Spontaneous and iatrogenic hypoglycaemia related to mortality in the ICU

Cichosz, Simon Lebech; Redke, Finn; Hejlesen, Ole K

Published in:
Diabetes & Metabolism

DOI (link to publication from Publisher):
10.1016/j.diabet.2019.02.001

Publication date:
2019

Document Version
Accepted author manuscript, peer reviewed version

Accepted Manuscript

Title: Spontaneous and iatrogenic hypoglycaemia related to mortality in the ICU

Authors: Simon Lebech Cichosz PhD, Finn Redke MD, Ole K. Hejlesen PhD

PII: S1262-3636(19)30028-X
DOI: https://doi.org/10.1016/j.diabet.2019.02.001
Reference: DIABET 1074

To appear in: *Diabetes & Metabolism*

Received date: 31 October 2018
Revised date: 11 January 2019
Accepted date: 3 February 2019

Please cite this article as: Cichosz SL, Redke F, Hejlesen OK, Spontaneous and iatrogenic hypoglycaemia related to mortality in the ICU, *Diabetes and Metabolism* (2018), https://doi.org/10.1016/j.diabet.2019.02.001

Spontaneous and iatrogenic hypoglycaemia related to mortality in the ICU

Simon Lebech Cichosz, PhD[1], Finn Redke, MD[2], Ole K. Hejlesen, PhD[1]

[1] Department of Health Science and Technology, Aalborg University, Denmark

[2] Anaesthesiology and Intensive Care, Aalborg University Hospital, Aalborg, Denmark

Corresponding author:

Simon Cichosz

Department of Health Science and Technology, Aalborg University, Fredrik Bajers Vej 7D2, DK-9220 Aalborg, Denmark

Tel: (+45) 9940 2020; Fax: (+45) 9815 4008

Email: simcich@hst.aau.dk

Receive 31 October 2018; Accepted 3 February 2019

Abstract

Aim. – Our study investigated the relationship between both spontaneous and iatrogenic hypoglycaemia and mortality.

Methods. – A total of 200,859 patients from the eICU Collaborative Research Database were grouped by whether they had registered episodes of hypoglycaemia or not. Patients with hypoglycaemia were then further divided into subgroups according to type of hypoglycaemia—whether spontaneous or iatrogenic.

Spontaneous hypoglycaemia during an ICU stay was defined as one or more registered blood glucose measurements < 70 mg/dL (3.9 mmol/L) with no evidence of insulin therapy.

Results. – Evidence of at least one hypoglycaemic episode during ICU hospitalization was associated with a significant increase in mortality: the observed mortality rate in such patients was 15.6% compared with 8% in patients without hypoglycaemia ($P < 0.001$). Multivariate logistic regression analysis was performed with APACHE scores, hypoglycaemia and baseline data (age, gender, ethnicity). Spontaneous hypoglycaemia remained a statistically significant predictor of mortality with an adjusted odds ratio (OR) of 1.61 (95% CI: 1.38–1.88; $P < 0.001$), whereas iatrogenic hypoglycaemia was not a significant predictor with an adjusted OR of 0.97 (95% CI: 0.82–1.14; $P = 0.71$).

Conclusion. – Spontaneous hypoglycaemia observed in ICU patients was associated with increased mortality and increased length of ICU stay. Although the present study, given its observational design, cannot provide a definitive answer, the clear difference between spontaneous and iatrogenic hypoglycaemia does not support a causal relationship between (short-lasting) hypoglycaemia and adverse outcomes, but instead indicates that (short-lasting) hypoglycaemia may be a marker of illness severity.

Keywords: Hypoglycaemia; ICU; Insulin; Length of stay; Mortality

Introduction

Hyperglycaemia frequently arises in patients treated in intensive care units (ICUs), and is associated with high morbidity and mortality [1,2]. However, Van den Berghe et al. [3] demonstrated that intensive insulin therapy to maintain blood glucose at < 110 mg/dL (6.1 mmol/L) reduces morbidity and mortality among critically ill patients in surgical ICUs. Therefore, for many years, intensive insulin therapy in critically ill patients has been recommended to improve patient outcomes [4–6], and newer evidence in relation to sepsis has led to recommendations for targeting an upper blood glucose level of ≤ 180 mg/dL rather than ≤ 110 mg/dL [7]. Nevertheless, insulin therapy increases the risk of hypoglycaemia in these patients, and several studies in recent years have indicated that hypoglycaemia may be a possible predictor of morbidity and mortality in critically ill ICU patients [3,8–10]. In fact, initial studies have suggested that the association between hypoglycaemia and mortality might be related to spontaneous hypoglycaemia as opposed to iatrogenic hypoglycaemia, which means that hypoglycaemia could be a biomarker of a poor prognosis rather than an actual cause of mortality [3,9,11]. Indeed, the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE–SUGAR) trial demonstrated that, in critically ill patients randomly assigned to either intensive or conventional glucose control, the former led to moderate and severe hypoglycaemia, both of which are associated with increased mortality [10,12,13].

Thus, the incidence of hypoglycaemia appears to be an important component of blood glucose control in critically ill patients, even though no causal link between hypoglycaemia and mortality has been established [8]. Moreover, studies have mainly focused on ICU patients from a limited number of hospitals/ICU units. Our present study therefore sought to investigate the relationship between both spontaneous and iatrogenic hypoglycaemia in more than 200,000 patients from the eICU Massachusetts Institute of Technology (MIT) database [14].

Methods

The study is based on a post-hoc analysis of the eICU Collaborative Research Database, a large multicentre critical-care database made available by Philips Healthcare in partnership with the MIT Laboratory for Computational Physiology. The database comprises data from a number of critical care units across the continental US and covers patients who were admitted to critical care units in 2014 and 2015. All data were stored and retrieved electronically using the Philips Healthcare (Best, Netherlands) eICU programme (Telehealth for the ICU). All data were made anonymous prior to research analyses by the eICU programme. Documentation of the database is available at www.eicu-crd.mit.edu. As our study was an independent research analysis of the already available eICU database, no approval was needed from our local ethics committee, although it was reviewed and approved by the review board of PhysioNet.

All of the patients studied were divided according to whether they had registered episodes of hypoglycaemia or not. Patients with hypoglycaemia were also further divided into subgroups according to type of hypoglycaemia: spontaneous hypoglycaemia or iatrogenic hypoglycaemia. Spontaneous hypoglycaemia during an ICU stay was defined as one or more registered blood glucose measurements < 70 mg/dL (3.9 mmol/L) and no evidence of insulin therapy, whereas iatrogenic hypoglycaemia was defined as having evidence of insulin therapy. Severe hypoglycaemia was defined as registered blood glucose measurements < 40 mg/dL (2.2 mmol/L). These divisions and subgroups of patients are illustrated in Fig. 1.

Three analyses were investigated in this study: (*i*) one compared all patients according to evidence of hypoglycaemia; (*ii*) another compared the subgroup of patients with spontaneous and iatrogenic hypoglycaemia; and (*iii*) the third compared the subgroup of patients receiving insulin treatment according to evidence or no evidence of hypoglycaemia. Each admitted patient was treated independently, although some patients in the dataset may have had multiple admissions.

Mortality was defined as death during ICU admission. Length of admission (LOS) to the ICU was calculated as the total time spent in the ICU during hospital admission. Severity of illness was assessed according to the Acute Physiology and Chronic Health Evaluation (APACHE) IV classification system during the initial transfer to the ICU. All blood glucose measurements were performed with an ICU blood gas analyzer at the participating hospital.

Evidence from observational and prospective randomized clinical trials (RCTs) in patients with and without diabetes, as well as critically ill and non-critically ill patients, has previously shown a link between hyperglycaemia and clinical outcomes [15,16]. Hyperglycaemia in hospital affects up to 46% of non-critically ill hospitalized patients [17]. The results of observational studies and RCTs indicate that hyperglycaemia in hospitalized patients with or without diabetes is associated with an increased risk of complications, mortality, longer hospital stays and a greater need for home care after hospital discharge [18]. Therefore, the central question relates to the risk of hypoglycaemia as a complication of treating hyperglycaemia. To assess this issue, the group receiving insulin was divided into patients with evidence of hypoglycaemia and patients with no evidence of hypoglycaemia for comparison.

Statistical analyses

The primary outcome of our investigation was hospital mortality related to hypoglycaemia. Patients with hypoglycaemia were separated into survivors and non-survivors. Categorical variables were summarized with the use of proportions, and comparisons between groups were conducted using a chi-squared test. Continuous variables were summarized using either the mean (standard deviation, SD) or median (interquartile range, IQR) as appropriate. Comparisons between groups were assessed with a *t* test or the Wilcoxon rank-sum test as suitable. A P value < 0.05 was considered statistically significant.

To predict the influence of hypoglycaemia on mortality, multivariate logistic regression models were developed using all available demographic variables and possible predictors of mortality (APACHE IV scores, hypoglycaemia, age, gender, ethnicity), and stepwise regression. Model calibration was determined using the Hosmer–Lemeshow goodness-of-fit test. A generalized linear model (GLM) was used to assess LOS in both unadjusted and adjusted analyses (adjusting for baseline characteristics and APACHE scores). All analyses were performed using either MATLAB R2016b version 9.1 (MathWorks, Inc., Natick, MA, USA) or IBM SPSS version 24 (IBM Corp., Armonk, NY, USA) software. Missing data were assumed to be missing at random (MAR) and were imputed using the ‘impute missing value’ function of IBM SPSS.

Thus, 10 complete baseline datasets were created. IBM SPSS uses linear regression for continuous variables and logistic regression for categorical variables. Imputation models included all baseline variables, but imputations were not used to generate hypoglycaemic events.

Results

Study participants

A total of 200,859 patients were included in our study. Their average age was 63.4 (17.1) years, their APACHE score was 55.1 (26.1), 54.4% were male, and there was a 22.8% prevalence of diabetes. A total mortality rate of 8.6% was observed in these patients; the median (25^{th}, 75^{th} percentile) ICU length of stay was 1.8 (0.9, 3.3) days and the total hospital length of stay was 5.6 (2.9, 10.1) days. Missing data accounted for 7% of all data, with 30% of cases missing one or more data points. Analysis of the missing data did not indicate that the data were not MAR.

Hypoglycaemia

The prevalence of identified hypoglycaemia in the ICU patients studied was 7.9%, equivalent to 15,844 patients [0.9% with severe hypoglycaemia, defined by glucose levels < 40 mg/dL (2.2 mmol/L)]. A comparison of patients with and without hypoglycaemia is presented in Table I. The evidence shows that having at least one hypoglycaemic episode during ICU hospitalization was associated with a significant increase in mortality: the observed mortality rate in patients with hypoglycaemia was 15.6% compared with 8% in patients without hypoglycaemia ($P < 0.001$), and the observed rate in patients with severe hypoglycaemia was 27.8%. Also, the length of ICU stay was longer for the group with *vs* without hypoglycaemia, with a median of 2.6 days *vs* 1.8 days ($P < 0.001$), respectively. The effect of hypoglycaemia on LOS was 1.12 days [95% confidence interval (CI): 1.06–1.18; $P < 0.001$] in the adjusted analysis and 1.58 days (95% CI: 1.52–1.65; $P < 0.001$) in the unadjusted analysis. In addition, the group with

hypoglycaemia also had a higher initial calculated APACHE score of 68.5 *vs* 53.8 in the non-hypoglycaemia group ($P < 0.001$). Moreover, a greater proportion of patients with diabetes was observed in this group.

Multivariate logistic regression analysis of APACHE scores, observed hypoglycaemia and baseline data (age, gender, height, weight, diabetes, ethnicity) revealed that general hypoglycaemia remained a statistically significant predictor of mortality, with an adjusted odds ratio (OR) of 1.22 (95% CI: 1.15–1.29; $P < 0.001$) compared with an unadjusted OR of 2.12 (95% CI: 2.02–2.22). Moreover, those with observed severe hypoglycaemia (glucose < 40 mg/dL, or 2.2 mmol/L) had an adjusted OR of 2.00 (95% CI: 1.75–2.30; $P < 0.001$). These ORs are presented in Table IV.

Spontaneous* vs *iatrogenic

Of the 15,844 patients with identified hypoglycaemia, 12,791 patients (81%) had spontaneous hypoglycaemia, and 3053 patients (19%) with iatrogenic hypoglycaemia were registered as having been given insulin (Table II). Both groups had higher incidences of mortality compared with the group without hypoglycaemia: mortality rates were 15.6% in patients with spontaneous hypoglycaemia and 11.5% in those with iatrogenic hypoglycaemia *vs* 8% in patients without hypoglycaemia ($P < 0.001$). The difference in mortality rates was also significant between the two hypoglycaemic groups ($P < 0.001$). In addition, both hypoglycaemic groups had greater lengths of ICU stays compared with the group without hypoglycaemia: the average length of ICU stay was 2.6 days for spontaneous hypoglycaemia and 2.7 days for iatrogenic hypoglycaemia. Furthermore, the effect of spontaneous hypoglycaemia on LOS was not significant in either the adjusted or unadjusted analysis.

Not surprisingly, the iatrogenic hypoglycaemia group had a greater prevalence of patients with diabetes, 57.8% compared with 30.1% for spontaneous hypoglycaemia. There was also a greater proportion of Asians, African Americans and Hispanics in the iatrogenic hypoglycaemia group, which could have been related to the larger proportion of patients with diabetes.

Multivariate logistic regression analysis of APACHE scores, hypoglycaemia type and baseline data (age, gender, height, weight, diabetes, ethnicity) showed that the type of hypoglycaemia remained a statistically significant predictor of mortality: for spontaneous hypoglycaemia, the adjusted OR was 1.61 (95% CI: 1.38–1.88; $P < 0.001$) *vs* the unadjusted OR of 1.54 (95% CI: 1.36–1.73).

Insulin treatment

Of the 200,859 patients studied, 26,430 (13.2%) received insulin therapy during ICU admission. In this group of patients, the incidence of at least one case of hypoglycaemia was 13.1%, which was equivalent to the percentage of the 3053 patients with iatrogenic hypoglycaemia (and the 23,377 without hypoglycaemia; Table III). In this subgroup, 1904 had diabetes, and the mortality rate for these patients was 5.7%.

APACHE scores differed between groups: 58.8 for non-hypoglycaemia patients; and 66.2 for iatrogenic hypoglycaemia patients ($P < 0.001$). In addition, mortality and length of ICU stay were also different between these groups: the mortality rate was 8.7% and median length of ICU stay was 2 days for non-hypoglycaemia patients *vs* 11.5% and 2.7 days, respectively, for hypoglycaemia patients ($P < 0.001$). The effect of having observed hypoglycaemia (*vs* no hypoglycaemia) on LOS in this group was 1.02 days (0.85–1.19; $P < 0.001$) in the adjusted analysis and 1.23 days (1.06–1.40; $P < 0.001$) in the unadjusted analysis.

Multivariate logistic regression analyses of the APACHE scores, observed hypoglycaemia and baseline data (age, gender, height, weight, diabetes, ethnicity) revealed that having hypoglycaemia was not a statistically significant predictor of mortality ($P = 0.71$), with an adjusted OR of 0.97 (95% CI: 0.82–1.14) compared with an unadjusted OR of 1.42 (95% CI: 1.26–1.61).

Discussion

Our present study aimed to investigate the relationship between hypoglycaemia and adverse events in a diverse population of ICU patients. It was found that 7.9% of admitted patients experienced at least one

blood glucose reading < 70 mg/dL (3.9 mmol/L). In general, hypoglycaemia was associated with increases in both incidence of mortality and length of ICU stay, an association that remained statistically significant even after adjusting for APACHE scores and baseline data. These findings are similar to those of a study by Egi et al. [8], who found an association between mild or moderate hypoglycaemia and mortality in 4946 patients from two teaching hospitals in Melbourne and Sydney, Australia. Egi et al. also found that the association persisted even after adjusting for insulin therapy.

Questions have been raised regarding the association between iatrogenic hypoglycaemia and mortality. The conceptual model suggests that spontaneous hypoglycaemia may be a biomarker of a poor prognosis or an underlying disease such as severe infection [19,20] rather than a direct causal relationship. This might imply that insulin therapy, in general, is not a risk factor for mortality, even though the risk of hypoglycaemia is increased [11]. As an interesting finding in relation to this, it was observed that patients with diabetes and iatrogenic hypoglycaemia had lower mortality rates than patients without diabetes. Van den Berghe et al. [3] showed that intensive insulin therapy to maintain blood glucose at ≤ 110 mg/dL (6.1 mmol/L) reduced morbidity and mortality among critically ill patients. However, the NICE–SUGAR trial found that patients randomized to intensive glucose control had higher rates of mortality, although that study still concluded that the data was not proof of a causal relationship.

The results of our present study likewise show that patients who experience iatrogenic hypoglycaemia also have a higher rate of mortality than patients without hypoglycaemia and patients receiving insulin therapy without hypoglycaemia. Nevertheless, on assessing the subpopulation receiving insulin therapy, this association was no longer present after adjusting for APACHE scores and baseline data. Therefore, our present results cannot support the hypothesis that insulin treatment is associated with increased mortality among ICU patients. Moreover, these results are in line with previous findings by Boucai et al. [21], who reported that drug-associated hypoglycaemia was not associated with any increased mortality risk in patients admitted to general wards.

Strengths and limitations

This study has several strengths, including a population size of more than 200,000 patients from a multicentre critical-care database. Also, the data were collected systematically and stored in electronic form. To our knowledge, the scale of the database makes our study of hypoglycaemia in ICU patients one of the most comprehensive thus far.

Nevertheless, our study also has several important limitations. Although our findings suggest that hypoglycaemia is a marker of illness severity rather than being causally related to outcome, a causal relationship cannot be ruled out, given the observational nature of the study. Moreover, the lack of an association between iatrogenic hypoglycaemia and mortality after adjusting for covariates in the subpopulation of patients receiving insulin therapy could potentially be subject to selection bias. However, our study used multivariate logistic regression, which is a means to account for some of the potential biases associated with observational studies.

Another potential limitation is the definition of hypoglycaemia. All patients with an observed glucose level < 70 mg/dL (3.9 mmol/L) were included in the hypoglycaemic group, yielding a high positive predictive rate, yet misclassification cannot be ruled out, as glucose measurements were taken by local procedures and therefore open to selection bias. Indeed, this is a limitation of all observational studies related to investigating hypoglycaemia.

It is also known that the amount of time spent in hypoglycaemia, and its severity, can profoundly influence patients' outcomes. As observed in our study, the mortality rate among patients with severe hypoglycaemia was considerably higher, thereby sparking a discussion on what level of glucose should be used to define (relevant) hypoglycaemia in the ICU. However, our study lacked data on the amount of time patients spent in the hypoglycaemic zone. Also, the definition of iatrogenic hypoglycaemia was based on evidence of insulin therapy in combination with hypoglycaemia, whereas it cannot be known with certainty whether every hypoglycaemia was caused by insulin. Finally, as the aim of our study was focused on hypoglycaemia as a broad concept of the ICU, the patients' underlying disease at admission were not taken into account.

Future studies

Even though several studies have investigated the relationship between hypoglycaemia and outcome, many questions still remain. It is not clear why the results of different studies are conflicting, especially those concerning the use of insulin treatment in critically ill patients. Also, why is hypoglycaemia associated with morbidity and mortality in hospitalized patients at all? While previous work has demonstrated a link between infections, mortality and observations of hypoglycaemia in ICU patients [19,20], the effect of infections was not included in the present study. However, this should be addressed in future studies to adjust for its possible effect on hypoglycaemia and outcomes.

In addition to future studies focusing on the underlying effects of hypoglycaemia on patient outcomes, studies are also needed to assess the cost–benefit relationship of reducing hyperglycaemia in the face of an increased risk of hypoglycaemia. Another important aspect to investigate in further detail is the impact of time spent in hypoglycaemia and the severity of hypoglycaemia in relation to patient outcomes. Finally, it may be that a universal glycaemic target for ICU patients is not optimal, as patients' age, underlying disease (such as diabetes), hospital procedures, other medical treatment and general health status have the potential to improve their overall treatment and prognoses.

Conclusion

Our study has found that the spontaneous hypoglycaemia observed in ICU patients is associated with increased mortality and longer ICU stays. Also, although our study cannot offer any definitive answers, given its observational design, the clear difference between spontaneous and iatrogenic hypoglycaemias does not support a causal relationship between (short-lasting) hypoglycaemia and adverse outcomes. Instead, our findings indicate that (short-lasting) hypoglycaemia may be a marker of illness severity.

Contributions

FR contributed to data interpretation and revision of the manuscript. OKH contributed to study design, data analysis, data interpretation and revision of the manuscript. SLC contributed to literature search, figures, study design, data analysis, data interpretation and writing of the manuscript. American Journal Experts (AJE.com), a paid service, was used for grammar and proofreading of the manuscript.

Financial Disclosure and Conflicts of Interest: Nothing to declare

Funding

No funding to report

Conflict of interest

The authors have no conflicts of interest

References

[1] Inzucchi SE. Clinical practice. Management of hyperglycemia in the hospital setting. N Engl J Med 2006;355:1903–11. doi:10.1056/NEJMcp060094.

[2] Cichosz SL, Schaarup C. Hyperglycemia as a predictor for adverse outcome in ICU patients with and without diabetes. J Diabetes Sci Technol 2017;11:1272– 3.

[3] Berghe G Van den, Wouters P, Weekers F. Intensive Insulin Therapy in Critically Ill Patients. N Engl J Med 1998;345:785–91. doi:10.1056/NEJMoa012295.

[4] Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Intensive Care Med 2004;30:536–55. doi:10.1007/s00134-004-2210-z.

[5] Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 2008;34:17–60. doi:10.1007/s00134-007-0934-2.

[6] Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care 2009;32:1119–31. doi:10.2337/dc09-9029.

[7] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. vol. 43. Springer Berlin Heidelberg; 2017. doi:10.1007/s00134-017-4683-6.

[8] Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Taori G, et al. Hypoglycemia and outcome in critically ill patients. Mayo Clin Proc 2010;85:217–24. doi:10.4065/mcp.2009.0394.

[9] Berghe G Van den, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive Insulin Therapy in the Medical ICU. N Engl J Med 2006;354:1991–2002. doi:10.1056/NEJMoa1414264.

[10] Finfer S, Liu B, Chittock DR, Norton R, Myburgh J a, McArthur C, et al. Hypoglycemia and Risk of Death in Critically Ill Patients. N Engl J Med 2012;367:1108–18. doi:10.1056/NEJMoa1204942.

[11] Hulkower RD, Pollack RM, Zonszein J. Understanding hypoglycemia in hospitalized patients. Diabetes Manag 2014;4:165–76. doi:10.2217/dmt.13.73.

[12] Gatell JM, D P, Rockstroh JK, Katlama C, Yeni P, Lazzarin A, et al. New England Journal. October 2008:339–54. doi:10.1056/NEJMoa1411087.

[13] Finfer S, Heritier S. The NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) Study: statistical analysis plan. Crit Care Resusc 2009;11:46–57.

[14] Goldberger AL, Amaral LAN, Glass L, Hausdorff JM, Ivanov PC, Mark RG, et al. PhysioBank, PhysioToolkit, and PhysioNet Components of a New Research Resource for Complex Physiologic Signals. Circulation 2000;101:215–20.

[15] Umpierez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglicemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002;87:978–82. doi:10.1210/jcem.87.3.8341.

[16] Falciglia M, Freyberg RW, Almenoff PL, David A, Alessio D, Render ML. Hyperglycemia-Related Mortality in Critically Ill Patients Varies with Admission Diagnosis. Crit Care 2010;37:3001–9. doi:10.1097/CCM.0b013e3181b083f7.Hyperglycemia-Related.

[17] Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: Systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. Lancet 2011;378:31–40. doi:10.1016/S0140-6736(11)60679-X.

[18] Jiang HJ, Stryer D, Friedman B, Andrews R. Multiple hospitalizations for patients with diabetes. Diabetes Care 2003;26:1421–6. doi:10.2337/diacare.26.5.1421.

[19] Miller SI, Wallace RJ, Musher DM, Septimus EJ, Kohl S, Baughn RE. Hypoglycemia as a manifestation of sepsis. Am J Med 1980;68:649–54.

[20] Toufen Junior C, Franca SA, Okamoto VN, Salge JM, Carvalho CRR. Infection as an independent risk factor for mortality in the surgical intensive care unit. Clinics 2013;68:1103–8.

[21] Boucai L, Southern WN, Zonszein J. Hypoglycemia-associated mortality is not drug-associated but linked to comorbidities. Am J Med 2011;124:1028–35. doi:10.1016/j.amjmed.2011.07.011.

Figure legend

Fig. 1. Distribution of patients according to evidence of hypoglycaemia and insulin treatment during intensive care unit (ICU) stays.

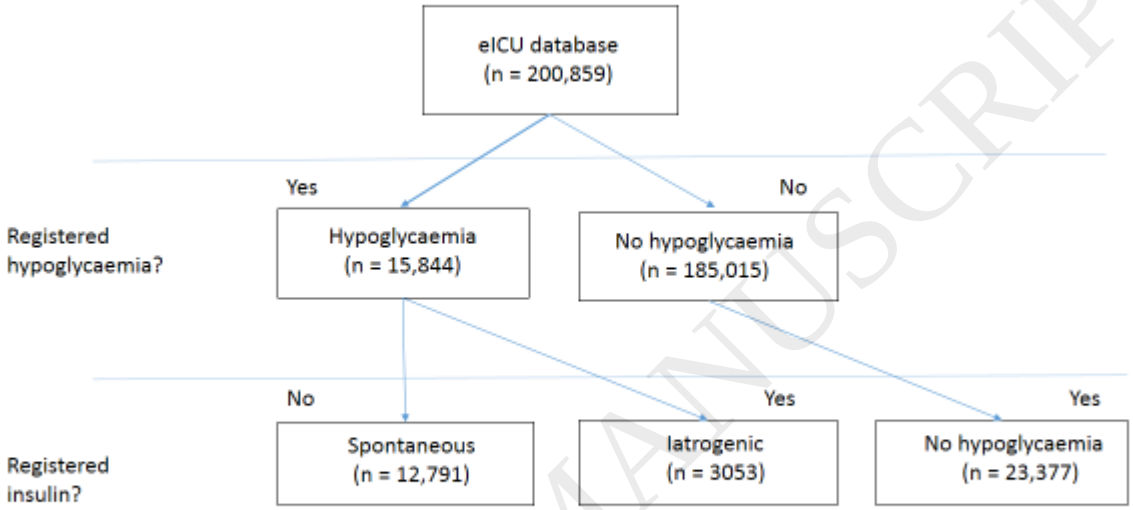

Table I
Patient groups according to evidence or not of hypoglycaemia during stays in the intensive care unit (ICU)

Parameter	**Hypoglycaemia**	**No hypoglycaemia**
Patients, n	15,844	185,015
APACHE score	68.5 (29.8)	53.8 (25.3)*
Mortality, %	15.6	8*
Age, years	63.2 (17)	63.4 (17.1)*
Gender, male %	48.8	54.4*
Height, cm	167.5 (13.8)	169.4 (13.5)*
Weight, kg	79.2 (26)	84.6 (26.9)*
Diabetes, %	35.7	22.8*
Ethnicity, %		
Asian	1.8	1.3*
Caucasian	69.2	78.1*
African American	17.6	10.4*
Native American	1.1	1
Hispanic	4.3	3.5*
ICU length of stay, days[a]	2.6 (1, 5)	1.8 (1, 3)*

Data are presented as means (standard deviation) unless stated as otherwise; * $P < 0.05$ between groups; [a] median (25^{th}, 75^{th} percentile);
APACHE: Acute Physiology and Chronic Health Evaluation

Table II
Patients with evidence of spontaneous and iatrogenic hypoglycaemias during intensive care unit (ICU) stays

Parameter	Spontaneous hypoglycaemia	Iatrogenic hypoglycaemia
Patients, n	12,791	3053
APACHE score	69.1 (30.4)	66.2 (27.6)*
Mortality, %	16.6	11.5*
Age, years	63.5 (17)	61.9 (17.1)*
Gender, male %	48.9	48.7
Height, cm	167.6 (13.6)	167.3 (14.7)
Weight, kg	79 (26.1)	79.9 (25.8)
Diabetes, %	30.1	57.8*
Ethnicity, %		
Asian	1.6	2.3*
Caucasian	71.2	60.7*
African American	16.4	23*
Native American	1.2	0.9
Hispanic	3.5	7.5*
ICU length of stay, days[a]	2.6 (1, 5)	2.7 (1, 5)

Data are presented as means (standard deviation) unless stated as otherwise; * $P < 0.05$ between groups; [a] median (25^{th}, 75^{th} percentile);
APACHE: Acute Physiology and Chronic Health Evaluation

Table III
Patients receiving insulin treatment during intensive care unit (ICU) stays according to evidence or not of hypoglycaemia

Parameter	Insulin treatment	
	No hypoglycaemia	Iatrogenic hypoglycaemia
Patients, n	23,377	3053
APACHE score	58.8 (25.9)	66.2 (27.6)*
Mortality, %	8.7	11.5*
Age, years	62 (16.9)	61.9 (17.1)
Gender, male %	54.6	48.7*
Height, cm	169.4 (15.2)	167.3 (14.7)*
Weight, kg	86.4 (26.5)	79.9 (25.8)*
Diabetes, %	50.9	57.8*
Ethnicity, %		
Asian	1.7	2.3*
Caucasian	67.4	60.7*
African American	17.1	23*
Native American	0.7	0.9
Hispanic	7.5	7.5
ICU length of stay, days [a]	2 (1, 4)	2.7 (1, 5)*

Data are presented as means (standard deviation) unless stated as otherwise; * $P < 0.05$ between groups; [a] median (25^{th}, 75^{th} percentile);
APACHE: Acute Physiology and Chronic Health Evaluation

Table IV
Adjusted and unadjusted odds ratios (95% confidence interval) for mortality in all study groups

Groups	Odds ratios	
	Adjusted	Unadjusted
Hypoglycaemia	1.22 (1.15–1.29)**	2.12 (2.02–2.22)**
Severe hypoglycaemia	2.00 (1.75–2.30)**	4.07 (3.67–4.52)**
Spontaneous *vs* iatrogenic	1.61 (1.38–1.88)**	1.54 (1.36–1.73)**
Insulin treatment	0.97 (0.82–1.14)	1.42 (1.26–1.61)**

* $P < 0.05$, ** $P < 0.001$ (between groups)