A patient-level meta-analysis of Intensive glucose control in critically ill adults

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ABSTRACT (269 words)

BACKGROUND

Whether intensive glucose control reduces mortality in critically ill patients remains uncertain. Patient-level meta-analyses can provide more precise estimates of treatment effects than are currently available.

METHODS

We pooled individual patient data from randomized trials investigating intensive glucose control in critically ill adults. The primary outcome was in-hospital mortality. Secondary outcomes included survival to 90 days and time to live cessation of treatment with vasopressors or inotropes, mechanical ventilation, and newly commenced renal replacement. Severe hypoglycemia was a safety outcome. Trials that did not supply individual data were analyzed to inform a prior probability for a Bayesian analysis of the primary outcome.

RESULTS

Of 38 eligible trials (n=29537 participants), 20 (n=14171 participants) provided individual patient data including in-hospital mortality status for 7059 and 7049 participants allocated to intensive and conventional glucose control, respectively. Of these 1930 (27.3%) and 1891 (26.8%) individuals assigned to intensive and conventional control respectively died, risk ratio 1.02 (95% confidence interval [CI] 0.96 to 1.07; P=0.52; moderate certainty). There was no apparent heterogeneity of treatment effect on in-hospital mortality in any examined subgroups. Intensive glucose control increased the risk of severe hypoglycemia; risk ratio 3.38 (95% CI 2.99 to 3.83, p<0.0001).

CONCLUSIONS

Intensive glucose control was not associated with reduced mortality risk but increased the risk of severe hypoglycemia. We did not identify a subgroup of patients in whom intensive glucose control was beneficial.

(PROSPERO registration number CRD42021278869)

Introduction

Insulin resistance and stress hyperglycemia are common in acute and critical illness.[1,2] While hyperglycemia is associated with worse outcomes in critically ill patients,[3-8] this might indicate a causal relationship or that hyperglycemia and its degree are markers of severity of illness.[2,9] The landmark trials of Van den Berghe and colleagues which compared intensive insulin therapy targeting normoglycemia with acceptance of hyperglycemia in critically ill adults provided evidence in favour of a causal relationship.[10-12] In these trials, targeting normoglycemia was associated with reduced mortality in patients in surgical ICUs,[10] and reduced morbidity in patients in medical ICUs.[12] However, these results have not been replicated by other investigators.[13-39] Notably, the NICE SUGAR trial which recruited 6104 adult patients in 42 ICUs in Australia, New Zealand, Canada and the USA reported that targeting normoglycemia was associated with increased 90-day mortality.[26] Subsequent trial level meta-analyses did not support the use of intensive insulin therapy targeting normoglycemia,[11,40-42] and this was reflected in clinical practice guidelines which recommended tolerating hyperglycemia up to a blood glucose concentration of 180 mg/dL (10.0 mmol/L), and targeting a blood glucose concentration of 140 – 180 mg/dL (7.7 - 10.0 mmol/L) when treatment with insulin was started, recommendations that persist to this day.[43]

Hypotheses advanced for the discordant results of randomized trials of intensive glucose control in critically ill patients included heterogeneity of effect in subgroups of patients with different clinical characteristics or premorbid conditions,[8,44,45] interaction with feeding regimens, notably parenteral nutrition,[41] differing accuracy of blood glucose monitoring devices,[46,47] method of blood sampling for blood glucose measurement, and experience of the nursing staff managing blood glucose.[48] With the possible exception of the interaction of intensive glucose control with feeding regimens,[49,50] these hypotheses have not been tested in randomized controlled trials. Trial level metaanalyses have limited ability to explore subgroups effects whereas meta-analysis of individual patient data allows patients to be allocated to subgroups even when those subgroups were not explored in the individual trials and allows checking and verification of the results of the included trials. We conducted an individual patient data meta-analysis of randomised controlled trials of intensive glucose control in critically ill adults to estimate the effect of intensive glucose control on mortality overall and in prespecified subgroups.[51]

Methods

PROTOCOL AND REGISTRATION

This systematic review was pre-registered in PROSPERO (CRD42021278869) and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (PRISMA-IPD).[52] The study was designed by the authors and adheres to a published prtocol,[51] the data were gathered by the authors and analyzed by The George Institute for Global Health Biostatistics and Data Science Division, the authors vouch for the data and analysis, wrote and made the decision to publish the article.

ELIGIBILITY CRITERIA

We included randomized clinical trials of critically ill adults (aged 18 years or older) that compared outcomes in those randomly assigned intravenous insulin administration to target a blood glucose concentration of 120 mg/dL or less ($\leq$ 6.6 mmol/L) versus those assigned to a higher blood glucose target using intravenous insulin and where the blood glucose target was maintained for duration of intensive care unit stay or a minimum of seven days. We excluded trials conducted in coronary care or stroke units, those using glucose-insulin-potassium infusions, and where loss to follow-up exceeded 10% by hospital discharge.

SEARCH STRATEGY AND TRIAL SELECTION.

Electronic searches in MEDLINE, EMBASE, CCTR, clinical trials.gov, and the Australian New Zealand Clinical Trials Registry were conducted from the initiation of the project until 12 February 2024; (Supplementary Appendix Supplementary method S1 and statistical analysis plan) we set a cut-off date of 1 June 2023 by which in-principle agreement to share the data had to be obtained from the trial's principal investigator for their data to be included in the analysis. The eligibility of identified trials was assessed independently by two of three reviewers (LY, RC and DA) with disagreement resolved by a fourth reviewer (SF).

DATA COLLECTION AND INTEGRITY

Individual patient data were requested from all trials identified in the search. We requested trialists send us their study database; data were amalgamated into a single database at The George Institute for Global Health (Australia). Data quality and the integrity of the combined database were assessed by replicating the primary analysis of each trial and comparing with the published results of each trial; trialists were informed of any discrepancies which were resolved by consensus.

Trial level data for trials that did not provide individual patient data were extracted independently by two authors with any discrepancies resolved by agreement.

DATA ITEMS

The individual participant data requested from the collaborating trialists, and definitions of the data points are listed in Supplementary Appendix (Supplementary method S2). In brief, we requested data on patient demographics, nature and severity of critical illness, advanced life support treatments before and after enrolment and management of blood glucose and outcome data. Additionally, we requested data on the practices of ICUs contributing data to the individual trials. Specifically, their method of blood glucose measurement within the ICU, site of blood sampling for glucose measurements, type of inulin infusion system, and parenteral feeding policy at the time of the trial.

OUTCOMES

The primary outcome was in-hospital mortality censored at 90-days. Secondary outcomes included survival to 90 days after randomization, proportion of patients treated with mechanical ventilation, vasoactive agents (inotropic agents or vasopressors) and new renal replacement therapy and the time to alive cessation of those treatments. Severe hypoglycemia, defined as a blood glucose concentration of less than 40 mg/dL (less than 2.2 mmol/L), was a safety outcome.

SUBGROUP ANALYSES

Subgroup analyses were only performed for the primary outcome in subgroups characterised by individual patient pre-randomization variables and hospital or trial level variables. Pre-specified patient characteristics were operative (admitted to the ICU direct from the operating room or recovery room) versus non-operative patients (all others), prior diagnosis of diabetes or not, sepsis at baseline or not, acute brain injury or not, severity of illness score above or below median. Post-hoc, we performed a subgroup analysis based on patient sex as recorded in the original trial databases. ICU or trial characteristics defining subgroups were early parenteral feeding policy or not, type of blood glucose monitoring and insulin infusion device, site of blood sampling for glucose monitoring, unit experience with intensive glucose control by ICU (number of patients treated with intensive glucose control in each ICU within trial), control group target classified as intermediate (target of 180 mg/dL [10 mmol/L] or less) or higher. Full details of prespecified subgroups and hypothesized direction of treatment effect are given in the Supplementary Appendix (Supplementary method S3) and published protocol available at evidence.nejm.org.[51]

RISK OF BIAS ASSESSMENT AND CERTAINTY OF EVIDENCE

Risk of bias in the included studies and certainty of the review evidence was assessed using the Cochrane Risk of bias tool and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach for assessing certainty.[53,54] For the plain language description of treatment effects, time to event analyses were converted to the proportion of participants alive and free of intervention to day 90 using the method of Tierney et al.[55] (Supplementary appendix Supplementary Method S4)

ETHICAL SECONDARY USE OF TRIAL DATA

We adopted the principles of The Cochrane Handbook in respect of the use of individual patient data in meta-analyses the handbook states, "In most cases participants will not have specifically consented to inclusion (of their data) in the meta-analysis. However, as the meta-analysis is posing the same research question as, and is essentially updating, the trial they did consent to, the usual view is that separate consent is not required. However, it is advisable that data received are anonymised." In keeping with this principle, our meta-analysis addressed the same question as the trials for which we have data, and all data were anonymised prior to transfer.

STATISTICAL ANALYSIS

We followed two main approaches. First, a one-stage approach pooling the individual patient data and fitting hierarchical models that include trial as a random effect. For the main binary outcome, we used a hierarchical log-binomial model to estimate a pooled risk ratio and its 95% confidence interval (CI). Additionally, to account for possible convergence issues we also attempted to fit hierarchical Poisson or Logistic models (therefore presenting results as rate ratios or odds ratios, respectively). For the time-to-event analyses, we used mixed-effects parametric survival-time models (shared frailty Cox regression with frailty at trial level) with a conditional distribution of the response given the random effects assumed to be a Weibull distribution and results presented as conditional hazard ratios. We used maximum likelihood estimation with Laplace approximation in hierarchical log binomial models for binary outcomes, penalized partial likelihood estimation in Frailty Cox regression models for time-to-event outcomes. Subgroup analysis of each covariate was performed based on a single multilevel/hierarchical log binomial model where trial was specified as a random effect, and an interaction term between treatment and a subgroup covariate of interest was included in addition to these main effects.

Base case models were based on (hierarchical) univariable regressions with only treatment as a fixed-effect covariate. As sensitivity analyses, we assessed multivariable models to adjust for potential confounding factors

which include the following pre-defined variables: sex, age, baseline blood glucose concentration, ICU admission type, diagnosis of diabetes mellitus, and severity of illness.

Second, we pooled aggregate data of all eligible trials and performed a Bayesian random-effects meta-analysis. The results of the non-high risk of bias trials for which individual participant data were not available were used to create a meta-analytic prior distribution for the effect size. This historical/objective prior, combined with a vaguely informative prior for the between-trial variance informed a Bayesian analysis of the aggregate data of the trials for which individual participant data was available. The resulting posterior distribution of the mean effect size allowed the estimate of the probability that intensive glucose control is associated with a lower (or higher) mortality.

For the primary outcome of death during index hospital admission we also assessed the robustness of the results using a two-stage approach, first calculating summary results of the individual trials for which individual participant data were available and then pooling those results using an appropriate meta-analytic model. For the latter we fitted a random effects model based on a Sidik-Jonkman-Hartung-Knapp estimate of the between-trial standard deviation (τ). For time-to-live cessation of mechanical ventilation, inotropic agents or vasopressors, and of new treatment with renal replacement therapy, we assessed subhazard ratios (SHRs) by fitting a competing risks model with death as a competing event. Where data were missing we provide the denominator for the analysis; we did not impute missing data. Other than tests for heterogeneity for subgroups, analyses were not adjusted for multiplicity. The statistical analysis plan was finalized before the final dataset was analysed. Statistical analyses were performed using R (for the Bayesian meta-analysis using the package bayesmeta),[56] and Stata version 18 (StataCorp LLC).

Results

Our search identified 14,726 unique reports of which 38 published between 2001 and 2023 met inclusion criteria, (n=29,537 trial participants);[10,12,13,15-39,50,57-66] of these, 20 trials contributed individual patient data (n=14,171 eligible participants out of a total of 15,773 enrolled),[13,15,17-23,25-27,29-31,34,35,57,58,65] individual participants ineligible due to age or identifiable subgroups assigned to ineligible treatments were excluded. (Details in Supplementary Appendix Tables S1 and S2). Of the 18 trials (n=13,692 participants) for which we did not obtain individual participant data, four (n=472 participants) were adjudicated to be at high risk of bias,[59-61,63] and were excluded from shaping the prior probability for the Bayesian analysis. Publication dates ranged from 2001 to 2023. The PRISMA flow diagram and reasons for exclusion of trials are presented in Figure 1.

CHARACTERISTICS OF THE INCLUDED TRIALS AND TRIAL PARTICIPANTS

The characteristics of the trials that did and did not contribute individual participant data are presented in Tables S1 and S2 in the Supplementary Appendix. Data integrity checks of the individual participant data found discrepancies in the reporting of deaths in seven trials. Details of these discrepancies and their resolution are shown in Supplementary appendix Table S3. The baseline characteristics of the participants included in the individual patient data meta-analysis are shown in Table 1, and Supplementary appendix Table S4.

Figure 1: PRISMA Flow diagram

RISK OF BIAS WITHIN TRIALS

The results of the risk of bias assessment for the trials for which we aggregate data and individual patient data are provided in the Supplementary Appendix (Tables S5 and S6 respectively). Of the 20 trials with individual participant data, one was judged to be of high risk of bias;[22] of the 18 trials without individual patient data four were judged to be of high risk of bias.[59-61,63]

PRIMARY OUTCOME

The primary outcome of in-hospital death within 90 days was available for 7059 and 7049 participants allocated to intensive and conventional glucose control, respectively. Of these 1930 (27.3%) and 1891 (26.8%) participants assigned to intensive and conventional glucose control respectively died, risk ratio 1.02 (95% confidence interval [CI] 0.96 to 1.07), P=0.52. The result was unchanged in the models that included hospital as a random effect and six predefined covariates as fixed effects (Table 2 and Supplementary appendix Table S7); the certainty of evidence was judged to be moderate (Table 3).

Analysis of the 14 trials for which we only had aggregated data yielded a pooled risk ratio for in-hospital death of 0.94 (95% CI 0.74 to 1.20), I^2 71.4%, (Supplementary appendix Figure S3). This trial-set shaped the meta-analytic prior for the Bayesian meta-analysis and yielded a pooled effect for the primary outcome of 1.00 (95% CrI 0.92 to 1.08); I^2 19.6%; posterior probability that intensive glucose control is superior to conventional glucose control of 48.5%. (Table 2 and Figures S4 and S5). The results were similar using a flat/vague prior: pooled risk ratio 1.01 (95% CrI 0.92 to 1.09), I^2 19.1% and posterior probability of intensive glucose control superior to conventional glucose control of 42.8%. (Supplementary appendix Table S7 and Figures S4 and S5).The certainty of evidence was judged to be moderate (Table 3).

The results of the two-stage analysis were similar; risk ratio for in-hospital death for intensive glucose control compared to conventional glucose control 1.02 (95% CI 0.97 – 1.07) (Table 2 and Supplementary appendix Table S7).

PRIMARY OUTCOME IN SUBGROUPS

Results for the primary outcome in subgroups are given in Figure 2A and 2B. After correction for multiple hypothesis testing there was no apparent heterogeneity of the treatment effect in any of the subgroups. (Figure 2A)

There was no apparent heterogeneity of the treatment effect in patients characterized by ICU or trial level characteristics (Figure 2B).

SECONDARY OUTCOMES

Data on vital status and time to death at day 90 were available for 7060 and 7048 participants assigned to intensive glucose control and conventional glucose control, respectively, of these 2056 (28.3%) and 1990 (28.3%) participants assigned to intensive and conventional glucose control, respectively, had died; survival analysis hazard ratio1.03 (95% CI 0.97-1.10) (Table 2 and Supplementary appendix Figure S6).

The proportion of participants treated with mechanical ventilation was 6308/6785 (93.0%) and 6273/6777 (92.6%) for intensive and conventional glucose control respectively; RR 1.00 (95% CI 0.97 to 1.04) (Table 2 and Supplementary appendix Table S7). Data on time to alive cessation of mechanical ventilation were available for 6238 and 6191 participants assigned to intensive and conventional glucose control respectively, hazard ratio 1.00 (95% CI 0.96-1.04) (Table 2 and Supplementary appendix Figure S7).

The proportion of participants treated with inotropic agents or vasopressors was 4133/6366 (64.9%) and 4109/6376 (64.4%) assigned to intensive and conventional glucose control respectively; RR 1.01 (95% CI 0.96 to 1.05) (Table 2 and Supplementary appendix Table S7). Data on time to alive cessation of vasoactive agents were available for 4115 and 4094 participants assigned to intensive and conventional glucose control respectively, hazard ratio 0.96 (95% CI 0.91-1.00) (Table 2 and Supplementary appendix Figure S8).

The proportion of participants newly treated with renal replacement therapy was 465/4373 (10.6%) and 431/4394 (9.8%) assigned to intensive and conventional glucose control respectively; RR 1.08 (95% CI 0.96 to 1.22) (Table 2 and Supplementary appendix Table S7). Data on time to alive cessation of renal replacement therapy were available for 403 and 370 participants assigned to intensive and conventional glucose control respectively, hazard ratio 0.93 (95% CI 0.79-1.10) (Table 2 and Supplementary appendix Figure S9).

The two-stage analysis of proportions treated with mechanical ventilation, inotropic agents or vasopressors, and newly treated with renal replacement therapy yielded similar results, RR (95% CIs) 1.00 (1.00 – 1.01), 1.00 (0.98 – 1.02) and 1.08 (0.96 – 1.22) respectively, (Supplementary appendix Figures S10 - S12)

Analysis of time to alive cessation of mechanical ventilation, inotropic or vasopressor agents and new renal replacement therapy treating death as a competing event produced similar results, subhazard ratio (95% CI) 1.00 (0.94 to 1.04), 0.96 (0.92 to 1.00) and 0.92 (0.79 to 1.08) respectively (Supplementary appendix Table S7 and Figures S13-15). Certainty of evidence was judged high for time to alive cessation of inotropes/vasopressors and moderate for all other secondary outcomes. (Table 3).

Safety outcome

In pooled individual participant data, severe hypoglycemia (blood glucose concentration of less than 40 mg/dL; 2.2 mmol/L) occurred in 933/7018 (13.3%) and 277/7023 (3.9%) participants assigned to intensive and conventional glucose control respectively; risk ratio 3.38 (95% CI 2.99 to 3.83, p <0.0001). (Tables 2 and Supplementary appendix Table S7)

Discussion

This patient level meta-analysis found that intensive glucose control did not reduce in-hospital death in critically ill patients. The result was robust being unaltered by multivariate analyses and consistent in a Bayesian analysis informed by the data from trials from which we did not obtain patient level data. We did not find a subgroup of patients who benefitted from intensive glucose control or that ICU practices in the conduct of glucose control or feeding policies affected the results. The use of intensive glucose control markedly increased the risk of severe hypoglycemia.

Our findings on the overall effect of intensive glucose control are consistent with those of trial level meta-analyses,[11,40-42] but add additional analyses of possible effect modifiers. Our finding that the effect was not substantively modified by the feeding policies of the ICUs in which patients were recruited appears to contradict the conclusion of a meta-analysis with meta-regression that concluded that beneficial and detrimental effects of intensive glucose control were dependent on the proportion of calories delivered as parenteral nutrition.[41] Early use of parenteral nutrition was standard treatment in the participants of the first two trials conducted by Van den Berghe and colleagues,[10,12] subsequently the same group investigated the role of early versus late initiation of parenteral nutrition in patients undergoing intensive glucose control and found that late initiation of parenteral nutrition was associated with faster recovery and fewer complications.[49] Most recently a large randomized trial from the same group reported that intensive glucose control conferred no mortality benefit in critically ill patients not receiving early parenteral nutrition.[50] We used a threshold of 400 kcal per day during the first 72 hours of ICU treatment to define early parenteral nutrition, this is less than the trials of Van den Berghe and colleagues which aimed to deliver 20-30 kcal per kg body weight with almost all those calories being delivered parenterally during the first 3 days.[10,12] Our analysis can neither confirm nor refute the hypothesis that the apparent benefit of intensive glucose control in critically ill patients receiving early high dose parenteral nutrition results from increased control group mortality from untreated feeding-induced hyperglycemia.

That intensive glucose control use in critically ill patients is associated with an increase in risk of severe hypoglycemia has been reported in previous randomized trials and meta-analyses; our analysis of patient level data confirms that finding.

The strengths of our study include following a predefined protocol and statistical analysis plan, a comprehensive literature search, repeated efforts to contact the authors of all eligible studies, obtaining full trial datasets from contributing trialists, reanalysing those data to check for discrepancies against published results, and resolving any discrepancies that were found.

Our study's main weakness was not obtaining patient level data from all eligible trials. We addressed this by using the results of the trials from which we did not have data to inform the prior probability of a Bayesian analysis. Additionally, we limited our study to critically ill adults and cannot comment on the possible benefits or harms of intensive glucose control in critically ill children. Our subgroup analyses may have had inadequate statistical power to exclude clinically important effects and we cannot exclude heterogeneity of treatment effect based on subgroups or endotypes that can be identified with emerging analytic techniques.[67] Our analysis is also dependent and potentially limited by the internal and external validity of the included data which were generated over more than 20 years.

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In conclusion, intensive glucose control was not associated with reduced mortality or other benefits in critically ill adults. We did not identify any subgroup of patients in who intensive glucose control was beneficial.

Our study supports current recommendations to tolerate mild hyperglycemia in all critically ill adults with insulin treatment being reserved for those in who blood glucose exceeds 180 mg/dL (10.0 mmol/L), and adopting a blood glucose target of 140 to 180 mg/dL (7.8 to 10.0 mmol/L) in those patients who are treated with intravenous insulin.[43,68,69]

Table 1: Baseline characteristics of patients. (Full details in supplementary appendix Table S4)

	Intensive Glucose Control (N=7076)	Conventional Glucose Control (N=7064)
Age, years, mean (SD)	59.7 (17. 5)	59.8 (17.1)
Age – missing	66 (0.9%)	70 (1.0%)
Female sex n/N (%)	2543/7018 (36.2)	2579/7006 (36.8)
Body Mass Index, (kg/m²) mean (SD)	27.2 (7.0)	27.2 (6.6)
Body Mass Index - missing	878 (12.4%)	892 (12.6%)
Operative Admissions , n/N (%)	2599/6723 (38.7)	2622/6723 (39.0)
Non operative admissions, n/N (%)	4124/6723 (61.3)	4101/6723 (61.0)
Diabetes mellitus n/N (%)	1334/6726 (19.8)	1411/6711 (21.0)
Sepsis at randomisation n/N (%)	1223/4595 (26.6)	1193/4599 (25.9)
APACHE II score, mean (SD)	20.1 (8.09)	20.2 (8.36)
SAPS II score, mean (SD)	51.8 (18.96)	51.8 (19.43)
APACHE II or SAPS II score - missing	466 (6.6%)	451 (6.4%)
Vasopressor treatment n/N (%)	2513/4663 (53.9)	2511/4684 (53.6)
Mechanical ventilation n/N (%)	4641/5175 (89.7)	4609/5198 (88.7)
Renal replacement therapy n/N (%)	314/4386 (7.2)	309/4407 (7.0)
Blood Glucose concentration (mg/dL), mean (SD)	158.2 (69.9)	158.0 (63.6)
Blood Glucose concentration (mmol/L), mean (SD)	8.78 (3.88)	8.77 (3.53)
Blood glucose concentration - missing	525 (7.4%)	523 (7.4%)
Parenteral nutrition strategy* n/N (%)	1010/6540 (15.4)	1009/6522 (15.5)
Type of glucose monitoring device n/N (%)		
>= 80% bedside point of care meter	4298/7076 (60.7)	4234/7064 (59.9)
>= 80% laboratory or blood gas analyzer	1519/7076 (21.5)	1549/7064 (21.9)
Site of blood sampling n/N (%)		
arterial or central venous >=80%	4407/6540 (67.4)	4430/6522 (67.9)
predominantly capillary (>=80%)	419/6540 (6.4)	388/6522 (5.9)
mixed	1714/6540 (26.2)	1704/6522 (26.1)
Experience with intensive insulin treatment n/N (%)		
Lower tertile of ICUs	268/7076 (3.8)	293/7064 (4.1)
Middle tertile of ICUs	1145/7076 (16.2)	1181/7064 (16.7)
Upper tertile of ICUs	5663/7076 (80.0)	5590/7064 (79.1)
Insulin infusion via Syringe driver n/N (%)	4804/7076 (67.9)	4770/7064 (67.5)
Insulin infusion via Volumetric pump n/N (%)	2272/7076 (32.1)	2294/7064 (32.5)
Conventional glucose control target n/N (%)		
High (>180 mg/dL)	1379/7076 (19.5)	1369/7064 (19.4)
Intermediate (180 mg/dL or less)	5697/7076 (80.5)	5695/7064 (80.6)

ICU = intensive care unit. SD = standard deviation.
Operative = patients admitted to the ICU direct from the operating or recovery room after surgery, non-operative = all others.
APACHE II = Acute Physiology and Chronic Health Evaluation II score, a severity of illness score with values from 0-71 with higher scores indicating an increased risk of death.

SAPS II – Simplified Acute Physiology II a severity of illness score with values from 0-163 with higher scores indicating an increased risk of death.

* Strategy to deliver at least 400 Kcal per day as intravenous glucose or parenteral nutrition during first 72 hours of treatment in ICU

Trials that did not supply data by variable: Age: Wang 2006; Sex: Wang 2006; Body mass index (BMI): Wang, Oksanen, Zhang, Annane, Green, Cappi; Admission type – Wang, Zhang, Green, Cappi; Diabetes – Mitchell, Wang; Sepsis – Wang, Mackenzie, Zhang, Preiser, Green, Kalfon, Bohe: Trauma – Wang, Savioli, Annane, Cappi, Kalfon: Traumatic Brain Injury – Mitchell, Wang, Zhang, Preiser, Savioli, Annane, Cappi, Kalfon, Bohe; Severity of illness (APACHE II or SAPS II score) – Bilotta, Green, Savioli: Vasopressor – Hoedemaekers, Mitchell, Wang, Oksanen, Arabi 2008, De La Rosa, Zhang, Green, Arabi 2011, Cappi, Kalfon; Mechanical ventilation – Wang, De La Rosa, Zhang, Cappi, Kalfon; Renal replacement therapy – Hoedemaekers, Wang, Brunkhorst, De La Rosa, Zhang, Preiser, Green, Cappi, Kalfon; Blood glucose – Hoedemaekers, Wang, Oksanen, Brunkhorst; Parenteral feeding strategy – Preiser; Glucose monitoring device – none; Site of blood sampling – Preiser; Unit experience with IGC – none; Type of insulin infusion device – none.

Table 2: Outcomes

Outcome	No. of trials contributing data	Participants assigned intensive control	Participants assigned conventional control	Effect estimate (# = risk ratio or * = hazard ratio)	95% CI (# 95% CrI)	P Value
PRIMARY OUTCOME						
One stage analysis of IPD						
Risk Ratio (Model 1 - primary analysis)	20	7059	7049	1.02	0.96 to 1.07	0.52
Risk Ratio (Model 2)##	20	5683	5677	1.02	0.95 to 1.09	
Risk Ratio (Model 3)	20	7059	7049	1.02	0.97 to 1.08	
Risk Ratio (Model 4)##	20	5683	5677	1.02	0.95 to 1.10	
Two stage analysis of IPD trials	20	7059	7049	1.02	0.97 to 1.07	
Bayesian analysis	20	7059	7049	1.00	0.92 to 1.08#	
SECONDARY OUTCOMES						
Survival at day 90	20	7060	7048	1.03*	0.97 to 1.10	
Proportion of patients treated with mechanical ventilation	18	6785	6777	1.00#	0.97 to 1.04	
Time to alive cessation of mechanical ventilation (Hours)	18	6238	6191	1.00*	0.96 to 1.04	
Proportion of patients treated with inotropic agents or vasopressors	14	6366	6376	1.01#	0.96 to 1.05	
Time to alive cessation of inotropic agents or vasopressors (Hours)	13	4115	4094	0.96*	0.91 to 1.00	
Proportion of patients newly treated with renal replacement therapy	11	4373	4394	1.08#	0.96 to 1.22	
Time to alive cessation of new renal replacement therapy (Hours)	9	403	370	0.93*	0.79 to 1.10	
ADVERSE EVENTS						
Incidence of severe hypoglycaemia^	20	7018	7023	3.38#	2.99 to 3.83	<0.0001

# denotes result is risk ratio; * denotes hazard ratio

IPD = individual patient data; CI = confidence interval; CrI = credible interval, intervals have not been corrected for multiplicity.

Model 1: Outcome ~ Treatment (fixed effect) + Trial (random effect).

Model 2: Outcome ~ Treatment (fixed effect) + Trial (random effect) + 6 predefined covariates (fixed effects), ## number of participants reduced due to missing covariate data.

Model 3: Outcome ~ Treatment (fixed effect) + Trial /Hospital (2-level random effect).

Model 4: Outcome ~ Treatment (fixed effect) + Trial /Hospital (2-level random effect) + 6 predefined covariates (fixed effects) ## number of participants reduced due to missing covariate data.

All secondary outcomes are from model 1.

The Bayesian analysis uses the objective prior which is the prior probability derived from the eligible studies for which we did not have individual patient data (Figures S3 and S4).

^Severe hypoglycemia = blood glucose concentration <40 mg/dL (< 2.2mmol/L).

Table 3: Certainty of Evidence

Intensive glucose control in critically ill adults					
Population	**Critically ill adults treated in an ICU**				
Intervention	**Intensive insulin therapy - Blood glucose target of ≤ 6.6mmol/L (≤120mg/dL)**				
Comparison	**Conventional insulin therapy - Blood glucose target >6.6mmol/L (>120mg/dL)**				
Outcome	**Effect estimate** (95% CI) Number of trials Number of participants	**Absolute effect estimates (number of participants)**		**Certainty of evidence** (Quality of the evidence)	**Plain language summary**
		Intensive glucose control (95% CI)	**Conventional glucose control**		
In hospital mortality	Risk ratio of 1.02 (0.96 to 1.07) 20 trials 14,108 participants	273 per 1000 5 more per 1000 (6 fewer to 16 more)	268 per 1000	Moderate[a] Imprecision	Intensive glucose control probably has little to no effect on in-hospital mortality
Survival to 90 days after randomization	Hazard ratio of 1.03 (0.97,1.10) 20 trials 14,108 participants	289 per 1000* 7 more per 1000 (7 fewer to 23 more)	282 per 1000*	Moderate[a] Imprecision	Intensive glucose control probably has little to no effect on survival to 90 days
Proportion treated with mechanical ventilation	Risk ratio of 1.00 (0.97 to 1.04) 18 trials 13,562 participants	926 per 1000 0 fewer per 1000 (28 fewer to 37 more)	926 per 1000	Moderate[a] Imprecision	Intensive glucose control probably has no effect on the proportion of patients who receive mechanical ventilation
Time to alive cessation of mechanical ventilation	Hazard ratio of 1.00 (0.96,1.04) 18 trials 12,429 participants	840 per 1000* 0 fewer per 1000 (12 fewer to 11 more)	840 per 1000*	Moderate[b] Inconsistency	Intensive glucose control probably has no effect on the proportion of patients who are alive and free of mechanical ventilation to day 90
Proportion of patients treated with inotropes/vasopressors	Risk ratio of 1.01 (0.96,1.05) 14 trials 12,742 participants	650 per 1000 6 more per 1000 (26 fewer to 32 more)	644 per 1000	Moderate[a] Imprecision	Intensive glucose control probably has little to no difference on the proportion of patients treated with inotropes/vasopressors

Time to alive cessation of inotropes/vasopressor	Hazard ratio of 0.96 (0.91,1.00) 13 trials 8,209 participants	837 per 1000* 12 fewer per 1000 (28 fewer to 0 fewer)	849 per 1000*	High	Intensive glucose control is associated with slightly fewer patients alive and free of vasopressors to day 90
Proportion of patients newly treated with renal replacement therapy	Risk ratio of 1.08 (0.96,1.22) 11 trials 8,767 participants	106 per 1000 8 more per 1000 (4 fewer to 22 more)	98 per 1000	Moderate[a] Imprecision	Intensive glucose control probably has little to no difference in the proportion of patients newly treated with renal replacement therapy
Time to alive cessation of new treatment with renal replacement therapy	Hazard ratio of 0.93 (0.79,1.10) 9 trials 773 participants	734 per 1000* 25 fewer per 1000 (84 fewer to 32 more)	759 per 1000*	Moderate[a] Imprecision	Intensive glucose control probably has little to no difference in the proportion of patients alive and free of renal replacement therapy to day 90
Incidence of severe hypoglycaemia (blood glucose <40 mg/dL [<2.2mmol/L])	Risk ratio of 3.38 (2.99,3.83) 20 trials 14,041 participants	133 per 1000 94 more per 1000 (78 more to 112 more)	39 per 1000	Moderate[c] Inconsistency	Intensive glucose control is probably associated with an increase in the incidence of severe hypoglycaemia

* Time to event analyses (Hazard ratios) converted to absolute risk of the event of interest occurring within 90 days of randomization. (See Supplementary Appendix Supplementary Method S4)
a: 95% CI do not exclude patient important differences
b: Heterogeneity in the results evidenced by $I^2 =73.6\%$
c: Heterogeneity in the results evidenced by $I^2=70.0\%$

Data sharing

Requests for access to data should be directed to the investigators of the included trials who retain ownership of their data. The authors of this meta-analysis do not have legal authority to share those data.

Conflict of interest statement

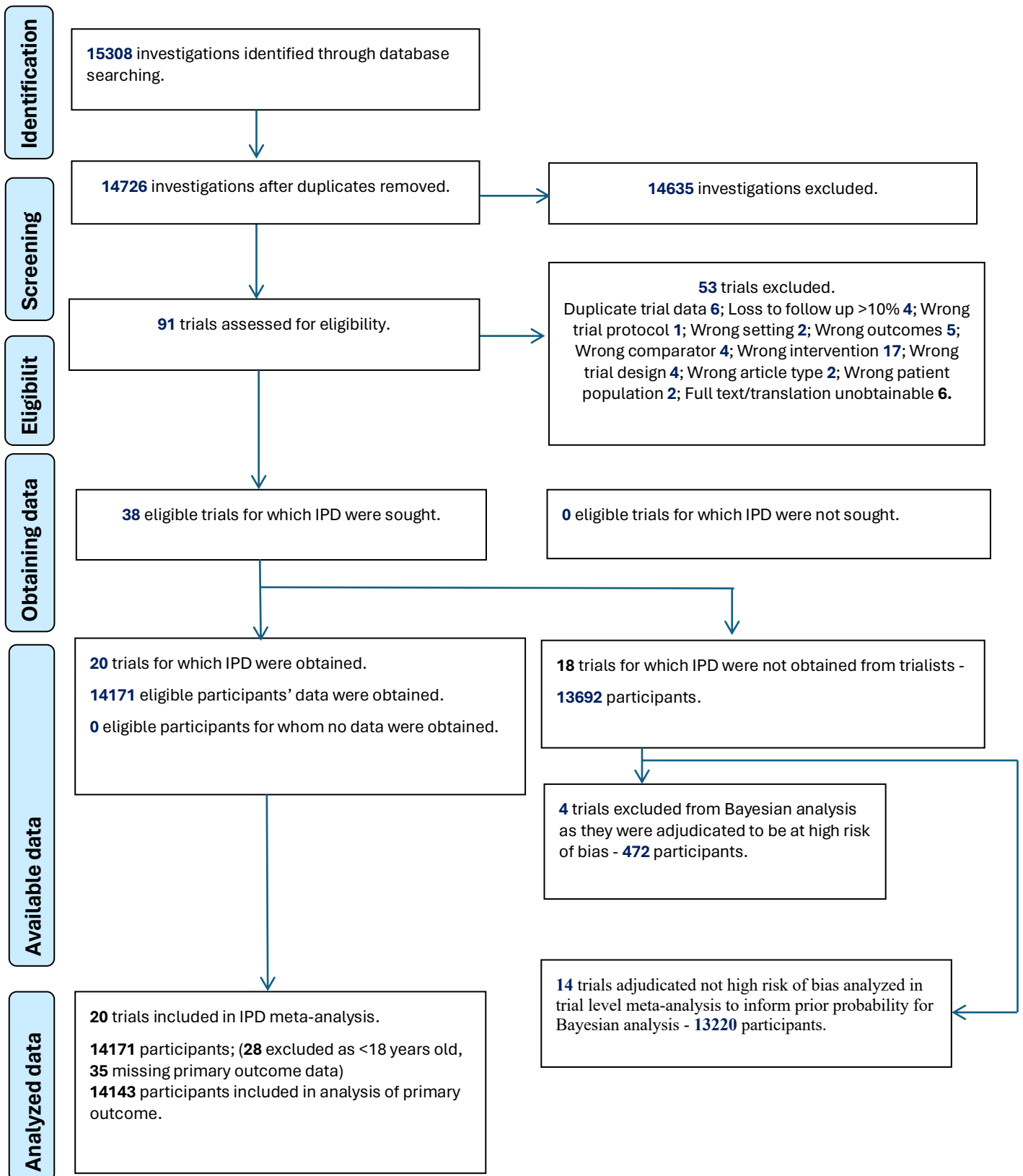The authors have declared no relevant conflicts.

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Identification

15308 investigations identified through database searching.

Screening

14726 investigations after duplicates removed.

14635 investigations excluded.

Eligibilit

91 trials assessed for eligibility.

53 trials excluded.
Duplicate trial data 6; Loss to follow up >10% 4; Wrong trial protocol 1; Wrong setting 2; Wrong outcomes 5; Wrong comparator 4; Wrong intervention 17; Wrong trial design 4; Wrong article type 2; Wrong patient population 2; Full text/translation unobtainable 6.

Obtaining data

38 eligible trials for which IPD were sought.

0 eligible trials for which IPD were not sought.

Available data

20 trials for which IPD were obtained.

14171 eligible participants' data were obtained.

0 eligible participants for whom no data were obtained.

18 trials for which IPD were not obtained from trialists - 13692 participants.

4 trials excluded from Bayesian analysis as they were adjudicated to be at high risk of bias - 472 participants.

14 trials adjudicated not high risk of bias analyzed in trial level meta-analysis to inform prior probability for Bayesian analysis - 13220 participants.

Analyzed data

20 trials included in IPD meta-analysis.

14171 participants; (28 excluded as <18 years old, 35 missing primary outcome data)
14143 participants included in analysis of primary outcome.

IPD = individual patient data

Figure 2A

Subgroup	IGC n/Total(%)	CGC n/Total(%)	Relative Risk [95% CI]	Relative Risk [95% CI]
Sex				
Female	723/2537 (28.5)	713/2569 (27.8)		1.01 [0.93, 1.10]
Male	1200/4464 (26.9)	1153/4422 (26.1)		1.04 [0.97, 1.11]
ICU admission type				
Non-operative	1294/4119 (31.4)	1306/4098 (31.9)		0.99 [0.93, 1.05]
Operative	586/2587 (22.7)	524/2610 (20.1)		1.13 [1.02, 1.25]
Diabetes mellitus				
No	1363/5381 (25.3)	1322/5288 (25.0)		1.02 [0.95, 1.09]
Yes	435/1328 (32.8)	428/1408 (30.4)		1.04 [0.93, 1.16]
Sepsis				
No	872/3371 (25.9)	846/3406 (24.8)		1.04 [0.96, 1.12]
Yes	429/1208 (35.5)	390/1179 (33.1)		1.09 [0.98, 1.21]
Brain injury				
No	1083/3710 (29.2)	1022/3721 (27.5)		1.06 [0.98, 1.13]
Yes	94/615 (15.3)	105/597 (17.6)		0.88 [0.68, 1.14]
Systemic corticosteroids treatment				
No	772/3121 (24.7)	706/3154 (22.4)		1.11 [1.01, 1.21]
Yes	265/701 (37.8)	260/677 (38.4)		0.99 [0.87, 1.13]
Severity of illness (median APACHE II or SAPS II score)				
<Median	489/3002 (16.3)	478/3082 (15.5)		1.05 [0.93, 1.19]
≥Median	1348/3591 (37.5)	1329/3516 (37.8)		0.99 [0.92, 1.07]

Favors IGC   Favors CGC

0.5   1.0   2.0

Figure 2B

Subgroup	IGC n/Total(%)	CGC n/Total(%)	Relative Risk [95% CI]	Relative Risk [95% CI]
Early parenteral feeding policy				
No	1509/5513 (27.4)	1462/5498 (26.6)		1.03 [0.97, 1.09]
Yes	296/1010 (29.3)	324/1009 (32.1)		0.93 [0.82, 1.05]
Type of glucose monitoring device				
Bedside point of care glucometer	1175/4282 (27.4)	1186/4219 (28.1)		0.98 [0.91, 1.05]
Laboratory or blood gas analyser	439/1519 (28.9)	408/1549 (26.3)		1.09 [0.97, 1.22]
Mixed	316/1258 (25.1)	297/1281 (23.2)		1.08 [0.94, 1.24]
Site of blood sampling				
Arterial or central venous	1230/4391 (28.0)	1190/4416 (26.9)		1.04 [0.97, 1.11]
Capillary	82/419 (19.6)	93/388 (24.0)		0.84 [0.67, 1.07]
Mixed	493/1713 (28.8)	503/1703 (29.5)		0.98 [0.88, 1.08]
Unit experience with IGC				
1st tertile [0,12 participants)	73/267 (27.3)	89/289 (30.8)		0.83 [0.65, 1.07]
2nd tertile [12,38 participants)	362/1131 (32.0)	381/1171 (32.5)		0.98 [0.87, 1.10]
3rd tertile (≥38 participants)	1495/5661 (26.4)	1421/5589 (25.4)		1.04 [0.98, 1.11]
Type of insulin-infusing system				
Syringe system	1277/4788 (26.7)	1252/4755 (26.3)		1.01 [0.95, 1.08]
Volumetric system	653/2271 (28.8)	639/2294 (27.9)		1.03 [0.94, 1.13]
Control group target				
Intermediate	1527/5695 (26.8)	1462/5694 (25.7)		1.04 [0.98, 1.11]
High	403/1364 (29.5)	429/1355 (31.7)		0.94 [0.84, 1.05]

Favors IGC   Favors CGC

0.5   1.0   1.5