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TITLE: The effect of a liberal approach to glucose control in critically ill patients with type 2 diabetes

RUNNING TITLE: The LUCID Randomized Clinical Trial

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The Liberal glUcose Control in critically Ill patients with pre-existing type 2 Diabetes (LUCID) is a collaboration of the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. The members of the management committee (listed as authors) assume responsibility for the overall content and integrity of this article.

A complete list of participating sites and investigators in the LUCID trial is provided in the Supplementary Appendix.

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Declaration of interests

Simon Heller has participated in advisory boards for Eli Lilly, NovoNordisk and Zealand Pharma concerning insulin treatment and treatment for hypoglycaemia for which his institution receives remuneration. He has given talks at meetings sponsored by NovoNordisk concerning approaches to reducing hypoglycaemia for which he and his institution have received remuneration.

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All authors contributed substantially to this manuscript, including to trial design, the acquisition, analysis, and interpretation of data, and manuscript drafting or revision. All authors approved the version to be published and are accountable for all aspects of the work.

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AT A GLANCE COMMENTARY

It is uncertain whether a more 'liberal' approach to blood glucose concentrations (intervention) when compared to usual care (comparator) reduce hypoglycemic episodes in critically ill patients with type 2 diabetes. This binational multicenter parallel group randomized clinical trial was conducted in 419 adult patients with type 2 diabetes expected to be in the ICU on at least three consecutive days. The liberal approach substantially reduced the number of hypoglycemic episodes but did not improve patient-centered outcomes. Given the lack of patient-centered benefit, a liberal approach to blood glucose in critically ill patients with pre-existing type 2 diabetes should be limited to evaluation within well-designed clinical trials.

ABSTRACT

Rationale

Blood glucose concentrations affect outcomes in critically ill patients but the optimal target blood glucose range in those with type 2 diabetes is unknown.

Objective

To evaluate the effects of a 'liberal' approach to targeted blood glucose range during intensive care unit (ICU) admission.

Methods

This mutlicenter, parallel-group, open-label, randomized clinical trial included 419 adult patients with type 2 diabetes expected to be in the ICU on at least three consecutive days.

In the intervention group intravenous insulin was commenced at a blood glucose >252 mg/dL and titrated to a target range of 180 to 252 mg/dL. In the comparator group insulin was commenced at a blood glucose >180 mg/dL and titrated to a target range of 108 to 180 mg/dL. The primary outcome was incident hypoglycemia (<72 mg/dL). Secondary outcomes included glucose metrics and clinical outcomes.

Main Results

By day-28 at least one episode of hypoglycemia occurred in 10 of 210 (5%) patients assigned the intervention and 38 of 209 (18%) patients assigned the comparator (incident rate ratio: 0.21 (95% CI, 0.09 to 0.49); P<0.001). Those assigned the intervention had greater blood glucose concentrations (daily mean, minimum, maximum), less glucose variability and less relative hypoglycaemia (P<0.001 for all comparisons). By day 90, 62 of

210 (29.5%) in the intervention and 52 of 209 (24.9%) in the comparator group had died (absolute difference 4.6 percentage points (95%CI, -3.9 to 13.2%); P=0.29).

Conclusions

A liberal approach to blood glucose targets reduced incident hypoglycemia but did not improve patient-centered outcomes.

Trial registration

Australian New Zealand Clinical Trials Registry (ACTRN number 12616001135404)

Key words

Blood glucose, critical illness, diabetes, hypoglycemia, intensive care

BACKGROUND

Patients with type 2 diabetes are frequently admitted to the intensive care unit (ICU) (1, 2). During critical illness glucose metabolism is markedly affected (3). In the ICU, blood glucose concentrations are monitored and maintained within a specified range using intravenous insulin (4). Data from multicenter trials of critically ill patients indicate that targeting a blood glucose concentration in the range of 108 to 180 mg/dL (6.0 to 10 mmol/L) with intravenous insulin leads to better outcomes than targeting 81 to 108 mg/dL (4.5 to 6.0 mmol/L) (5, 6). However, previous trials included only a small proportion of patients with type 2 diabetes.

Observational studies in critically ill patients without pre-existing diabetes consistently identify associations between hyperglycemia and harm; however, data from patients with type 2 diabetes suggest that blood glucose up to 252 mg/dL (14 mmol/L) may not be harmful, and may even be beneficial in such patients (1, 7-9).

Hypoglycemia provides a plausible mechanistic link between insulin therapy and adverse patient outcomes (2, 10-12). Treatment with insulin increases the risk of hypoglycemia, and this risk is exacerbated in critically ill patients with diabetes (2, 13-16). Moreover, in critically ill patients with diabetes, blood glucose concentrations substantially less than the pre-hospital admission average, termed ‘relative hypoglycemia’, are associated with harm even in the absence of absolute hypoglycemia (17, 18). Finally, marked changes in blood glucose, so-called ‘glycemic variability’, are exacerbated in this group and may also be harmful (19).

Given that the physiological response to acute hyper- and hypoglycemia appears to differ based on pre-existing diabetes (20-22), and the evidence supporting a target range of 108 to 180 mg/dL comes predominantly from trials which included few patients with diabetes (23), a randomized clinical trial was conducted to evaluate the effects of a 'liberal' approach to blood glucose control in critically ill patients with pre-existing type 2 diabetes. The primary hypothesis was, in patients with pre-existing type 2 diabetes, targeting a more liberal blood glucose range when compared to usual care, would reduce incident hypoglycemia.

METHODS

Trial design

This was an investigator-initiated, parallel-group, open-label, randomized clinical trial. The trial was registered at the Australian New Zealand Clinical Trials Registry (2 August 2016, ACTRN Trial ID: 12616001135404). The trial protocol and statistical analysis plan have been published (24).

Ethics approval was provided by all relevant local institutional review boards. An independent data and safety monitoring board provided trial oversight. Written informed consent for enrolment, or consent to continue participation was obtained from each patient or their legal surrogate.

Study Participants

Eligible patients were 18 years of age or older with type 2 diabetes, who were expected to remain in the ICU beyond the calendar day after randomization (i.e., for at least three consecutive days), had either an arterial or central venous catheter in situ, and for whom the treating intensivist believed there was a reasonable likelihood that a blood glucose ≥180 mg/dL would be recorded at some stage during the ICU admission.

Patients were excluded because of type 1 diabetes, previous hypoglycemia without neurological recovery, admission to ICU for ≥24 hours prior to randomization, death in ICU was considered inevitable, pregnancy, an expectation they would be eating before the end of the next calendar day, previous participation in LUCID, admission for treatment of diabetic ketoacidosis or hyperosmolar state, or the treating doctor determined that a specific blood

glucose target was required (5, 25). Prior to randomization patients had insulin commenced and titrated as per the pre-existing protocol for that institution.

Study randomization

The concealed 1:1 ratio random allocation sequence was generated by the statistical coordination center (University of Adelaide) using computer-generated random numbers with variable permuted block sizes stratified by site. The sequence was then embedded into the Research Electronic Data Capture (REDCap) system(26). Randomization was performed using REDCap at each study site with the allocation sequence concealed from all investigators, site personnel and participants.

Data verification

On site source data monitoring was conducted by the primary author including >20% source data verification for the primary end point and partial source data verification of other variables for >20% of patients.

Intervention and comparator

Two blood glucose thresholds, with non-overlapping target ranges, for the initiation and management of insulin therapy in critically ill patients with type 2 diabetes were compared.

Participants assigned to liberal glucose control (the intervention group) had intravenous insulin commenced at a blood glucose >252 mg/dL and titrated to a target range 180 to 252 mg/dL. If the blood glucose was <180 mg/dL, no attempt to increase blood glucose was made, with the exception of local protocols for management of hypoglycemia.

Participants assigned to usual care (comparator group) had intravenous insulin commenced and titrated as per pre-existing protocols for the institution. These protocols were aligned with the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) results, with insulin commenced at blood glucose >180 mg/dL and titrated to a target range of 108 to 180 mg/dL (5).

Study protocol

Frequency of blood glucose measurement and the changes to insulin administration was achieved at each site according to local hospital protocols.

Once enrolled, study participants were managed as intervention or comparator whilst in the ICU for a maximum of 28 days from randomization. The intervention or comparator was ceased if consent was withdrawn, the treating clinician determined that it was in the patient's best interest, or the treating clinician wished to transition the participant to an alternative regimen, e.g. long-acting insulin or oral agents in preparation for discharge from ICU.

Blood glucose concentrations on days 1 to 7 that were recorded as part of routine clinical care nearest to the trial timepoints of 0600, 1200, 1800 and 2400 hours were recorded as trial blood glucose values. If no sample was taken as part of routine clinical care within 3 hours of the designated interval, this timepoint was recorded as missing. If the daily minimum or maximum blood glucose concentrations obtained as part of routine clinical care occurred outside of the set trial timepoints (0600, 1200, 1800 and 2400 hours), these values were recorded separately. On study days 8 to 14 the blood glucose closest to 0800 hours was

recorded. The choice of arterial, venous or capillary blood and testing technique was at the discretion of the treating clinician.

All processes of care including nutrition, steroid and catecholamine administration occurred as per local policy and as directed by the treating clinician. The mode of nutrition and use of exogenous steroid was recorded daily for the first 14 days and catecholamine infusion for 7 days. When glycated haemoglobin (HbA1c) was measured prior to randomization, this was recorded (27).

Outcomes

The primary outcome was incident hypoglycemia within 28 days of randomization. This threshold was <72 mg/dL (<4.0 mmol/L) (13, 28) and reported as the event rate adjusted for within-patient correlation. An incident event was defined as hypoglycaemia without recorded hypoglycaemia within the preceding 4 hours. The raw number of hypoglycemic events and proportion of patients experiencing one or more events were also assessed.

Secondary glycemic outcomes

Relative hypoglycemia was defined as >30% drop from 'premorbid estimated average glucose', calculated using the formula: mg/dL=18 x (mmol/L=1.59 x HbA1c (%) − 2.59) (17), and severe hypoglycemia <39.6 mg/dL. Glycemic variability was recorded using both the coefficient of variation (CoV) and standard deviation (SD) over the first 7 study days(17, 18). Maximum, minimum and group mean glucose concentrations were also reported.

Clinical outcomes

Clinical outcomes, including day 90 all-cause mortality, length of ICU and hospital stay, hospital discharge destination, location at day 90, and infectious complications were planned outcomes of interest. Participants who survived to hospital discharge were contacted at day 90 to determine if they remained alive. To assess for a potential difference in infectious complications we recorded positive blood cultures and determined those likely to be pathogenic (supplemental material), as well as highest daily white blood cell count and C-reactive protein concentrations. Post-hoc outcomes included ICU-free survival days.

Statistical analyses

Results are presented as proportions (n/N, %) for categorical data, mean and standard deviation (SD) or median and interquartile range [IQR] for continuous data, with between group comparisons by difference in proportions, t-test or generalized Hodges-Lehmann median difference with 95% confidence interval. The incident rate of hypoglycemia was estimated using Poisson regression referenced to the hours of study exposure, with the corresponding 95% confidence interval (95% CI) based upon robust standard errors to allow for overdispersion. This outcome is also presented as the raw number of events per group and the proportion of individuals experiencing one or more events. P-values were only calculated for the primary outcome and no adjustment was made for repeated interim analysis. Secondary outcomes are presented as point estimates with 95% confidence intervals adjusted for within-subject correlation using generalized estimating equations regression with robust standard errors.

Mortality at day 90 was analyzed as the difference in proportions, with 95% CI, and by logistic regression adjusted for pre-defined covariates (age, sex, APACHE II score, invasive

mechanical ventilation and post-operative admission), with standard errors adjusted for ICU site. Missing data were not imputed. Based on an observational study reporting reduced mortality in patients with a HbA1c ≥7% (53 mmol/mol) and mean blood glucose >180 mg/dL during ICU admission (7), a planned exploratory subgroup analysis was conducted for this group. A post-hoc analysis was conducted using the American Diabetes Association and the European Association for the Study of Diabetes position statement hypoglycemic threshold of <54 mg/dL (29).

Sample size was based on a relative risk of hypoglycemia of 0.47(30), and assumed baseline incident hypoglycemia of 17.5% (5) (supplemental material). A sample size of 408 participants provided 80% power to detect a reduction of 9.3% in incident hypoglycemia with an α error of 0.05. This sample size was inflated by 10% to 450 to allow for consent refusal, loss to follow up, and for unexpectedly short periods of observation. All analyses were performed using Stata MP/16.1 (StataCorp LLC).

Data safety monitoring committee

An interim safety analysis was planned after 200 patients. The independent Data Safety Monitoring Committee identified that a substantial proportion of patients in both arms had not been maintained within the intended glycemic range and the number of deaths in the intervention arm was numerically greater. Given these findings the trial was paused for several months while the management committee sought to improve the time in range through additional training and an additional interim analysis was recommended after the 350th patient had complete 90-day data. Given the primary study aims had been effectively addressed, the lower than anticipated loss to follow-up (recruited n=419), and the non-

significant point-estimate of increased mortality in the intervention group, the management committee was advised to cease ongoing recruitment. The Data Safety Monitoring Committee were working within a pre-written Charter that stipulated advice to stop was the prerogative of the Data Safety Monitoring Committee with no pre-determined stopping rules.

RESULTS

Study participants

From May 2017 to November 2020 we identified 2525 patients in 16 ICUs in Australia and New Zealand who met inclusion criteria, with 2056 meeting at least one exclusion criterion and 434 being randomized (Figure 1). Fifteen patients (8 (3.7%) in the intervention and 7 (3.2%) in the comparator groups) either withdrew, refused consent to continue participation or were randomized in error, leaving 419 participants. Primary outcome analysis included 210 participants in the intervention and 209 participants in the comparator group (Figure 1). There were no marked between-group differences at baseline (Table 1).

Blood glucose measurements and insulin administration

There were 9067 blood glucose measurements recorded (intervention=4425 and comparator=4642), most being from a blood gas analyzer (blood gas analyzer 62%, glucose meter 37%, local laboratory <1%). The method used to measure blood glucose was similar between groups (Figure S1).

Insulin was administered on any study day in 188 (90%) patients in the intervention group and 198 (95%) patients in the comparator. The intervention group received less insulin per

patient per day (median [IQR] 34 [10, 72] vs. 52 [22, 91]; group difference -13.3 (95%CI, -21.4 to -5.3) units, Figure S2). The proportion of blood glucose concentrations within target range was approximately 50% in both groups (Figure 2).

Primary outcome

At least one episode of hypoglycemia occurred in 10 of 210 (5%) patients assigned the intervention and 38 of 209 (18%) the comparator. When adjusting for duration of observation, the intervention reduced incident hypoglycemia (incident rate ratio 0.21 (95% CI, 0.09 to 0.49); P<0.001). When analyzed as the number of events per patient (Table 2) or using a different threshold to define hypoglycaemia (Table S1) results were consistent.

Secondary outcomes

Blood glucose

The mean blood glucose per patient per day, (median [IQR] 212 [191, 227] vs. 167 [152,190] mg/dL; group difference (36 (95%CI, 31 to 42) mg/dL) and mean blood glucose over time (Figure 3) were greater with the intervention. Both the minimum (122 [99, 142] vs. 92 [77, 108] mg/dL, difference 28.8 (95%CI, 23.4 to 34.2) mg/dL) and maximum (304 [270, 337] vs. 265 [225, 312] mg/dL, difference 37.8 (95%CI, 25.2 to 50.4) mg/dL) blood glucose per patient were greater in the intervention group.

Glucose variability, as the percent coefficient of variation (23 [19, 30] vs. 29 [23, 34]% (median difference -4.8 (95%CI, -6.4 to -3.1)), and relative hypoglycemia, 18 [5.9, 43] vs. 50 [29, 78]% (median difference -25 (95%CI, -31 to -19)) were reduced in the intervention group; however, there was no difference in glucose variability when measured as standard deviation (48 [38, 64] vs. 47 [38, 61] mg/dL, difference 0.59 (95%CI, -2.95 to 4.17)). Mean (95%CI) for blood glucose levels by site and study group (Figure S3) support no meaningful heterogeneity between sites, I^2<1% and P>0.99.

There were three patients with severe hypoglycemia (<39.6 mg/dL, 1 intervention and 2 comparator).

Clinical outcomes

A total of 62 of 210 (29.5%) patients in the intervention group and 52 of 209 (24.9%) in the comparator had died by day 90 (absolute difference 4.6 percentage points (95%CI, -3.9 to 13.2%)). Findings were not materially affected when mortality was adjusted for pre-defined covariates (Table S2). Given the observed mortality, a post-hoc decision was made to plot time to death as Kaplan-Meier curves (Figure S3), with no significant difference between curves observed (P=0.20).

There was no significant difference for the duration of ICU admission (127 [83, 206] vs. 154 [77, 252] hours; median difference -12.3 (95% CI, -32.4 to 5.8) hours) and hospital admission (14 [8, 24] vs. 16 [9, 27] days; difference -1.4 (95% CI, -3.6 to 0.7) days) and ICU-free survival days (83 [0, 87] vs. median 82 [16, 87] ICU-free days; median difference 0 (-

1.0, 0) ICU-free days). These durations remained non-significant when analyzed by competing risks regression (Tables S3 and S4). At day 90 there were no marked differences in the proportions of survivors remaining in hospital, or discharged to rehabilitation or a long-term care facility (Table S5)

Ten (5%) participants in the intervention group and 12 (6%) in the comparator group recorded a new positive blood culture. When analyzed as pathogenic the result was similar (6 (3%) vs. 9 (4%)). Biomarkers of infection were not different between groups (Figures S5 and S6).

Processes of care

The nutrition mode was liquid enteral 1205 (57.1%), fasted 499 (23.7%), oral diet 306 (14.5%), parenteral 58 (2.8%) and combined (enteral and oral and/or parenteral) 42 (2.0%) of study days. There was no difference between groups in the route of nutrition, or administration of vasopressors or steroids (Figures S7 and S8).

Protocol deviations, adverse and serious adverse events

Randomization occurred in nine participants who were ineligible (Table S6). Protocol deviations related to insulin administration were documented on 30 occasions and referred to concerns for patient safety on four occasions (Table S6). Adverse events were reported on eight occasions with no serious adverse events (Table S6).

Subgroup analyses

Glycated hemoglobin was available in 316 (75%) participants, with 98 in each group recording a value ≥7%. Mean daily blood glucose profiles (Figure S9) and point estimates for outcomes in this pre-planned subgroup are reported in Tables S7-S9.

DISCUSSION

This randomized clinical trial was conducted in critically ill patients with type 2 diabetes to evaluate the effect of a 'liberal' approach to blood glucose control. The rate of incident hypoglycemia was reduced with the liberal approach. When compared to titrating insulin to target blood glucose less than 180 mg/dL, the liberal approach also reduced glycemic variability and relative hypoglycemia, with increased minimum, mean and maximum blood glucose concentrations. Based on the observed 95% confidence intervals in this sample, the true effect of a liberal approach on glucose control could have been to increase day-90 mortality by up to 13.2% or reduce it by 3.9%.

This trial evaluated glucose control exclusively in critically ill patients with pre-existing type 2 diabetes. Similar to the majority of glucose management trials conducted in ICU, it was open label, with the associated risk of bias. The incidence of hypoglycemia in studies that have included a high proportion of patients with diabetes is reported between 9 and 35% (5, 6, 18, 30, 31). Accordingly, the observed reduction in hypoglycemia is not due to an inflated event rate in the comparator group.

This trial has additional limitations. Only target ranges were compared and, due to the pragmatic nature of this trial, sites were allowed to pursue these blood glucose targets using local practices, rather than implementing strict protocols or using sophisticated technology. This approach has been used by other multicenter trials (5) and has the advantage that the comparator group better represents 'usual care' at trial sites. However, prior to participating, no site had a specific protocol for blood glucose control in patients with diabetes (32). This, combined with insulin resistance in patients with diabetes (33), may explain why the mean blood glucose concentration in the comparator group (167 mg/dL) was greater, and time in range was less than expected. While previous multicenter trials reporting time in range found similar periods out of range (6), the results of this trial may have been different had protocols or technology that are more effective at maintaining blood glucose concentrations within a target range been used (34-36). To prevent contamination bias, a target population was identified soon as possible after ICU admission, which was dependent on a diagnosis of pre-existing diabetes. While pragmatic, this is somewhat simplistic in that 'personalization' of glucose control during critical illness may be more nuanced than dichotomizing patients based on an existing diagnosis (21, 37). The trial was designed with a single interim analysis planned but following this the Data Safety Monitoring Committee recommended one more interim analysis and subsequently advised early termination. Early termination does increase the risk of an alpha error occurring (38).

This trial was designed with statistical power to detect a difference in an important biomarker of harm, hypoglycemia, rather than a patient-centered outcome. The biomarker of hypoglycemia was chosen because it is strongly associated with harm; there are plausible mechanistic pathways linking frequency, depth, duration and recurrent hypoglycemia with adverse clinical outcomes, and it had the capacity to be affected by the intervention(39).

Despite observing a significant decrease in incident hypoglycemia with the intervention, a corresponding improvement in patient-centered outcomes was not observed. Indeed, the point estimate of day 90 mortality treatment effect suggested a higher possibility of harm than benefit. While this trial was not adequately powered to determine the effect on mortality, the results suggest that the use of a liberal or personalized approach to blood glucose in critically ill patients should not be implemented outside carefully designed clinical trials. As quantification of HbA1c becomes quicker, trialists can more robustly test whether targeting blood glucose during critical illness based on pre-existing glucose metabolism improves outcomes.

Conclusions

When compared to commencing insulin at 180 mg/dL and targeting a range of 108 to 180 mg/dL, a 'liberal' approach to blood glucose reduced incident hypoglycemia but was not associated with improvement in patient-centered outcomes.

Author contributions

All authors contributed equally to this manuscript

Data sharing statement

Non-identifiable individual participant data that underlie the results reported in this trial will be made available after 4 years following publication and ending 7 years after publication. Availability will only be made to researchers who provide a written proposal for data evaluation that is judged to be methodologically sound by a committee approved by the LUCID Investigators. Proposals should be directed to alexis.poole@adelaide.edu.au and/or Adam.deane@mh.org.au. If the proposal is approved applicants will be required to sign a data access agreement and will remain solely responsible for all costs incurred with obtaining approval, drafting agreements and ensuring secure sharing of data.

Figure 1. Screening and randomisation in the LUCID Trial of a liberal approach to glucose control in critically ill patients with type 2 diabetes

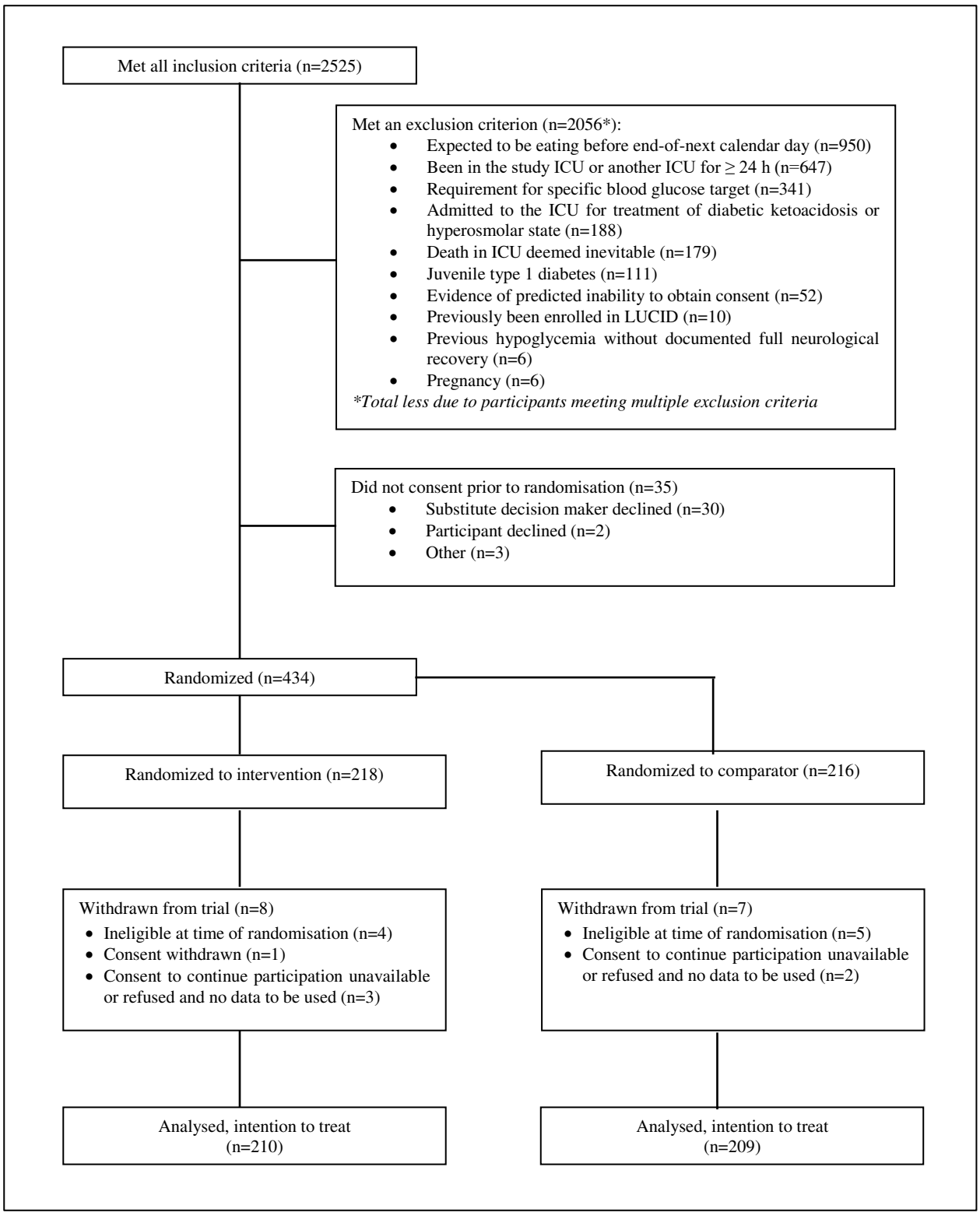

Figure 2. Proportion of blood glucose measurements within defined ranges by study group, days 1 to 7.

Blood glucose ranges:

- Below the comparator target range < 108 mg/dL (< 6 mmol/L)
- Within the comparator target range 108- <180 mg/dL (6- <10 mmol/L)
- Within the intervention target range 180- <252 mg/dL (10- <14 mmol/L)
- Above the intervention target range ≥ 252 mg/dL (≥ 14 mmol/L)

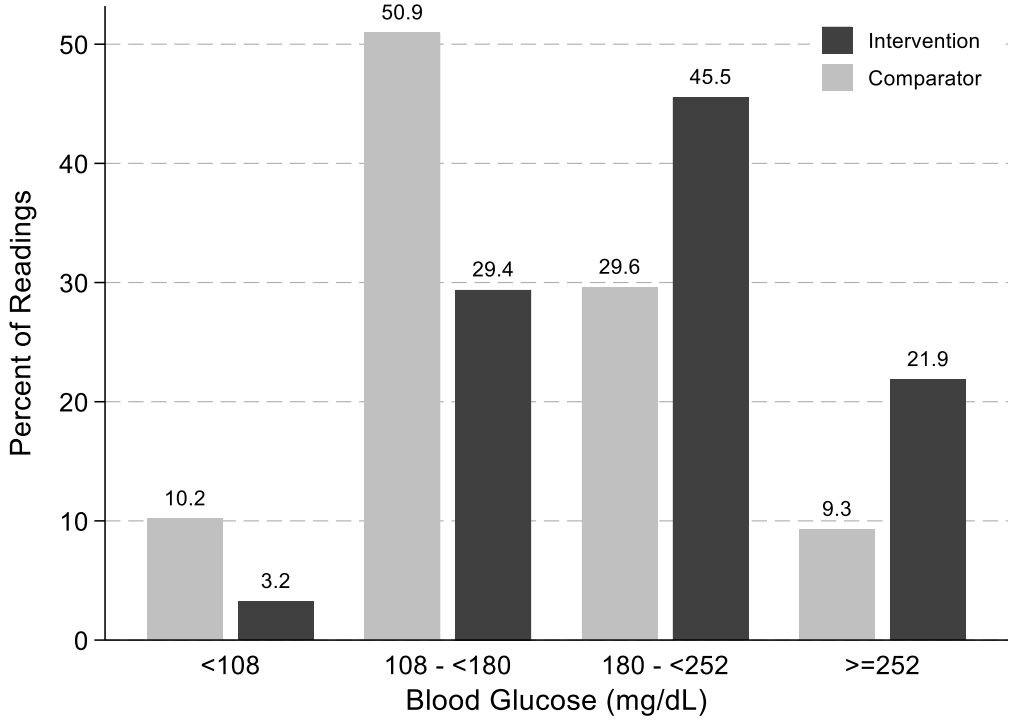

Figure 3. Mean blood glucose levels by study group for days 1 to 7. Solid circles = intervention, open circles = comparator group, error bars = 95% confidence interval for the mean, with the number of observations shown adjacent.

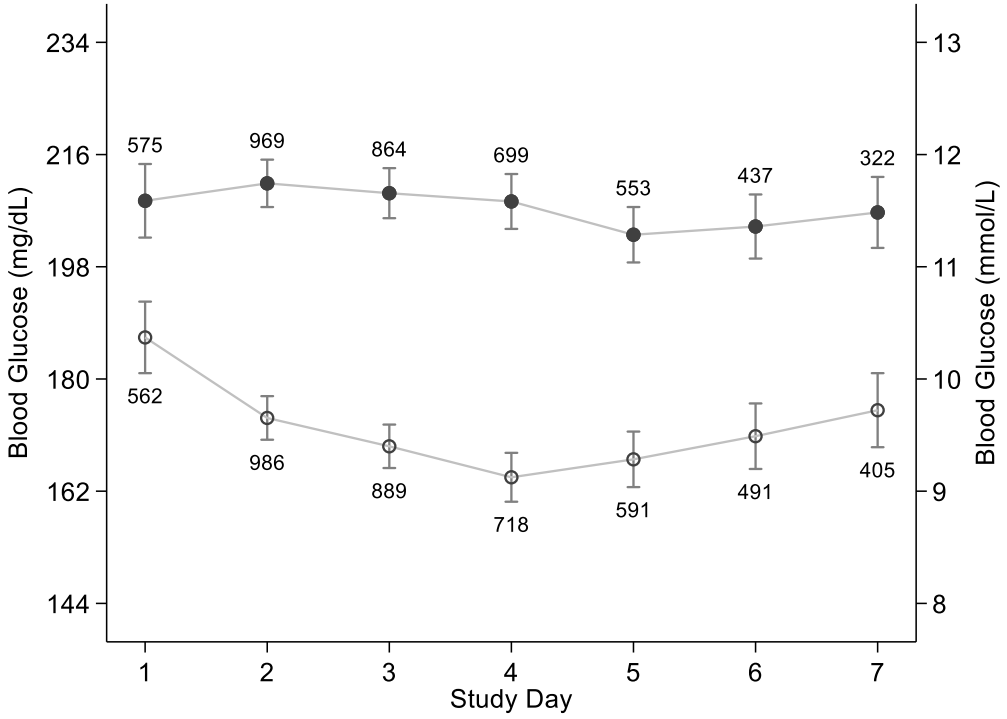

Table 1. Baseline characteristics

	Intervention	Comparator
Study subjects, N	210	209
Age (years), median [IQR]	67 [58, 75]	66 [58, 73]
Male, n (%)	138 (66)	136 (65)
APACHE II - Score, median [IQR]	20 [16, 26]	20 [16, 26]
APACHE III - Score, median [IQR]	74 [55, 95]	71 [58, 93]
SOFA Score, median [IQR]	8 [6, 10]	7 [6, 10]
HbA1c measured, n (%)	159 (76)	157 (75)
HbA1c %, median [IQR]	7.3 [6.4, 8.6]	7.3 [6.5, 8.8]
N ≥ 7% *(53 mmol/mol)*	94/159 (59)	91/157 (58)
Premorbid estimated average glucose (mg/dL)[a]	162 [137, 200]	162 [139, 205]
Diabetes Management, n/N (%)		
Diet only[b]	32/181 (18)	29/190 (15)
Oral metformin[c]	130/196 (66)	129/195 (66)
Other oral agent(s)[d]	79/189 (42)	69/184 (38)
Insulin (sub-cutaneous)	76/210 (36)	80/209 (38)
Insulin regimen,	76	80
≤ 2 doses per day[e]	51 (67)	53 (66)
> 2 doses per day[f]	11 (15)	17 (21)
Other[g]	14 (18)	10 (13)
APACHE IIIj Admission Diagnosis, n/N (%)		
Post-operative	82/209 (39)	74/206 (36)
Trauma	26/209 (12)	23/206 (11)
Sepsis / Septic Shock	25/209 (12)	34/206 (17)
Cardiothoracic Surgery	22/209 (11)	19/206 (9)
ICU source of admission, n (%)	210	209
Emergency Department	77 (37)	61 (29)
Ward	33 (16)	46 (22)
Other Hospital	20 (9.5)	16 (7.7)
Other ICU	6 (2.9)	11 (5.3)
OT/Recovery (Elective)	28 (13)	23 (11)
OT/Recovery (Emergency)	46 (22)	52 (25)
Mechanical ventilation, n (%)	187 (89)	191 (91)

Table 1. Baseline characteristics (continued)

	Intervention	Comparator
Chronic cardiovascular disease [h], n (%)		
No	96 (46)	93 (45)
Yes	111 (53)	113 (54)
Unknown	3 (1)	3 (1)
Retinopathy [i], n (%)		
No	162 (77)	157 (75)
Yes	23 (11)	31 (15)
Unknown	25 (12)	21 (10)
Nephropathy [j], n (%)		
No	154 (74)	149 (71)
Yes	41 (20)	41 (20)
Unknown	15 (7)	19 (9.1)

[a] 'premorbid estimated average glucose' calculated as (mg/dL) = 18 x (1.59 x HbA1c (%) − 2.59)

[b] 'Diet only' recorded if the participant used diet and no medication to control blood glucose prior to hospitalization.

[c] 'Oral metformin' recorded if the participant was taking metformin prior to hospitalization.

[d] 'Oral other' recoded if the participant was taking other oral therapies including but not limited to sulfonylureas prior to hospitalization.

[e] Insulin subcutaneous ≤2 recorded if the participant administered any type of subcutaneous insulin less than or equal to two times per day prior to hospitalization.

[f] Insulin subcutaneous >2 if the participant administered any type of subcutaneous insulin more than twice per day prior to

[g] Insulin via infusion or other means, or used another subcutaneous drug (e.g. Exenatide) prior to hospitalization.

[h] Chronic cardiovascular disease recorded any documented chronic cardiovascular disease including, but not limited to, hypertension or ischemic heart disease.

[i] Retinopathy recorded any documented pre-existing diabetes related disease of the retina.

[j] Nephropathy recorded documented pre-existing diabetes related nephropathy.

Table 2. Hypoglycemic episodes

	Intervention n=210	**Comparator n=209**	**p-Value**
Hypoglycemic Episodes [a], n (%)			<0.001
1	9 (4)	28 (13)	
2	0 (0)	6 (2.9)	
3	1 (1)	3 (1.4)	
4 or more	0 (0)	1 (0.5)	

Raw number of events without adjusting for hours of exposure using chi-squared analysis

[a] Hypoglycemic episode defined as blood glucose < 72 mg/dL (< 4.0 mmol/L)

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