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**Hospital-acquired Complications in Intensive Care Unit Patients with Diabetes: A Before-and-after Study of a Conventional versus Liberal Glucose Control Protocol**

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**Abstract**

**Background**

Critically ill patients with diabetes mellitus (DM) are at increased risk of in-hospital complications and the optimal glycemic target for such patients remains unclear. A more liberal approach to glucose control has recently been suggested for patients with DM, but uncertainty remains regarding its impact on complications.

**Methods**

We aimed to test the hypothesis that complications would be more common with a liberal glycemic target in ICU patients with DM. Thus, we compared hospital-acquired complications in the first 400 critically ill patients with DM included in a sequential before-and-after trial of liberal (glucose target: 10-14 mmol/l) versus conventional (glucose target: 6-10 mmol/l) glucose control.

**Results**

Of the 400 patients studied, 165 (82.5%) patients in the liberal and 177 (88.5%) in the conventional-control group were coded for at least one hospital-acquired complication (p=0.09). When comparing clinically relevant complications diagnosed between ICU admission and hospital discharge, we found no difference in the odds for infectious (adjusted odds ratio [aOR] for liberal-control: 1.15 [95% CI: 0.68-1.96], p=0.60), cardiovascular (aOR 1.40 [95% CI: 0.63-3.12], p=0.41) or neurological complications (aOR: 1.07 [95% CI: 0.61-1.86], p=0.81), acute kidney injury (aOR 0.83 [95% CI: 0.43-1.58], p=0.56) or hospital mortality (aOR: 1.09 [95% CI: 0.59-2.02], p=0.77) between the liberal and the conventional-control group.

**Conclusion**

In this prospective before-and-after study, liberal glucose control was not associated with an increased risk of hospital-acquired infectious, cardiovascular, renal or neurological complications in critically ill patients with diabetes.

**Key words:** Intensive care; glucose control; insulin; hypoglycemia; glycated hemoglobin A1c; diabetes, in-hospital complications, Classification of Hospital Acquired Diagnoses (CHADx)

## Introduction

The prevalence of diabetes mellitus in ICU patients is as high as 30%, and such patients are at increased risk of experiencing in-hospital complications, compared to patients without diabetes [1–4]. Current recommendations for insulin therapy in the critically ill [5,6] suggest targeting a blood glucose level (BGL) of 6-10mmol/L. However, such 'conventional glucose control' may increase the risk of hypoglycemia and mortality in patients with pre-existing diabetes, especially in those with poor pre-morbid glycaemic control [7,8] . Thus, a more liberal glucose control in patients with diabetes has been suggested [9–12]. In this regard, in a recent sequential before-and-after study trial comparing the impact of liberal (BGL 10-14mmol/L) versus conventional (BGL 6-10mmol/L) glucose control in ICU patients with diabetes, liberal glucose control was not associated with ICU or hospital mortality, duration of mechanical ventilation or ICU-free days [13].

In ambulant patients with type-2 diabetes, chronic hyperglycaemia predisposes to infections [14]. Because higher blood glucose concentrations impair leukocyte function[15], infective complications may be reduced with lower blood glucose concentrations. Moreover, in critically ill patients without diabetes, hyperglycaemia is associated with increased mortality, risk of infection[16], kidney injury and cardiovascular complications [17] and some studies have reported fewer complications with so-called tight glycaemic control in unselected cohorts [18–20]. However, whether a conventional glucose control compared to a more liberal strategy has any impact is unknown.

Given the above uncertainties, we aimed to test the hypothesis that liberal glucose control is associated with higher risk of hospital-acquired complications in critically ill patients with diabetes.

## Methods

This study was approved by the local research Ethics Committee, who waived the need for informed consent (Austin Hospital Research Ethics Committee No. LNR/14/Austin/487).

### *Study design*

The present study was a post-hoc exploratory analysis of a single-centre, before-and-after observational trial in ICU patients with diabetes (Safety of glucose Elevation Evaluation Trial in Diabetes [SUEET Diabetes]). In the SUEET Diabetes trial, patients included between January and October 2015 were treated according to a liberal glucose protocol (insulin therapy if BGL >14 mmol/l, target: 10-14 mmol/l) and compared with patients included between February and December 2013 who received a conventional glucose control protocol (insulin therapy if BGL >10 mmol/l, target: 6-10 mmol/l). In both groups, intravenous glucose was not given unless the patient developed absolute hypoglycaemia (defined as BGL ≤3.9 mmol/l). Glucose variability was assessed using the following measures: standard deviation (SD), percentage coefficient of variation (%CV), and glycemic lability index (GLI) [13,16].

Patient data were matched with the hospital "Classification of Hospital Acquired Diagnoses" (CHADx) coding system to obtain information on their hospital-acquired complications. The CHADx is based on the International Classification of Diseases (ICD-10) coding system [21] and was developed for the Australian Commission on Safety and Quality in Health Care [22,23]. It allows hospitals to identify, count and monitor hospital-acquired adverse events using existing data from the patient medical clinical records. Furthermore, it has been evaluated and compared with the Clavien-Dindo system to identify surgical complications [24].

*Data collection*

As part of the SUEET trial, we collected specific information such as demographic data, comorbidities and illness-severity using the APACHE III scoring system, ICU admission diagnosis, pre-ICU diabetes therapy, serum glycated hemoglobin A1c (HbA1c) levels, blood glucose measurements and assessment of glycaemic control in the ICU. A patient receiving therapy that suppresses resistance to infection, eg. immuno-suppression, chemotherapy, radiotherapy, long term or recent high dose steroids, or having a disease sufficiently advanced to suppress resistance to infection (eg leukaemia, lymphoma, AIDS) was considered to have chronic immunodeficiency.

We defined relative hypoglycaemia as a BGL ≤ 70% of the expected average glucose (eAG = (1.59*HbA1c) - 2.59)) [25], and absolute hypoglycaemia as a BGL≤3.9 mmol/l . To avoid surveillance bias due to more frequent blood sampling in more severely ill patients or those with more deranged blood glucose values, we calculated the time-weighted average (TWA) blood glucose concentration during the entire ICU length of stay.

The medical records of patients coded for clinically relevant CHADx complications were individually reviewed by two intensivists (NL and LC), in order to differentiate between events that occurred before or leading to ICU admission and those that occurred during or after ICU admission. The following were considered clinically relevant CHADx codes: acute kidney injury, sepsis, pneumonia, urinary tract infections, wound infections, acute myocardial infarction, heart failure, pulmonary oedema and pleural effusion, pulmonary embolism and deep venous thrombosis, stroke, delirium and myopathy (an excel list containing all ICD 10 codes for each CHADx can be downloaded from: https://www.safetyandquality.gov.au/our-work/indicators/classification-of-hospital-acquired-diagnoses).

All complications diagnosed before or leading to the ICU admission were excluded from the analyses.

*Study outcomes*

The co-primary outcomes were the proportion and number of clincally relevant infectious, cardiovascular, renal and neurological complications, diagnosed between admission to ICU and hospital discharge, and hospital mortality.

*Statistical analysis*

Continuous data are presented as median (interquartile range [IQR]) and compared using the Mann-Whitney U test or Kruskal Wallis test (if >2 groups). Categorical data are summarized as number (percentage) and compared using the chi-square test or the Fisher's exact test.
To assess the association between glucose control and hospital-acquired complications we used multivariable logistic regression analysis. We considered all baseline variables for inclusion in the regression model. In the primary analysis, we included variables with P <0.01 on univariate analysis. In sensitivity analyses we selected variables using a stepwise (backward and forward) approach (P≥0.2 for exit and P<0.1 for entry). Calibration of the fitted models was re-assessed using Pearsons's goodness-of-fit test and receiver operating characteristic (ROC) curves were used to assess discrimination.

We performed subgroup analyses to explore the association between glucose control and hospital-acquired complications in patients with an HbA1c <7% and ≥7% and in patients undergoing cardiovascular surgery. We also assessed complications across tertiles of TWA glucose and glycemic lability index (GLI) stratified by HbA1c irrespective of the glucose control protocol.
A two-sided P-value <0.05 was considered statistically significant for the final analysis. Data analysis was performed using STATA® version 14.2 (Stata Corp., College Station, TX, USA).

**Results**

*Patients*

We obtained a complete, matched dataset for the first 400 ICU patients with diabetes included in the SUEET trial. The majority of patients (94.5%) had type 2 diabetes, and about a third (34%) were insulin-dependent prior to ICU admission (Table 1). Median serum glycated hemoglobin A1c (HbA1c) levels were similar between the liberal and conventional control group (6.9 [6.2-7.9]% vs 7.0 [6.1-8.0]%, p=0.77). Patients in the liberal group were more likely to be male (liberal vs conventional control group: 154 vs 130 males, p=0.01) and also had a slightly but non-significant higher APACHE III score upon ICU admission. In both groups, surgical admission diagnoses accounted for about half (52%) of the ICU admissions, with cardiovascular surgery being the major contributor. A detailed list of admission diagnoses is provided in Table S1 in Supplemental Digital Content 1.

*Glycaemic control and process of care in the ICU*

In this sub-study, the average BGL on ICU admission was similar in both glucose control groups (Table 1). The median time-weighted average blood glucose level in the ICU was significantly higher in the liberal-control (10.0 [7.9-12.0] mmol) compared to the conventional-control group (9.0 [8.1-10.0] mmol, p<0.001). Liberal-control patients spent 56 [18-82] % of the time above 10mmol/L compared to 36 [13-55] % of the time in the conventional-control group (p<0.001). Liberal-control patients were also less likely to receive intravenous insulin therapy (46% vs 61%, p=0.003) during their ICU stay. There were no differences in the indices of glycemic variability nor the incidence of absolute hypoglycaemia between the two groups. However, fewer patients in the liberal-control group experienced episodes of relative hypoglycaemia compared to the conventional-control group (33% vs 49.5%, p=0.001).

*Primary outcome*

Out of 400 patients, 165 (82.5%) patients from the liberal-control and 177 (88.5%) from the conventional-control group were coded for a total of 1'965 hospital-acquired complications in the CHADx database (Table S2 in Supplemental Digital Content 1).

Between ICU admission and hospital discharge, 75 (37.5%) patients in the liberal and 64 (32.0%) in the conventional group were diagnosed with at least one clinically relevant infectious, cardiovascular, renal and/or neurological complication (aOR for liberal glucose control: 1.19 [0.78-1.80], P=0.42) (Table 2 and 3). Hospital mortality was 20.0% (n=40) in the liberal group and 16.0% (n=32) in the conventional group, respectively (aOR for liberal glucose control: 1.09 [95% CI: 0.59-2.02], p=0.77).

Overall, 99 (49.5%) patients from the liberal and 81 (40.5%) patients from the conventional group reached the co-primary outcome (aOR for liberal glucose control: 1.25 [95% CI: 0.81-1.91], p=0.31).

*Infectious complications*

Between ICU admission and hospital discharge, 37 (18.5%) patients in the liberal and 32 (16%) in the conventional glucose control group experienced at least one of the following infectious complications: sepsis, pneumonia, urinary tract and/or surgical wound infection (Table 2).

After adjusting for sex and APACHE III score, liberal glucose control was not associated with increased combined risk for infectious complications (aOR for liberal glucose control: 1.15 [95% CI: 0.68-1.96], p=0.60) (Table 3). In both groups, 80% of the urinary tract infections were diagnosed on the hospital ward after discharge from ICU.

On multivariable logistic regression, chronic immunodeficiency and lower HbA1c but not glucose control protocol were independently associated with higher risk of hospital-acquired sepsis (Table S3, Supplemental Digital Content 1).

*Acute kidney injury*

There was no difference in numbers of patients who developed acute kidney injury (aOR for liberal glucose control: 0.83 [95% CI: 0.43-1.58], p=0.56). In the second model, male gender and surgical admission but not glucose control protocol were associated with higer risk for developing acute kidney injury (Table S4, Supplemental Digital Content 1).

*Cardiovascular complications*

The risk of cardiovascular complications such as acute myocardial infarction, heart failure, pulmonary edema and pleural effusions did not differ between the two groups (aOR for liberal glucose control: 1.40 [95% CI: 0.63-3.12], p=0.41). Female gender and surgical admission diagnosis but not glucose control protocol were associated with higher risk of cardiovascular complications (Table S5, Supplemental Digital Content 1).

*Neurological complications*

Acute delirium was the most common neurological complication in both groups and liberal glucose control was not associated with increased risk to be diagnosed with acute delirium or stroke (aOR for liberal glucose control: 1.07 [95% CI: 0.61-1.86], p=0.81) (Table 3). However, higher age and male gender, were independently associated with increased risk for delirium (Table S6, Supplemental Digital Content 1).

*Subgroup analyses*

We found no significant association between liberal control and any of the selected hospital-acquired complications in the subgroup of patients with HbA1c ≥7% or below 7%, or in the subgroup of patients undergoing cardiac surgery, respectively (Tables S7-9, Supplemental Digital Content 1). Similarly, we found no difference in the co-primary outcome when comparing patients with an episode of relative hypoglycemia in ICU with patients without such an episode (Table S10, Supplemental Digital Content 1).

However, when we analysed all patients according to tertiles of mean glycemia and tertiles of glycemic lability index (GLI) stratified by HbA1c and irrespective of glucose control protocol, we found higher hospital mortality, but not overall hospital-acquired complications, in the group with the highest GLI and HbA1c < 7% with a similar trend in patients with HbA1c ≥7%, (Table S11-12, Supplemental Digital Content 1).

## Discussion

*Key findings*

In this before-and-after study of ICU patients with diabetes, liberal glucose control was not associated with an increased risk of hospital-acquired infectious, cardiovascular, renal or neurological complications, compared to conventional glucose control.

*Relationship to previous studies*

In critically ill patients *without* diabetes, several studies have reported that hyperglycaemia was associated with higher mortality, more complications and prolonged hospital length of stay [12,26,27]. However, in a recent systematic review of ICU patients *without* diabetes, hyperglycaemia during the ICU stay was not associated with new infectious events or ICU mortality [28], which is in line with our results in patients with diabetes.

In the Leuven trials [18,19], intensive insulin therapy targeting normoglycemia resulted in significantly lower incidence of acute kidney injury, lower infection rates and biomarkers of infection. However, these studies included only a small proportion of patients with diabetes (<20%), and their findings could not be confirmed in subsequent trials [29–31]. Moreover, and of specific relevance to this study, a subgroup analysis of both Leuven trials [32] showed no significant benefit from intensive insulin therapy in patients with diabetes. Similarly, we observed no significant trend towards higher risk for infectious complications in our patients treated with liberal glucose control. Furthermore, the majority of hospital-acquired urinary tract infections in our study were diagnosed after discharge from ICU during a period

where glycaemic targets were not different between the two groups. However, a large randomised controlled trial of empagliflozin in patients with type 2 diabetes [33] showed higher rates of urogenital infections in the treatment group as possible complication of drug-induced glycosuria. Although this study included a different population of ambulant patients with diabetes, we have no information about prevalence of glycosuria in our patients during liberal glucose control.

Currently, the recommendations for blood glucose management in the ICU are based on the NICE-SUGAR trial [29] and are commonly applied to all critically ill patients, irrespective of their pre-morbid diabetes status. However, in ICU patients with diabetes, several observational studies have found no association between peak [34] or mean [12,26] blood glucose levels above 10 mmol/L (180 mg/dL) and mortality, and some studies even suggest that mild hyperglycaemia might be beneficial in patients with poor chronic glycemic control [7,10]. Relevant to such concerns and in accordance with our findings, a recent network meta-analysis of 18,098 patients from 35 studies found no significant difference in the risk of mortality and infection among different BGL target ranges in critically ill patients, but a higher risk of hypoglycemia with BGL targets of <6.1 mmol/L (110mg/dL) and 6.1-8mmol/L (110-144 mg/dL) [35].

When comparing patients stratified by HbA1c regardless of BGL target, we found increased hospital mortality with higher glycemic variability. This is in line with previous studies where high glycaemic variability (GV) but not mean BGL was associated with higher risk of ICU mortality [16]. Moreover, in our exploratory sub-group analysis the co-primary outcome occurred numerically more often in patients treated with liberal glucose control who had HbA1c levels < 7% (p = 0.08). This finding suggests that a potential association between glucose control and complications is modified by the degree of pre-ICU glycemia. However, the SUEET trial[13] included 353 patients with HbA1c < 7% and found no difference in hospital mortality in ICU patients with diabetes treated with liberal glucose control.
In cardiac surgery patients, several observational and randomized controlled trials have evaluated the impact of hyperglycaemia on complications and hospital mortality [17,20,36–39]. Although some studies reported a reduction in postoperative complications with tight glycaemic control, this benefit was not consistently found in patients with pre-existing diabetes mellitus [17,36,40]. Moreover, several studies found no difference in perioperative complications, hospital length of stay, and mortality between intensive insulin therapy and control treatment [37,38]. Finally, Greco et al. even suggested better outcomes for insulin-dependent patients who had postoperative hyperglycaemia [39].

*Implications of study findings*

Our findings that liberal glucose control in critically ill patients with diabetes is not associated with a higher risk for hospital-acquired complications imply that such a liberal approach to glycaemic control may not expose patients to additional risks. Moreover, they imply that hyperglycemia may be a physiological response to acute illness, rather than being the source of further complications in this patient population. Finally, *hypoglycemia* (both absolute and relative) appears undesirable and increases stress hormone release [27,41–43] and, as expected, liberal glucose control reduced the risk of

relative hypoglycemia implying that, in critically ill patients with diabetes, a liberal glucose control may minimise the risk of undesirable decreases in glucose levels.

*Strengths and limitations*

Our study has several strengths. First, we used a standardized hospital administration database to identify patients with hospital-acquired complications and were therefore able to perform an unbiased analysis of all types of adverse events. Second, we reviewed all medical records to identify clinically relevant complications that occurred after ICU admission (after the patient had been exposed to one of the two glucose protocols), thus minimising the risk of ascertainment bias. Third, we used multivariable logistic regression analysis, adjusted for differences in baseline characteristics, and, even without correcting for multiple comparisons, we observed no statistically significant difference between the liberal and the control group. Therefore, our results appear reasonably robust, with limited risk of type II error. Finally, this study was performed in a large tertiary hospital, with a mixed patient cohort and is, therefore, likely to reflect similar ICU populations in developed countries.

Our study has some limitations. It is a follow-up analysis of a prospective observational trial and is thus hypothesis-generating and unable to assess causality. However, our findings support the conduct of future randomized studies to prospectively explore the impact of liberal glucose control in ICU patients with diabetes. Our sample may be too small and therefore lack statistical power to detect minor differences between rare adverse events and all our conclusions should therefore be considered exploratory. However, changing well-established glucose target was a controversial action, why we believe that this study was a necessary step to demonstrate safety. In addition, we believe that we were able to provide valuable information to help in the design of future prospective studies in this field.

Finally, we do not have detailed information about in-hospital glycemic control after ICU discharge. However, at our institution, liberal glucose control is applied only to critically ill patients with diabetes while they are in the ICU. Therefore, our results are unlikely to have systematically affected glucose management on the wards. Moreover, no studies of different glucose control protocols in ICU patients so far have reported data on any differential glucose management after ICU discharge.

**Conclusions**

In this prospective before-and-after study, liberal glucose control was not associated with an increased risk of hospital-acquired infectious, cardiovascular, renal or neurological complications in critically ill patients with diabetes. Although our observations should be considered exploratory, they support the safety of cautious ongoing exploration of more liberal glycemic targets in ICU patients with diabetes mellitus.

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# SUEET Complications: Tables

**Table 1. Baseline characteristics and process of ICU care in the liberal and conventional glucose control group**

| Characteristic | Liberal control (n = 200) | Conventional control (n = 200) | P Value |
|---|---|---|---|
| Age, years | 66 (59, 74) | 67 (60, 75) | 0.34 |
| Male sex, n (%) | 154 (77.0) | 130 (65.0) | 0.01 |
| BMI, kg/m$^2$ | 30 (26, 35) | 29 (26, 34) | 0.40 |
| HbA1c, % (n=392) | 6.9 (6.2, 7.9) | 7.0 (6.1, 8.0) | 0.77 |
| Type 2 diabetes, n (%) | 189 (94.5) | 189 (94.5) | >0.99 |
| Insulin-dependent diabetes, n (%) | 73 (36.5) | 63 (31.5) | 0.29 |
| Comorbidities, n (%) | | | |
| Chronic hemodialysis | 23 (11.5) | 15 (7.5) | 0.23 |
| Chronic heart failure (NYHA IV) | 12 (6.0) | 19 (9.5) | 0.19 |
| Immunosuppressed (by disease or therapy)[1] | 19 (9.5) | 11 (5.5) | 0.13 |
| APACHE III score | 61 (46, 81) | 56 (43, 72) | 0.08 |
| Surgical admission diagnosis, n (%) | 100 (50.0) | 109 (54.5) | 0.37 |
| Cardiovascular surgery, n (%) | 68 (34.0) | 76 (38.0) | 0.41 |
| Vasopressor infusion at ICU admission, n (%) | 80 (40.0) | 68 (34.0) | 0.26 |
| Mechanically ventilated at ICU admission, n (%) | 132 (66.0) | 115 (57.5) | 0.10 |
| **Glycemic control and variability in ICU** | | | |
| Blood glucose level at ICU admission, mmol/l | 8.6 (6.7, 11.0) | 8.6 (7.0, 12.0) | 0.62 |
| Time-weighted average blood glucose level in ICU, mmol/l | 11.0 (8.6, 12.0) | 9.4 (8.5, 11.0) | <0.001 |
| Glycemic variability | | | |
| Glycemic lability index, [mmol/L]$^2$/hour/week] | 61 (24-113) | 66 (33-120) | 0.25 |
| Standard deviation, mmol/l | 2.2 (1.6-3.0) | 2.1 (1.5-2.8) | 0.26 |
| Coefficient of variation, % | 22 (16-28) | 22 (17-28) | 0.21 |
| Received insulin therapy in ICU, n (%) | 92 (46.0) | 122 (61.0) | 0.003 |
| Patients having at least one episode of absolute hypoglycemia, n (%)[a] | 14 (7.2) | 16 (8.4) | 0.66 |
| Patients having at least one episode of relative hypoglycemia, n (%)[b] | 61 (32.5) | 92 (48.9) | 0.001 |
| Proportion of time in target range, % | 41 (14-54) | 50 (33-70) | <0.001 |
| Proportion of time above 10mmol/L, % | 56 (17-81) | 36 (13-55) | <0.001 |

Values are expressed as median (IQR) or n (%) unless otherwise stated.

Abbreviations: ICU, intensive care unit; HbA1c, Glycated haemoglobin; APACHE, acute physiology and chronic health evaluation; NYHA, New York Heart Association

[1]Patient has received therapy that suppresses resistance to infection, eg. immuno-suppression, chemotherapy, radiotherapy, long term or recent high dose steroids, or has a disease sufficiently advanced to suppress resistance to infection (eg leukaemia, lymphoma, AIDS)

[a]Blood glucose ≤3.9 mmol/l

[b]Blood glucose ≤ 70% of expected average glucose (eag = (1.59*HbA1c)-2.59))



**Table 2. Outcomes in the liberal and conventional glucose control group**

| Variable | Liberal group (n = 200) | Conventional group (n=200) | P-Value |
|---|---|---|---|
| **Patients coded with ≥ 1 hospital-acquired complication (CHADx), n (%)** | 165 (82.5) | 177 (88.5) | 0.09 |
| **Patients with co-primary outcome[1], n (%)** | 99 (49.5) | 81 (40.5) | 0.07 |
| **Patients with ≥ 1 clinically relevant CHADx complication after ICU admission, n (%)** | 75 (37.5) | 64 (32.0) | 0.25 |
| **Infectious complications, n (%)** | 37 (18.5) | 32 (16.0) | 0.51 |
| - Sepsis | 7 (3.5) | 6 (3.0) | 0.78 |
| - Pneumonia | 25 (12.5) | 24 (12.0) | 0.88 |
| - Urinary tract infections[2] (UTI) | 7 (3.5) | 3 (1.5) | 0.20 |
| - Wound infection (excluding sepsis) | 4 (2.0) | 8 (4.0) | 0.24 |
| **Cardiovascular complications, n (%)** | 15 (7.5) | 12 (6.0) | 0.55 |
| - Acute myocardial infarction | 1 (0.5) | 1 (0.5) | >0.99 |
| - Pulmonary oedema, pleural effusion | 10 (5.0) | 7 (3.5) | 0.46 |
| - Heart failure | 2 (1.0) | 3 (1.5) | 0.65 |
| - Pulmonary embolism | 2 (1.0) | 2 (1.0) | >0.99 |
| - Deep venous thrombosis | 1 (0.5) | 0 | 0.32 |
| **Acute kidney injury, n (%)** | 21 (10.5) | 22 (11.0) | 0.87 |
| **Neurological complications, n (%)** | 33 (16.5) | 29 (14.5) | 0.58 |
| - Cerebro-vascular accident (incl. TIA) | 4 (2.0) | 3 (1.5) | 0.70 |
| - Delirium | 28 (14.0) | 26 (13.0) | 0.88 |
| - Myopathy | 2 (1.0) | 0 | 0.50 |
| **Hospital mortality, n (%)** | 40 (20.0) | 32 (16.0) | 0.30 |

| | | | |
|---|---|---|---|
| **Length of ICU stay (days)** | 2.7 (1.2-5.7) | 2.1 (1.1-4.1) | 0.09 |
| **Length of hospital stay (days)** | 13.0 (7.0-23.0) | 11.0 (7.0-21.0) | 0.40 |

[1] Clinically relevant CHADx complication after ICU admission and hospital mortality combined

[2]All patients, except 1 in each group, developed UTI on the hospital ward after ICU discharge.

Abbreviations: CHADx = Classification of Hospital Acquired Diagnoses; TIA=transitory ischemic attack; UTI=urinary tract infection

**Table 3. Unadjusted and adjusted Odds ratios (95% CI) for clinically relevant complications in liberal compared to conventional glucose control**

| **Outcome** | **Unadjusted OR (95% CI)** | **[1]Adjusted OR (aOR) (95%CI)** | **P-value for aOR** |
|---|---|---|---|
| **Co-primary outcome[2]** | **1.44 (0.97-2.14)** | **1.27 (0.83-1.95)** | **0.37** |
| **Clinically relevant CHADx complication after ICU admission** | **1.28 (0.84-1.93)** | **1.19 (0.78-1.80)** | **0.42** |
| Infectious complications | 1.19 (0.71-2.00) | 1.15 (0.68-1.96) | 0.60 |
| Cardiovascular complications | 1.27 (0.58-2.79) | 1.40 (0.63-3.12) | 0.41 |
| Acute kidney injury | 0.95 (0.50-1.79) | 0.83 (0.43-1.58) | 0.56 |
| Neurological complications | 1.17 (0.68-2.00) | 1.07 (0.61-1.86) | 0.81 |
| **Hospital mortality** | **1.31 (0.79-2.19)** | **1.09 (0.59-2.02)** | **0.77** |

[1]Adjusted for sex and APACHE III score

[2]Clinically relevant CHADx complication after ICU admission and hospital mortality combined

CHADx = Classification of Hospital Acquired Diagnoses

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