartile) and SD glucose (reference: third quartile). The multivariate model for peak glucose included the following confounders: the APACHE II score, elective versus non-elective admission, the median blood glucose level during stay in ICU, duration of hypoglycemia in minutes and one versus more than one hypoglycemic episode; the multivariate model for delta glucose included the APACHE II score, elective versus non-elective admission, the median blood glucose level during ICU, the lowest blood glucose level during the hypoglycemic episode, the duration of hypoglycemia and one versus more than one hypoglycemic episode; the multivariate model for SD glucose included the median blood glucose level during ICU, the lowest blood glucose level during the hypoglycemic period and the duration of hypoglycemia.
way hypoglycemia was corrected and ICU mortality, as we had neither access to (changes in) insulin infusion rates (during and after hypoglycemia) nor the amount of dextrose, if given in boluses in response to hypoglycemia. Notably, the associations between changes in blood glucose levels after hypoglycemia were independent from the blood glucose control guidelines in use.

Findings in our study are, at least in part in line with those from previous studies. A previous study in critically ill children showed no association between hypoglycemia and neurocognitive impairment in critically ill children [5, 23]. The investigators suggested that transient hyperglycemia during critical illness might be more dangerous than brief hypoglycemia [23]. Notably, duration of hypoglycemia has been found to be significantly different between surviving and non–surviving ICU patients [24]. The finding that duration of hypoglycemia was a confounder for the associations between the peak glucose, delta glucose and SD glucose and ICU mortality in the present analysis is also in line with these earlier findings.

The results of the present study are in contrast with finding in animal studies and non–critically ill patients suggesting harm from transitions from hypoglycemia to hyperglycemia [12, 13, 25]. It should be noted, though, that we focused on ICU mortality, an outcome that is influenced by several factors beyond glucose control. Also, we cannot exclude detrimental effects of transition of hypoglycemia to hyperglycemia, such as neuronal death, endothelial dysfunction or increased oxidative stress as found in the abovementioned previous studies [12, 13, 25]. Additional studies are needed to test these hypotheses.

The median time between last hypoglycemic event and death in patients who died in the ICU of 24 [9–66] suggests that patients had refractory hypoglycemia, i.e., as part of multi–organ failure at the end of life, which could even have been left untreated. Unfortunately, the design of the study did not allow a further analysis of neither the cause of hypoglycemia, nor its treatment. This could explain the found associations between poor recovery from hypoglycemia and ICU mortality.

The median time between the blood glucose measurement showing hypoglycemia and the first follow–up measurement was approximately 80 minutes, and the median time between follow–up blood glucose measurements within the time frame of eight hours was shorter than the median time between measurements outside this time window, suggesting that there was an urgency to monitor the blood glucose levels more intensely after hypoglycemia. Nevertheless, 80 minutes could be seen as far too long. Even though one could say that ‘not measuring a blood glucose level’ is not similar to ‘not acting upon a low blood glucose level’, we cannot exclude the possibility that the link between poor recovery from hypoglycemia and mortality may be explained by a substandard handling of hypoglycemia. Timing of follow–up measurement should improve.

Our study has several limitations. First, as pointed out above, we only assessed ICU mortality and not more subtle endpoints such as neurocognitive outcomes. Furthermore, as also mentioned above we could only analyze changes in blood glucose levels following hypoglycemia, and not the way in which hypoglycemic episodes were corrected. We chose the timeframe of eight hours rather arbitrarily, and it could be that results differ when using other timeframes. Furthermore, we chose to analyze the data by creating quartiles; consequently we had blood glucose levels within eight hours after hypoglycemia in the lowest quartile that are not considered
‘hypoglycemic’, and in the highest quartile that are not considered ‘hyperglycemia’.

Furthermore, the current dataset involved blood glucose metrics under three different guidelines of blood glucose control with differences in blood glucose monitoring, insulin titrations and administration, and, most important different advices on how to treat hypoglycemia: the strict guideline recommended a more gradual recovery from hypoglycemia while the ‘loose’ guidelines allowed nurses to give (too large) boluses of dextrose. In addition, measurements were performed with blood gas analyzer, in central laboratory but also with less accurate meters at the bedside. Especially in the lower ranges the measurements performed with bedside meters are less accurate [26], which might influenced the results. However, the associations found were independent from the protocol in use.

Strengths of our study includes its generalizability, due to the size and the variety of patients, from university and community hospitals, treated with three different guidelines of blood glucose control with different guidelines on how to treat hypoglycemia. The three guidelines provided us with the opportunity to investigate a wide range of peak glucose, delta glucose and SD glucose values.

Conclusions
In patients under moderately strict to strict glucose control poor recovery from hypoglycemia is independently associated with increased ICU mortality, while a transition from hypoglycemia to hyperglycemia is not.

Competing Interest
R.T.M. van Hooijdonk reported consulting work for Medtronic Inc., GlySure Ltd and research support from Medtronic Inc and Optiscan Biomedical – all fees and financial supports were paid to the institution. M.J. Schultz reported receiving consultant fees from Medtronic Inc., GlySure Ltd., Edwards Life Sciences and Roche Diagnostics and financial support from Medtronic Inc. and OptiScan Biomedical – all fees and financial supports were paid to the institution. J.M. Binnekade, J. Horn, N.P. Juffermans, F. van Braam Houckgeest, J.P. van der Sluijs, A. Abu–Hanna and P.E. Spronk reported no relevant disclosures.

Funding/Support
The project of implementation of strict glucose control was supported in full by a peer–reviewed grant from ZonMW (Netherlands Organization for Health Research and Development (Zorgonderzoek Medische Wetenschappen), a national organization that promotes quality and innovation in the field of health research and health care, initiating and fostering new developments. As a peer–review funding body, ZonMW provided constructive comments on the study design. ZonMW had no role in guideline development; the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

Authors’ Contributions
Study concept and design: R.T.M. van Hooijdonk, J.M. Binnekade, M.J. Schultz
Acquisition of data: R.T.M. van Hooijdonk, J.M. Binnekade, F. van Braam Houckgeest,
## Data Supplement

### Table S1. Local guidelines for blood glucose control with insulin

<table>
<thead>
<tr>
<th></th>
<th>Moderately strict</th>
<th>Strict</th>
<th>University</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycemic targets</strong></td>
<td>&lt; 150 mg/dL</td>
<td>80–110 mg/dL</td>
<td>90–144 mg/dL</td>
</tr>
</tbody>
</table>
| **Insulin administra-
  tion**             | Infusion of insulin intravenously or subcutaneously | Continuous infusion of insulin intravenously | Continuous infusion of insulin intravenously |
| **Type of blood glu-
  cose monitor**     | Bedside or central laboratory | Bedside blood glucose | Blood gas analyzer |
| **Source of blood**  | Capillary or arterial | Arterial blood  | Arterial blood      |
| **Timing of measure-
  ments**             | No recommendations | Every 4 hours at fixed times, and in between as frequent as deemed necessary by attending | 30 minutes to 4 hours |
| **Correction of hypo-
  glycemias**         | No recommendation, often established with abrupt stops and large boluses of dextrose infusion | Gradually recover from hypoglycemia, explicitly avoiding abrupt stops of insulin infusion as well as the administration of dextrose that might lead to hyperglycemia after hypoglycemia | Insulin infusion was stopped, and a bolus of glucose was usually given when the blood glucose level dropped < 61 mg/dL |
| **Which data is used?** | 6 ‘control’ hospitals during 3 year | 3 ‘implementation’ hospitals during 2 years after implementation of guideline for strict glucose control | 1 university hospital during 6 years |

P.E. Spronk, J.P. van der Sluijs, A. Abu–Hanna.
Analysis and interpretation of data: R.T.M. van Hooijdonk, J.M. Binnekade, M.J. Schultz
Drafting of the manuscript: R.T.M. van Hooijdonk, M.J. Schultz
Critical revision of the manuscript for important intellectual content: R.T.M. van Hooijdonk, J.M. Binnekade, J. Horn, N.P. Juffermans, F. van Braam Houckgeest, J.P. van der Sluijs, A. Abu–Hanna, P.E. Spronk and M.J. Schultz
All authors read and approved the manuscript.
Table S2. APACHE score and admission type per quartile of the peak glucose, the delta glucose and the SD glucose

<table>
<thead>
<tr>
<th></th>
<th>Peak Glucose</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 101 mg/dL</td>
<td>101-126 mg/dL</td>
<td>126-160 mg/dL</td>
<td>&gt; 160 mg/dL</td>
</tr>
<tr>
<td>Admission type, non-elective admission no (%)</td>
<td>903 (80)</td>
<td>889 (77)</td>
<td>836 (78)</td>
<td>785 (78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta Glucose</td>
<td>&lt; 43 mg/dL</td>
<td>43-69 mg/dL</td>
<td>69-106 mg/dL</td>
<td>&gt; 106 mg/dL</td>
</tr>
<tr>
<td>Admission type, non-elective admission no (%)</td>
<td>894 (79)</td>
<td>862 (77)</td>
<td>862 (76)</td>
<td>885 (79)</td>
</tr>
<tr>
<td>SD Glucose</td>
<td>&lt; 20 mg/dL</td>
<td>20-31 mg/dL</td>
<td>31-47 mg/dL</td>
<td>&gt; 47 mg/dL</td>
</tr>
<tr>
<td>Admission type, non-elective admission no (%)</td>
<td>894 (80)</td>
<td>883 (79)</td>
<td>852 (76)</td>
<td>874 (78)</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE, acute physiology age and chronic health II score; IQR, interquartile range

Table S2 presents the dispersion of APACHE II score and admission type per quartile of the peak glucose, the delta glucose and the SD glucose. The APACHE scores and admission types are similar for every quartile.
Chapter 7

Post-hoc analysis with hypoglycemia with cut–off of 60 mg/dL
Comparable to the analysis using 70 mg/dL as a cut–off for hypoglycemia, patients who died in the ICU were older, sicker according to the disease severity scores in the first 24 hours of stay in ICU, and were more frequently after emergency surgery. Length of stay in the ICU was shorter in patients who died in the ICU (Table S3).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Died in ICU N = 729</th>
<th>Survived ICU N = 2,404</th>
<th>P–value</th>
<th>All patients N = 3,133</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years, median [IQR]</td>
<td>70 [58-78]</td>
<td>67 [56-76]</td>
<td>&lt;0.001</td>
<td>68 [57-76]</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>431 (59.1)</td>
<td>1382 (57.5)</td>
<td>0.459</td>
<td>1813 (57.9)</td>
</tr>
<tr>
<td>Non–elective admission, no (%)</td>
<td>663 (91.3)</td>
<td>1831 (76.5)</td>
<td>&lt;0.001</td>
<td>2494 (79.9)</td>
</tr>
<tr>
<td>APACHE II scores, median [IQR], 12 missing</td>
<td>28 [22-34]</td>
<td>21 [16-26]</td>
<td>&lt;0.001</td>
<td>22 [17-28]</td>
</tr>
<tr>
<td>SAPS II median [IQR]</td>
<td>62 [50-75]</td>
<td>45 [36-56]</td>
<td>&lt;0.001</td>
<td>49 [38-61]</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; BMI, body–mass index; APACHE, Acute Physiology and chronic Health Evaluation; SAPS, Simplified Acute Physiology Score LOS, length of stay ICU, intensive care unit; N.A., not applicable

Commonly used metrics of blood glucose control for patients with hypoglycemia with cut–off of 60 mg/dL are presented in Table S4. There were differences in blood glucose metrics calculated over the entire stay in ICU between patients who died in the ICU and patient who survived: time interval between blood glucose measurements was shorter, the median blood glucose level and minimum blood glucose levels were slightly but significantly lower.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Died in ICU N = 729</th>
<th>Survived ICU N = 2,404</th>
<th>P–value</th>
<th>All patients N = 3,133</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of blood glucose measurements, median [IQR]</td>
<td>51 [26-110]</td>
<td>56 [28-102]</td>
<td>0.259</td>
<td>55 [28-104]</td>
</tr>
<tr>
<td>Time interval between measurements – minutes, median [IQR]</td>
<td>94 [68-130]</td>
<td>110 [80-151]</td>
<td>&lt;0.001</td>
<td>106 [76-147]</td>
</tr>
<tr>
<td>Median blood glucose level – mg/dL, median [IQR]</td>
<td>113 [100-132]</td>
<td>113 [104-131]</td>
<td>0.019</td>
<td>113 [103-132]</td>
</tr>
<tr>
<td>Standard deviation of blood glucose level – mg/dL, median [IQR]</td>
<td>41 [31-58]</td>
<td>40 [31-53]</td>
<td>0.108</td>
<td>40 [31-54]</td>
</tr>
<tr>
<td>Minimum blood glucose level – mg/dL, median [IQR]</td>
<td>47 [38-54]</td>
<td>49 [41-56]</td>
<td>&lt;0.001</td>
<td>49 [40-56]</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range
Table S5. Peak glucose, delta glucose and SD glucose calculated from blood glucose measurements obtained within 8 hours after occurrence of hypoglycemia < 60 mg/dL.

<table>
<thead>
<tr>
<th>Blood glucose target of the guideline for blood glucose control in use</th>
<th>80–110 mg/dL (N = 941)</th>
<th>90–144 mg/dL (N = 972)</th>
<th>&lt; 150 mg/dL (N = 1,220)</th>
<th>P-value</th>
<th>All patients (N = 3,133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak glucose – mg/dL, median [IQR]</td>
<td>121 [97- 151]</td>
<td>146 [114-191]</td>
<td>128[104-160]</td>
<td>&lt;0.001</td>
<td>130 [104- 166]</td>
</tr>
<tr>
<td>Delta glucose – mg/dL, median [IQR]</td>
<td>70 [49- 103]</td>
<td>97 [65- 143]</td>
<td>77 [52-112]</td>
<td>&lt;0.001</td>
<td>81 [54-119]</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; SD, standard deviation

The peak glucose, the delta glucose and the SD glucose after occurrence of hypoglycemia < 60 mg/dL are presented in Table S5. As in the original analysis using 70 mg/dL as a cut-off for hypoglycemia, all three metrics were lower in patients who were treated with the new guideline for blood glucose control, in line with its recommendation to have a patient gradually recover from hypoglycemia, explicitly avoiding abrupt stops of insulin infusion as well as avoiding administration of dextrose.

Figure S1. Intensive care unit (ICU) mortality per quartile of peak glucose (A and D), quartiles ranging from < 104, 104-130, 130-166 and >166 mg/dL, per quartile of delta glucose for all patients (B and E) and per quartile of SD glucose (C and F); upper graphs (A to C) show mortality for all patients, lower graphs (D to F) show mortality of elective (open bars) and non-elective patients (closed bars). Ranges of the quartiles of the peak glucose, delta glucose and SD glucose are presented in Table S5.
Figure S2. Odds ratios in the univariate (squares), in the multivariate model including baseline confounders (open circles) and in the multivariate model including all confounders (closed circles) per quartile of the peak glucose (reference: second quartile), delta glucose (reference: second quartile) and SD glucose (reference: second quartile). The multivariate model for peak glucose included the following confounders APACHE II score, elective versus non–elective admission, the local guideline for blood glucose control median blood glucose level during ICU, duration of hypoglycemia in minutes and one versus more than one hypoglycemic episode. The multivariate model for delta glucose included the following confounders APACHE II score, elective versus non–elective admission, the local guideline for blood glucose control median blood glucose level during ICU, the lowest blood glucose level in the hypoglycemic period, duration of hypoglycemia in minutes and one versus more than one hypoglycemic episode. The multivariate model for SD glucose included the following confounders the local guideline for blood glucose control, median blood glucose level during ICU, duration of hypoglycemia and one versus more than one hypoglycemic episode.
Visual inspection suggested a U–shaped relationship between the peak glucose, the delta glucose and the SD glucose and ICU mortality, with the highest mortality in the lowest and highest quartiles. In non–electively admitted patients a U–shaped relationship was suggested between all three metrics and ICU mortality; in electively admitted patients, a U–shaped relationship was only suggested for the SD glucose (figure S1).

In the univariate analysis, only the lowest quartile of the peak glucose, the delta glucose and the SD glucose were associated with increased ICU mortality compared to the reference categories. In multivariate analysis, only the lowest quartile of SD glucose remained to show a significant association with ICU mortality (figure S2).

**Post–hoc analysis per guideline of blood glucose control**

All blood glucose metrics calculated over the entire stay in ICU, were different between patients treated with different guidelines of blood glucose control (table S6).

In post–hoc analysis for the three different guidelines for blood glucose control, a similar relationship was seen between the peak glucose, the delta glucose and the SD glucose and ICU mortality, with the highest mortality in the lowest quartiles.

<table>
<thead>
<tr>
<th>Table S6. Glucose metrics calculated from blood glucose levels obtained during the entire stay in ICU per guideline of blood glucose control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood glucose target of the guideline for blood glucose control in use</strong></td>
</tr>
<tr>
<td><strong>P–value</strong></td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; SD, standard deviation
Figure S3. Intensive care unit (ICU) mortality per quartile of peak glucose (A, D and G), per quartile of delta glucose for all patients (B, and H) and per quartile of SD glucose (C, F I); upper graphs (A to C) show mortality for patients treated with the local guideline targeting blood glucose levels between 80–110 mg/dL, middle graphs (D to F) show mortality for patients treated with the local guideline targeting blood glucose levels between 90–144 mg/dL, lower graphs (G to I) show mortality for patients treated with the local guideline targeting blood glucose levels between <150 mg/dL lower graphs.

References

Chapter 7

a randomized controlled trial. JAMA 2010, 303:341–8.
24. Egi M, Bellomo R, Stachowski E, French...
