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ORIGINAL

Glycemic control, mortality, and hypoglycemia in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials

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Abstract

Purpose: It is unclear whether tight glycemic control is warranted in all critically ill adults. We employed network meta-analysis to examine the risk of mortality and hypoglycemia associated with different glycemic control targets in critically ill adults.

Methods: Electronic databases were searched up to 2016 for randomized controlled trials comparing various insulin regimens in critically ill adults with hyperglycemia. Two reviewers independently extracted information and evaluated quality with the Cochrane risk-of-bias tool. Four glycemic control groups were compared: tight (blood glucose: 4.4 < 6.1 mmol/l), moderate (6.1 < 7.8 mmol/l), mild (7.8 < 10.0 mmol/l), and very mild (10.0 to < 12.2 mmol/l). Network meta-analysis was performed by a frequentist approach with multivariate random effects meta-analysis.

Results: Thirty-six randomized trials (17,996 patients) were identified. Compared with very mild control, tight control did not reduce the risk of short-term mortality [relative risk (RR) 0.94 (95 % CI 0.83–1.07, $p = 0.36$)], and neither did mild control [RR 0.88 (0.73–1.06), $p = 0.18$] or moderate control [RR 1.1 (0.66–1.84), $p = 0.72$]. However, severe hypoglycemia (<2.2 mmol/l) was more frequent with tight control than very mild control [RR 5.49 (3.22–9.38), $p < 0.001$] or mild control [RR 4.47 (2.5–8.03), p < 0.001]. Stratified analyses (cause of death, ICU type, time period, or diabetes) did not find significant between-group differences. Ranking analysis revealed the following hierarchy for avoiding death (highest to lowest rank): mild control, tight control, and very mild control.

Conclusions: Network meta-analysis showed no mortality benefit of tight glycemic control in critically ill patients, but fivefold more hypoglycemia versus mild or very mild control.

Keywords: Glycemic control, Hypoglycemia, Mortality, Meta-analysis

Introduction

Most observational studies have found that hyperglycemia and hypoglycemia are strongly associated with adverse outcomes in patients receiving critical care [1–3]. It is unclear whether tight glycemic control is warranted in all critically ill adults. Early randomized controlled trials (RCTs) suggested that intensive treatment of hyperglycemia improved hospital outcomes [4, 5]. However, most of the trials performed subsequently in critically ill patients have failed to show significant improvement of mortality with tight glycemic control or have even shown an increased risk of mortality [6]. Moreover, RCTs have highlighted the risk of severe hypoglycemia resulting

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Take-home message: Network meta-analysis showed no mortality benefit of tight glycemic control in critically ill patients, but fivefold more hypoglycemia versus mild or very mild control.

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from efforts to maintain tight glycemic control [7, 8]. Four previous meta-analyses of RCTs examined the risks and benefits of tight glycemic control compared with care in critically ill adult patients [9–12]. However, all these studies were traditional pairwise meta-analyses and only the pooled relative risk (RR) was calculated by direct comparison, although these studies had heterogeneous target blood glucose levels that limits the meaningfulness of making comparisons among them. The American Diabetes Association recommends a target glucose range of 7.8–10.0 mmol/l (140–180 mg/dl) for the majority of critically ill patients receiving insulin therapy for persistent hyperglycemia (Grade A) [13]. However, no meta-analysis has confirmed the clinical significance of these recommendations.

In the present study, our objective was to systematically evaluate the mortality rate and frequency of severe hypoglycemia associated with various target glucose levels in critically ill patients with hyperglycemia receiving insulin therapy. We investigated RCTs using a network meta-analysis approach, which enabled us to assess four glucose targets by mixed and direct comparison to determine their efficacy and safety.

Methods

Search strategy

We searched PubMed (from 1950 to March 2, 2016), the Cochrane library (to issue 3, 2016), and Web of Science (from 1970 to March 2, 2016) for original reports of RCTs that compared different glycemic control strategies using insulin in critically ill patients with hyperglycemia (Supplementary Table 1). We checked the reference lists of the original studies, review articles, and meta-analyses identified by our electronic searches to find other eligible trials. There were no language restrictions on the search.

Study selection

Eligible randomized trials fulfilled the twin criteria of (1) comparing various insulin regimens in critically ill (e.g., ICU) adult patients (≥18 years old) with hyperglycemia, and (2) reporting outcomes of interest. Studies were excluded if other aspects of care apart from the target glucose level (e.g., oral hypoglycemic agents) differed between the groups. Studies assessing children or glucose-potassium-insulin (GKI) regimens were also not eligible. Furthermore, reviews and abstracts reported at scientific sessions were excluded.

Quality assessment

Two authors (T.Y., N.S.) independently assessed the eligibility of each trial, extracted data, and evaluated trial bias risk. Disagreements were resolved by consensus. We used the trial risk of bias assessment scheme recommended by the Cochrane Collaboration for assessment of quality [14]. Trials with a high or unclear risk of bias for any components were classed as trials with a high risk of bias, while all other trials were classed as having a low risk of bias.

Data extraction and synthesis

Baseline demographic data, trial design, insulin therapy, and outcomes were extracted from each trial. The investigators of each study were contacted by e-mail to obtain missing information as needed. For this analysis, four treatment groups were identified: (1) a tight glycemic control group (target glucose level of 4.4 to <6.1 mmol/l), (2) a moderate glycemic control group (target glucose level of 6.1 to <7.8 mmol/l), (3) a mild glycemic control group (target glucose level of 7.8 to <10.0 mmol/l), and (4) a very mild glycemic control group (target glucose level of 10.0 to <12.2 mmol/l). When the glucose targets of candidate trials were not consistent with the above four categories, the trials were excluded. We chose these four target glucose ranges in accordance with the 2015 clinical practice recommendations of the American Diabetes Association [13].

Study outcomes

In accordance with a previous meta-analysis [9–12], the primary efficacy outcome was short-term mortality, which was defined as 90-day mortality or (if unavailable) hospital mortality, 28-day mortality, ICU mortality, or 6-month mortality. The secondary efficacy outcomes were (1) ICU mortality, (2) 28-day mortality, (3) hospital mortality, (4) 90-day mortality, and (5) 6-month mortality. The primary safety outcome was hypoglycemia (defined as a blood glucose level <3.3 mmol/l), while the secondary safety outcome was severe hypoglycemia (defined as a blood glucose level <2.2 mmol/l). Other definitions of hypoglycemia (e.g., <4.4 mmol/l) were not classified as hypoglycemia and were excluded from the analysis.

Statistical analyses

Comparison of treatments

Network meta-analysis was performed by a frequentist-based approach with multivariate random effects meta-analysis [15–18]. The covariance between two estimates from the same study (sharing a common treatment group) is the variance of data in the shared arm and is calculated by the multivariate meta-analysis method. Inconsistency of the network model was estimated by using inconsistency factors and their uncertainty.

In addition, ranking plots (rankograms) were constructed using the probability that a given treatment had the highest event rate for each outcome. The surface

under the cumulative ranking curve (SUCRA), which is a simple transformation of the mean rank, was used to set the hierarchy of the treatments. As the SUCRA becomes larger, the treatment in question receives a lower rank [19, 20]. In addition, clustered ranking plots were constructed using SUCRA values for efficacy (mortality) and safety (hypoglycemia) outcomes to obtain information on treatments that maximized the benefit for both mortality and hypoglycemia. We performed ranking analysis of three regimens [tight control (4.4 to <6.1 mmol/l) vs. mild control (7.8 to <10.0 mmol/l) vs. very mild control (10.0 to <12.2 mmol/l) and excluded moderate control (6.1 to <7.8 mmol/l)] because fewer studies ($n = 4$) assessed this regimen than any other regimen, and one of the four studies [21] had a high risk of bias that might have led to misinterpretation of the results.

Direct comparison meta-analysis

In addition to network meta-analysis, direct comparison meta-analysis was performed by using data for the closed loop in the network analysis. Meta-analyses were performed in line with the recommendations of the Cochrane Collaboration, the Preferred Reporting Items for Systematic Reviews, Meta-Analyses (PRISMA) statement [14, 22], and the GRADE Working Group approach (Checklists 1, 2) [23].

Heterogeneity was assessed by using the I^2 statistic [24]. Summary effect sizes and their 95 % confidence intervals were calculated by the random effects model of DerSimonian and Laird [24]. Publication bias was estimated visually with funnel plots, and also by using Begg's test and the weighted regression test of Egger. All analyses were performed using standard software (Stata 13.0, Stata, TX, USA) and $p < 0.05$ indicates statistical significance.

Sensitivity analyses

Three sensitivity analyses were performed to assess heterogeneity by (1) investigating trial quality, (2) by excluding studies in which the glycemic control regimen differed somewhat from the four categories that we selected, and (3) by stratification for the cause of death [sepsis (septic shock), or cardiovascular mortality] and the intensive care unit (ICU) setting. The ICU setting was stratified into 3 categories: (1) surgical (including general surgical, cardiothoracic, neurosurgical, and trauma ICUs); (2) medical (including general medical, cardiac, and neurologic ICUs); and (3) mixed medical–surgical ICUs. For trials that did not specify the ICU setting, we categorized it as mixed medical–surgical. Analyses stratified for the presence of diabetes were also performed, and we used the method of Altman et al. [25] to evaluate whether the pooled RRs differed between groups stratified by diabetes. Moreover, we performed a meta-regression analyses to explore the sources of heterogeneity, and we examined whether variables such as diabetes had a significant influence on the risk of mortality.

Results

Selection and characteristics of the studies

We identified 36 randomized trials that satisfied the inclusion criteria, which covered a total of 17,996 patients ($n = 8956$ in the intensive care group and $n = 9050$ in the control care groups) [4–6, 21, 26–57] (Supplementary Fig. 1). The network of treatment comparisons are displayed in Fig. 1.

The baseline characteristics of the trials are presented in Table 1 and Supplementary Table 2. Trials were conducted in diverse countries, but most often at a single center. The prevalence of hypoglycemia ranged widely among the studies. The definition of hypoglycemia was heterogeneous, and five studies were excluded from analysis of hypoglycemia because of the lack of data describing hypoglycemic events [26–29] or an unsuitable definition of hypoglycemia (<4.4 mmol/l) [30].

Risk of bias

Supplementary Fig. 2 summarizes the risk of bias for the domains included in the Cochrane tool of risk assessment. In all 36 studies, the risk of bias was high for blinding of participants and personnel because physicians were not blinded to the interventions in any study. Fourteen studies (39 %) had a high (6 %) [21, 29] or unclear (33 %) risk of bias in the domain of allocation concealment. Conversely, there was generally a low risk of bias for blinding of outcome assessment, generation of the randomization sequence, and incomplete outcome data. However, one study [21] had a high risk of bias with regard to generation of the randomization sequence because it was a randomized quasi-experimental trial. The attrition rate was reasonable in most studies with loss to follow-up of 0–2 %, but was unknown for 5 studies. All studies employed intention-to-treat (ITT) analysis.

Network meta-analysis

Efficacy outcomes

All-cause mortality Analysis performed with mixed treatment comparison models (data from 36 randomized trials including 17,996 patients and 4684 events) using very mild glycemic control as the reference revealed no statistically significant difference of all-cause mortality among the glycemic control regimens [RR 0.88 (0.73–1.06), $p = 0.18$ for mild control; RR 1.1 (0.66–1.84), $p = 0.72$ for moderate control; and RR 0.94 (0.83–1.07), $p = 0.36$ for tight control] (Fig. 2). Ranking analysis revealed that the hierarchy for efficacy in avoiding death (highest to lowest rank) was mild control (SUCRA 14.0), followed by

Checklist 1 PRISMA checklist

Section/topic	No.	Checklist item	Reported on page no.
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2–3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	–
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	5–6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	5–6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	5–6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	6–7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis	7–9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	8–9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	8–9
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	10–13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	10–13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	12–13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16])	12–14

Checklist 1 continued

Section/topic	No.	Checklist item	Reported on page no.
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers)	15–17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	17–18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	18–19
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	19

From: [63]. For more information, visit: www.prisma-statement.org

tight control (SUCRA 52.6) and then very mild control (SUCRA 81.4) (Supplementary Fig. 3a, b).

There was no evidence of statistical inconsistency between the direct and indirect estimates ($p = 0.05$ for the very mild–mild–tight control loop vs. $p = 0.92$ for the mild–moderate–tight control loop). Similarly, when very mild glycemic control was used as the reference, there was no significant difference in the rate of all-cause death compared with the other regimens (Fig. 3; Supplementary Fig. 4). There was no evidence of statistical inconsistency between the direct and indirect estimates (data not shown).

Safety outcome

Hypoglycemia In the mixed treatment comparison models with data from 31 randomized trials including 17,502 patients and 1449 events, tight control was associated with a higher risk of hypoglycemic events when compared with very mild glycemic control and mild control [RR 5.64 (95 % confidence interval 3.69–8.61, $p < 0.001$) vs. very mild control and RR 4.67 (95 % confidence interval 2.75–7.94), $p < 0.001$ vs. mild control] (Fig. 2).

Ranking analysis revealed that the hierarchy for safety in avoiding hypoglycemia (highest to lowest rank) was very mild control (SUCRA 14.6), followed by mild control (SUCRA 35.4) and tight control (SUCRA 100.0) (Supplementary Fig. 5a, b).

There was no evidence of statistical inconsistency between the direct and indirect estimates (data not shown). There was also no evidence of a small-study effect in any of the models (data not shown).

Severe hypoglycemia Similarly, analysis of data from 22 randomized trials including 16,120 patients and 1020 events showed that tight control was associated with a higher risk of severe hypoglycemic events compared with very mild control and mild control (RR 5.49 (95 % confidence interval 3.22–9.38), $p < 0.001$ vs. very mild control and RR 4.47 (95 % confidence interval 2.5–8.03), $p < 0.001$ vs. mild control] (Fig. 2). There was no evidence of statistical inconsistency between the direct and indirect estimates (data not shown).

Clustered ranking plot

Figure 4 showed a plot of the combined ranking for both all-cause mortality (efficacy) and hypoglycemia (safety). The ideal glycemic control regimen would decrease mortality and also reduce the occurrence of hypoglycemic events. Unfortunately, none of the reported regimens maximized the benefit for both mortality and hypoglycemia. However, the results of our analysis suggested that mild glycemic control (7.8 to <10.0 mmol/l) achieves the best outcome for all-cause mortality.

Sensitivity analyses

The results were largely similar for sensitivity analysis (1) based on trial quality (excluding data [21] that were considered to have a high risk of selection bias) and sensitivity analysis (2) excluding studies in which the glycemic control regimen differed somewhat from our 4 categories (e.g., the target glucose level was <12.2 mmol/l with no lower limit, which we categorized as very mild control). The sensitivity analysis employing stratification by the type of ICU revealed no significant difference of mortality among the four glycemic control targets (Fig. 5).

Analyses stratified by presence of diabetes also revealed no significant interaction for this relationship (all p values for interaction >0.05) (Supplementary Fig. 6).

Furthermore, we performed a sensitivity analysis stratified by the cause of death (Supplementary Figs. 7, 8). Similar to the findings for all-cause mortality, this analysis indicated that mortality due to sepsis or cardiovascular causes did not differ significantly between treatment groups (all p values were >0.05, as shown in Supplementary Fig. 7).

Ranking analysis suggested that the hierarchy for avoiding death due to sepsis (highest to lowest rank)

Checklist 2 Confidence in the relative risk of all-cause mortality assessed by the GRADE system

	Study limitations	Imprecision	Heterogeneity	Indirectness	Publication bias	Confidence in relative risk of the event
Tight vs. very mild	In RCTs using insulin to attain the target glycemic level, it is impossible to employ blinding of physicians	0.94 (0.83–1.07), not serious	No significant heterogeneity by the *I*-squared test	Not serious	Not suggested by head-to-head funnel plots	Moderate (downgraded by one level due to study limitations)
Moderate vs. very mild		1.1 (0.66–1.84), not serious	No significant heterogeneity by the *I*-squared test	Not serious	Not suggested by head-to-head funnel plots	Moderate (downgraded by one level due to study limitations)
Mild vs. very mild		0.88 (0.73–1.06), not serious	–	Serious (no head-to-head trial)	–	Low (downgraded by two levels due to study limitations and no head –to-head trial)
Tight vs. mild		1.07 (0.93–1.23), not serious	No heterogeneity by the *I*-squared test	Not serious	Not suggested by head-to-head funnel plots	Moderate (downgraded by one level due to study limitations)
Moderate vs. mild		1.25 (0.75–2.08), not serious	No significant heterogeneity by the *I*-squared test	Not serious	Not suggested by head-to-head funnel plots	Moderate (downgraded by one level due to study limitations)
Tight vs. moderate		0.86 (0.52–1.41), not serious	No significant heterogeneity by the *I*-squared test	Not serious	Not suggested by head-to-head funnel plots	Moderate (downgraded by one level due to study limitations)

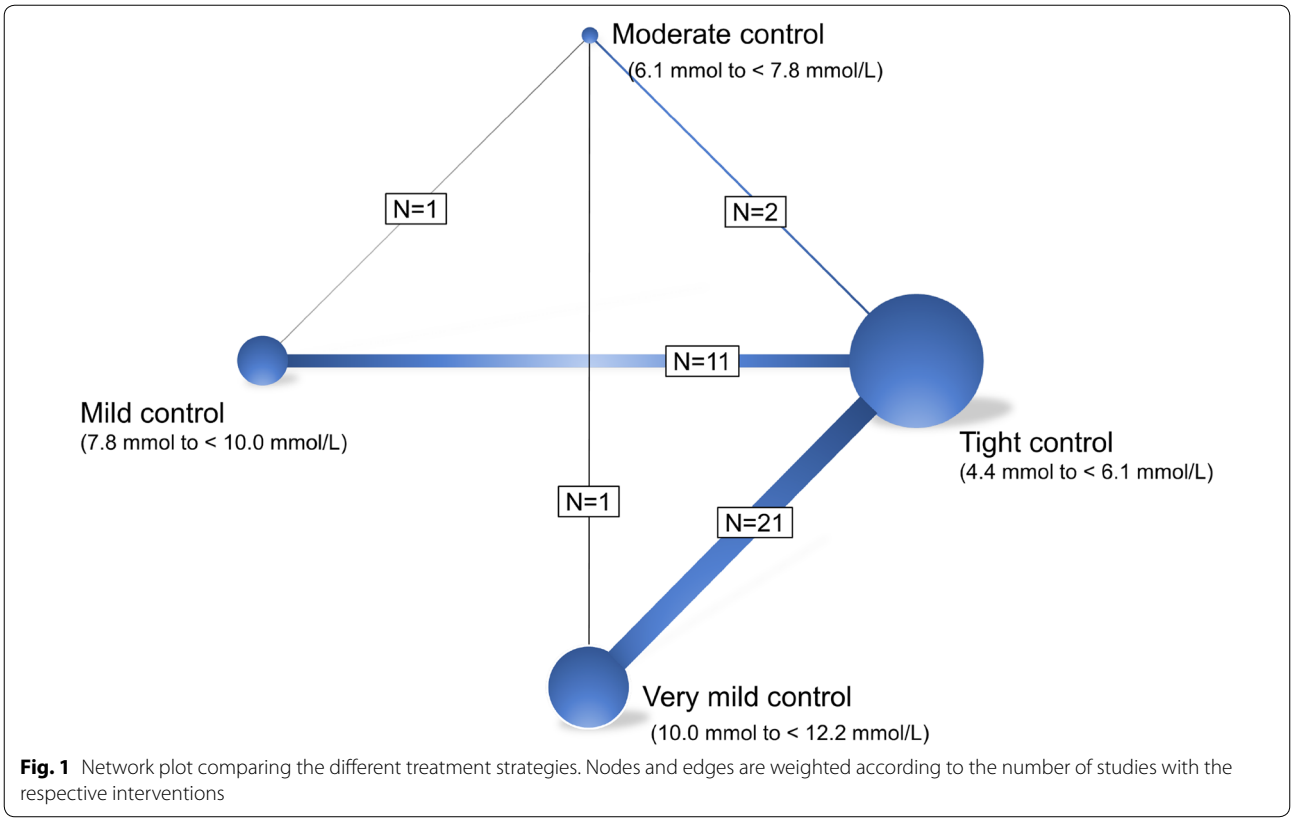


Fig. 1 Network plot comparing the different treatment strategies. Nodes and edges are weighted according to the number of studies with the respective interventions

was mild glycemic control (target glucose level: 7.8 to <10.0 mmol/l), followed by tight control (4.4 to <6.1 mmol/l) and then very mild control (10.0 to <12.2 mmol/l). However, the hierarchy for avoiding cardiovascular mortality was very mild glycemic control (target glucose level: 10.0 to <12.2 mmol/l), followed by mild control (7.8 to <10.0 mmol/l) and then tight control (4.4 to <6.1 mmol/l) (Supplementary Fig. 8).

Direct comparison

Regarding the efficacy outcomes, the direct comparison meta-analysis found that there was no statistically significant difference of short-term mortality between tight glycemic control and very mild control [pooled RR 0.95 (95 % CI 0.83–1.08), $p = 0.46$, $I^2 = 0$ %)] (Supplementary Fig. 9) or mild control (pooled RR 1.06 (95 % CI 0.97-1.15), $p = 0.18$, $I^2 = 0$ %)] (Supplementary Fig. 10). These results were similar to those obtained using the fixed comparison model. Funnel plots showed relatively good symmetry, arguing against the presence of publication bias (Supplementary Fig. 11). There was also no evidence of publication bias according to Begg's test and Egger's test (see p values in the figures).

Analysis stratified by the presence of diabetes showed similar results [with diabetes: RR 1.07 (0.9–1.28), $p = 0.42$, $I^2 = 0$ %, p for heterogeneity =0.75; without diabetes: RR 1.0 (0.91–1.1), $p = 0.99$, $I^2 = 50$ %, p for heterogeneity =0.054; p for interaction 0.52] (Supplementary Fig. 12a and b).

Finally, meta-regression analysis demonstrated that the presence of diabetes at baseline was not significantly related to the risk of mortality ($p = 0.96$) (Supplementary Fig. 13).

Discussion

The present network meta-analysis of randomized trials of intensive insulin therapy in critically ill patients failed to find any benefit of tight glycemic control for all-cause mortality, but tight glycemic control increased the frequency of hypoglycemia and severe hypoglycemia by about fivefold compared with mild or very mild glycemic control. All stratified analyses of mortality [stratified by the type of ICU (medical, surgical, or mixed), the time period (ICU stay, hospital stay, 28 days, 3 months, or 6 months), or the presence of diabetes] did not identify any significant differences among the glycemic control groups. Even though better glycemic control is potentially beneficial, achieving tight control for a short period could have too small an effect to influence mortality.

Our network meta-analysis did not assess whether short-term hypoglycemia actually increased mortality. Even though hypoglycemia itself has a potential adverse

Table 1 Target glucose levels and mean achieved levels in all trials included in the network meta-analysis

Author, year	Mortality (setting and duration)	No. of patients total (stricter/std)	Stricter control			Standard control		
			Target glucose[a]	Mean achieved glucose (mmol/l)[b]	Severe hypoglycemia	Target glucose[a]	Mean achieved glucose (mmol/l)[b]	Severe hypoglycemia
Mitchell (2006) [31]	ICU, hospital	70 (35/35)	Tight	5.4	14 %	Very mild	7.8	0 %
McMullin (2007) [32]	ICU, hospital	20 (11/9)	Tight	6.6	55 %	Mild	9.5	11 %
Brunkhorst (2008) [33]	28-day, 90-day	536 (247/289)	Tight	6.2	17 %	Very mild	8.4	4 %
Iapichino (2008) [26]	ICU, 90-day	72 (36/36)	Tight	6.1	NA	Very mild	9.1	NA
De La Rosa (2008) [34]	ICU, 28-day, hospital	504 (254/250)	Tight	6.7	8 %	Very mild	8.3	1 %
Arabi (2008) [35]	ICU, hospital	523 (266/257)	Tight	6.4	29 %	Very mild	9.5	3 %
NICE-SUGAR (2009) [6]	ICU, 28-day, hospital, 90-day	6022 (3010/3012)	Tight	6.4	7 %	Mild	8.0	0 %
Van den Berghe (2006) [5]	ICU, 28-day, hospital, 90-day	1200 (595/605)	Tight	6.2	19 %	Very mild	8.5	3 %
Farah (2007) [27]	ICU, 28-day, hospital	89 (41/48)	Moderate	7.9	NA	Mild	9.7	NA
Oksanen (2007) [36]	28-day	90 (39/51)	Tight	5.0	0 %	Moderate	6.4	0 %
Bruno (2008) [37]	90-day	46 (31/15)	Tight	7.4	6 %	Very mild	10.6	0 %
Van den Berghe (2001) [4]	ICU, hospital	1548 (765/783)	Tight	5.7	5 %	Very mild	8.5	1 %
Grey (2004) [38]	Hospital	61 (34/27)	Tight	6.9	NA	Very mild	9.9	NA
Bilotta (2007) [28]	6-month	78 (40/38)	Tight	5.0	NA	Very mild	8.3	NA
Preiser (2009) [39]	ICU, 28-day, hospital	1078 (536/542)	Tight	6.5	8 %	Mild	8.0	2 %
Staszewski (2011) [40]	28-day	50 (26/24)	Tight	6.0	0 %	Mild	6.8	0 %
Green (2010) [41]	90-day	81 (45/36)	Tight	6.2	4 %	Mild	7.9	0 %
Coester (2010) [42]	ICU, hospital, 6-month	79 (39/40)	Tight	6.7	15 %	Mild	7.8	0 %
Johnston (2009) [43]	90-day	73 (24/49)	Tight	6.2	NA	Very mild	8.4	NA
Yang (2009) [44]	Hospital, 6-month	233 (117/116)	Tight	NA	3 %	Very mild	NA	3 %
Kreisel (2009) [45]	6-month (4 month)	40 (20/20)	Tight	6.5	NA	Very mild	8.0	NA
Azevedo (2007) [46]	ICU	48 (31/17)	Tight	7.7	6 %	Mild	8.2	6 %
Cappi (2012) [47]	28-day, hospital	63 (28/35)	Tight	5.5	7 %	Mild	8.6	6 %
COIITSS (2010) [48]	28-day, hospital, 90-day	543 (255/288)	Tight	6.7–7.8	16 %	Very mild	7.8–8.9	8 %
Savioli (2009) [29]	ICU	90 (45/45)	Tight	6.2	NA	Very mild	8.8	NA

Table 1 continued

Author, year	Mortality (setting and duration)	No. of patients total (stricter/std)	Stricter control			Standard control		
			Target glucose[a]	Mean achieved glucose (mmol/l)[b]	Severe hypoglycemia	Target glucose[a]	Mean achieved glucose (mmol/l)[b]	Severe hypoglycemia
Rosso (2012) [49]	90-day	180 (90/90)	Tight	5.7	NA	Moderate	6.5	NA
Gandhi (2007) [50]	28-day	371 (185/186)	Tight	6.3	NA	Very mild	8.7	NA
Bilotta (2009) [51]	6-month	482 (241/241)	Tight	5.1	NA	Very mild	8.0	NA
Cao (2011) [52]	Hospital	179 (92/87)	Tight	5.5	7 %	Very mild	9.9	1 %
Arabi (2011) [53]	ICU, 28-day, hospital, 6-month	240 (120/120)	Tight	6.2	32 %	Very mild	8.6	7 %
Desai (2012) [54]	28-day	189 (91/98)	Tight	NA	2 %	Mild	NA	0 %
Lazar (2011) [30]	28-day	82 (40/42)	Tight	5.7	NA	Mild	7.5	NA
Giakoumidakis (2013) [21]	28-day, hospital	212 (105/107)	Moderate	8.6	0 %	Very mild	9.7	0 %
Chan (2009) [55]	28-day	109 (54/55)	Tight	7.1	NA	Very mild	9.3	NA
Kalfon (2014) [56]	ICU, 28-day, hospital, 90-day	2648 (1317/1284)	Tight	6.5	13 %	Mild	6.9	6 %
Henderson (2009) [57]	28-day	67 (32/35)	Tight	6.2	25 %	Very mild	8.3	3 %

NA not available because lack of data or different criteria for severe hypoglycemia (e.g., <4.4 or <3.3 mg/dl; we defined severe hypoglycemia as <2.2 mg/dl)

[a] Tight glycemic control group (target glucose level of 4.4–6.1 mg/dl), Moderate glycemic control group (target glucose level of 6.1–7.8 mg/dl), Mild glycemic control group (target glucose level of 7.8–10.0 mg/dl or <10.0 mg/dl), and Very mild glycemic control group (target glucose level of 10.0–12.2 mg/dl or <11.1 mg/dl or <12.2 mg/dl)

[b] If the mean achieved glucose level was not reported, we used the median value

influence on the risk of death, transient hypoglycemia in the hospital setting over a short period (several days to weeks) might not have a significant impact. However, hypoglycemia could cause other harms that are less obvious than death, but may well be clinically significant, such as cognitive and vision-related sequelae [58, 59]. Complex trade-offs may occur between tight glycemic control and hypoglycemia in critically ill patients. Moreover, it is possible that there was no statistically significant impact due to the short follow-up period.

Ranking analysis suggested that the hierarchy for avoiding death due to sepsis (highest to lowest rank) was in the order of mild control, tight control, and then very mild control, while the hierarchy for avoiding cardiovascular mortality was very mild control, mild control, and then tight control.

Since sepsis was the chief cause of death in all of the studies used for analysis of cause-specific mortality, we considered that sepsis might have the strongest influence on all-cause mortality in relation to glycemic control. It is possible that sepsis-related mortality was lowest in patients managed with mild glycemic control (target glucose: 7.8 to <10.0 mmol/l) due to the balance between the adverse influence of hyperglycemia on immune function and the adverse influence of hypoglycemia on infection. In contrast, the finding that cardiovascular mortality was highest with tight glycemic control (target glucose: 4.4 to <6.1 mmol/l), followed by mild control (target glucose: 7.8 to <10.0 mmol/l) and then very mild control (target glucose: 10.0 to <12.2 mmol/l) suggested that hypoglycemia might have an adverse influence on cardiovascular events. These differing results indicate that the optimal glycemic target might vary depending on the cause of death.

It is also possible that these results of ranking analysis (probability analysis) represent random chance, because there were no significant differences among the different glycemic control regimens with regard to sepsis-related or cardiovascular-related death.

In contrast to our present results, most observational studies have found that hyperglycemia and hypoglycemia

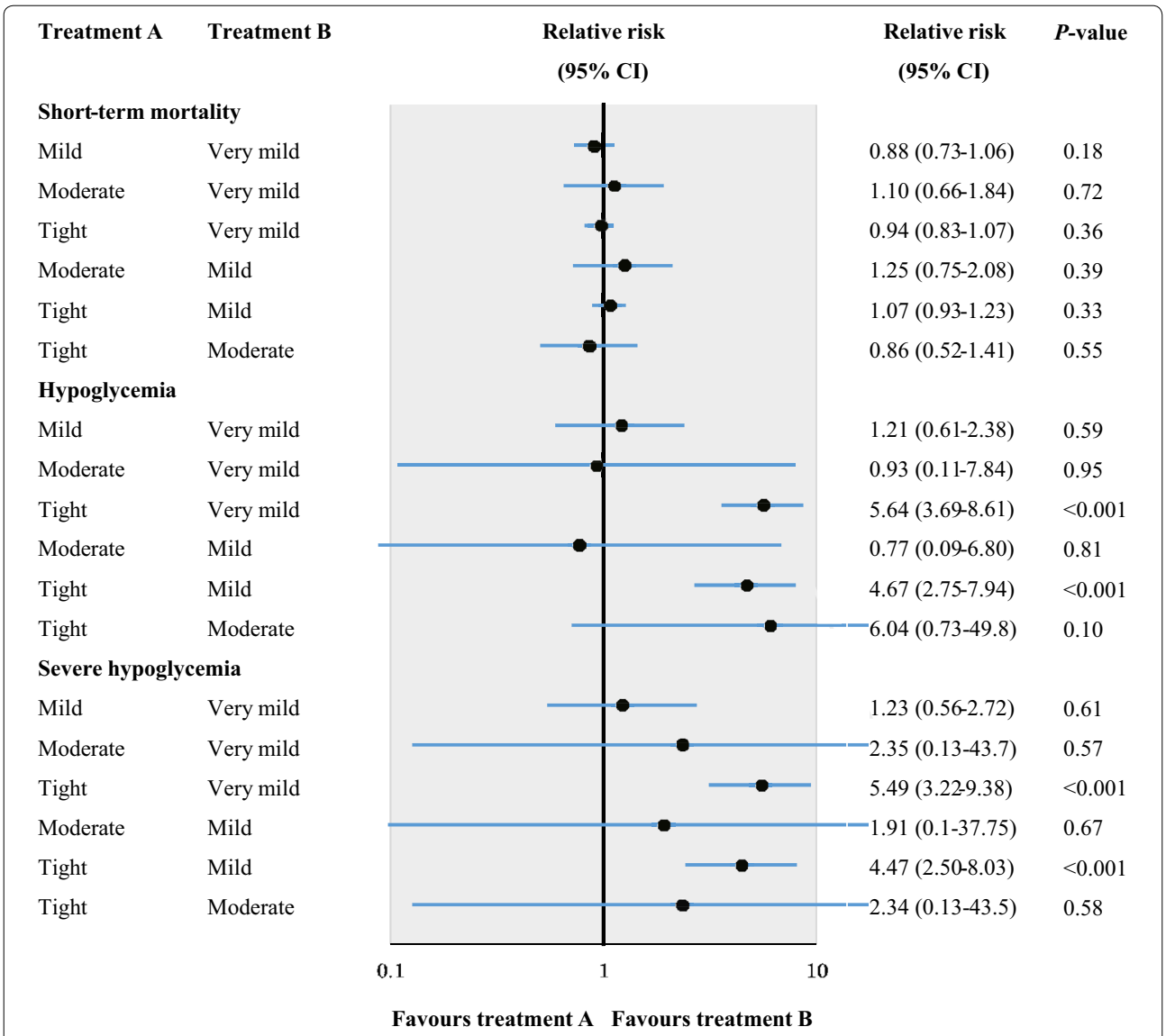
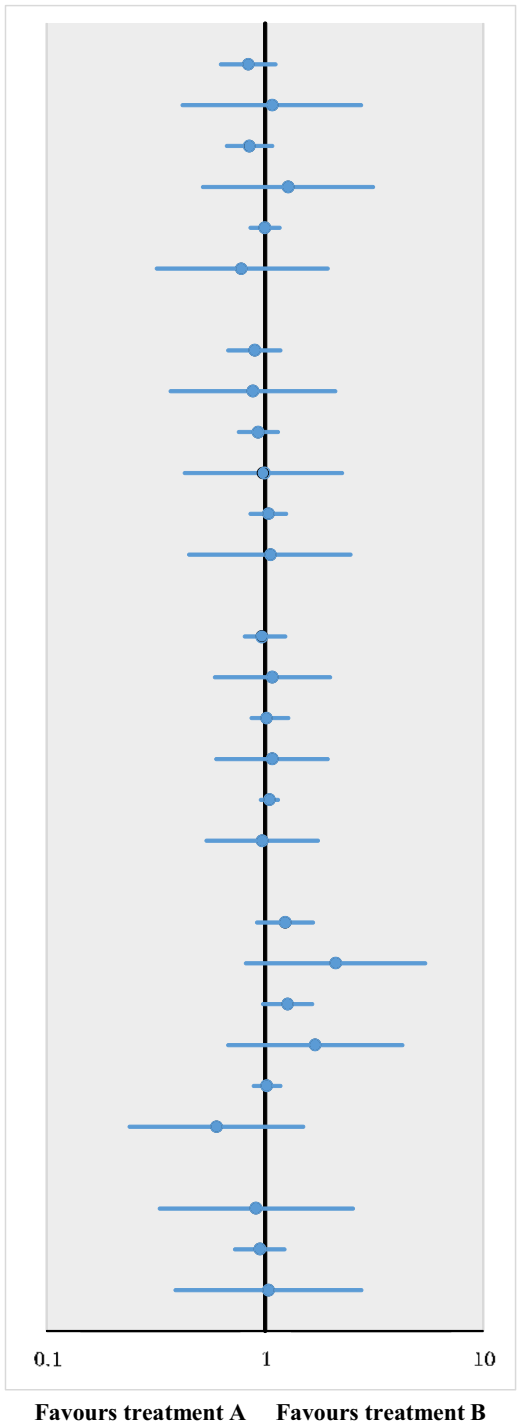


Fig. 2 Comparison of various glycemic targets using the mixed treatment comparison model with respect to (**a**) short-term mortality, (**b**) hypoglycemia, and (**c**) severe hypoglycemia

are strongly associated with adverse outcomes in critically ill patients [1–3], which suggests that observational studies are inevitably influenced by various biases. It is also possible that patients with better glycemic control were healthier than patients with poor control, so the difference in mortality might simply reflect a difference in the severity of their underlying diseases (reverse causality). There is no doubt that the influence of reverse causality could explain some of the discrepancies between our findings and those reported previously.

The controversy concerning glycemic control was initiated by the first report of van den Berghe et al. [4] and continued by the results of studies such as the NICE-SUGAR trial [6]. While van den Berghe et al. [4] reported that intensive glycemic control was beneficial for ICU patients, the NICE-SUGAR trial did not show any such benefit, and actually demonstrated an increase of mortality in the intensive insulin therapy group [6]. Many authors and editorialists have since argued that the differing results could be explained by differences in patient characteristics (reason for hospitalization, glycemic control before admission, dialysis, septicemia, etc.) and the setting (surgical vs. medical vs. mixed ICU). Other factors have also been suggested, such as the age, sex, comorbidities, staff-to-patient ratio, staff experience, and frequency of blood glucose measurement.



Treatment A	Treatment B	Relative risk (95% CI)	*P*-value
ICU mortality			
Mild	Very mild	0.84 (0.63-1.12)	0.24
Moderate	Very mild	1.08 (0.42-2.76)	0.87
Tight	Very mild	0.85 (0.67-1.08)	0.18
Moderate	Mild	1.28 (0.52-3.13)	0.59
Tight	Mild	1.00 (0.86-1.17)	0.95
Tight	Moderate	0.78 (0.32-1.94)	0.60
Hospital mortality			
Mild	Very mild	0.86 (0.68-1.10)	0.23
Moderate	Very mild	0.87 (0.38-1.99)	0.74
Tight	Very mild	0.89 (0.74-1.08)	0.24
Moderate	Mild	1.00 (0.45-2.26)	0.99
Tight	Mild	1.04 (0.89-1.21)	0.64
Tight	Moderate	1.03 (0.45-2.34)	0.93
28-day mortality			
Mild	Very mild	0.94 (0.75-1.16)	0.55
Moderate	Very mild	1.02 (0.55-1.88)	0.96
Tight	Very mild	0.99 (0.81-1.20)	0.88
Moderate	Mild	1.09 (0.61-1.95)	0.78
Tight	Mild	1.05 (0.96-1.15)	0.26
Tight	Moderate	0.97 (0.54-1.74)	0.92
90-day mortality			
Mild	Very mild	1.11 (0.83-1.50)	0.48
Moderate	Very mild	1.89 (0.73-4.88)	0.19
Tight	Very mild	1.14 (0.88-1.48)	0.33
Moderate	Mild	1.70 (0.68-4.27)	0.26
Tight	Mild	1.02 (0.89-1.18)	0.74
Tight	Moderate	0.6 (0.24-1.50)	0.28
6-month mortality			
Mild	Very mild	0.91 (0.33-2.53)	0.86
Tight	Very mild	0.95 (0.73-1.23)	0.68
Tight	Mild	1.04 (0.39-2.77)	0.94

Fig. 3 Comparison of various glycemic targets using the mixed treatment comparison model with respect to (**a**) ICU mortality, (**b**) hospital mortality, (**c**) 28-day mortality, (**d**) 90-day mortality, and (**e**) 6-month mortality

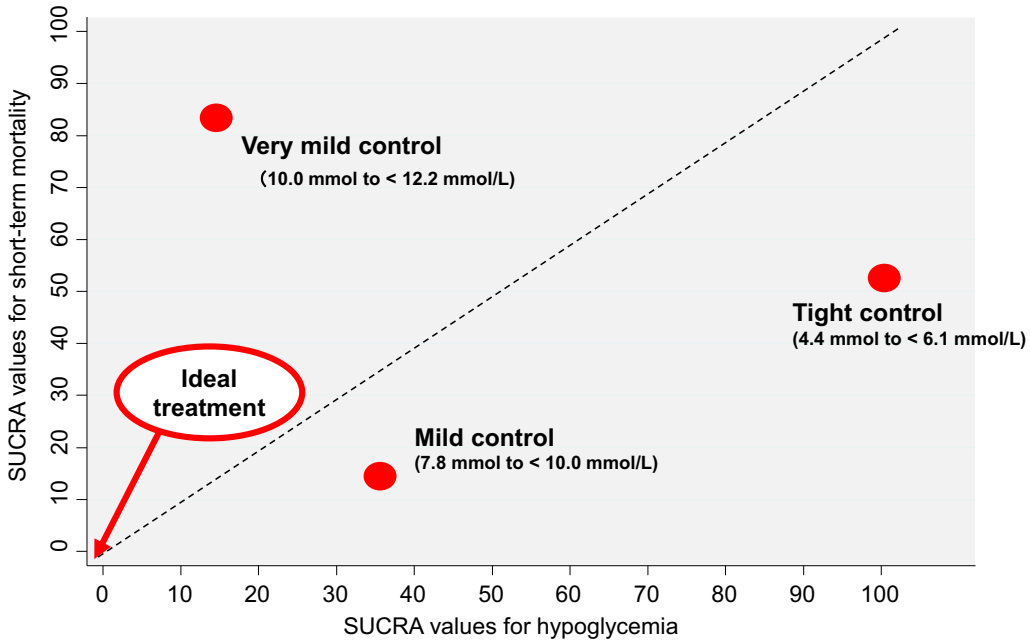


Fig. 4 Clustered ranking plot of short-term mortality and hypoglycemia with various glycemic control strategies. As the surface under the cumulative ranking curve (SUCRA) value becomes higher, the efficacy (no short-term mortality) and safety (no hypoglycemia) both decrease. The hypothetical ideal glycemic control regimen has the best outcomes for both mortality and hypoglycemia

The present network meta-analysis found no increase in the risk of mortality with tight glycemic control, while previous studies have demonstrated an increase. This difference may have arisen because previous investigations employed simple pairwise meta-analysis and ignored the differing glycemic control targets of the studies analyzed. Accordingly, the present network meta-analysis may provide more precise risk estimates and better information about the hierarchy of target glucose ranges for achieving safe and effective glycemic control with insulin in critically ill patients. The clustered ranking plot (Fig. 4) suggests that mild glycemic control (7.8 to <10.0 mmol/l) achieves the best outcome in relation to all-cause mortality and hypoglycemia, which is consistent with the American Diabetes Association guideline [13] and the AACE/ADA target glucose levels [60].

Strengths and limitations

The strengths of this network meta-analysis were as follows. First, it included several large-scale randomized controlled trials based on intention-to-treat analysis of target glycemic control goals. Second, we performed sensitivity analyses of cause-specific mortality that yielded important findings.

Regarding limitations, we did not review all the available research because we did not include grey literature (conference proceedings and unpublished data) due to concern about the reliability and quality of such information and the potential for large biases. However, we consider that the sample of studies was adequate because we carefully reviewed the references of all literature identified (including reviews) and analyzed approximately 40 articles. In addition, we evaluated publication bias and confirmed that there was no significant bias. Second, there was no blinding of the patients and physicians in any of the RCTs that we analyzed. Also, there were wide variations among the studies with regard to baseline patient characteristics (e.g., age and sex), insulin protocols, target glucose levels, and nutritional supplementation, all of which might have significantly impacted the endpoints.

Third, although network meta-analysis allowed us to compare the efficacy and safety of several glycemic control strategies, we acknowledge the limitation that interpretation of a network meta-analysis relies on there being sufficient homogeneity among trials to allow indirect comparison of target outcomes through common comparators [61].

Fourth, there are practical difficulties with implementing tight glucose control both inside and outside the clinical trial setting. It can be very hard to actually achieve the target glucose level, even in a clinical trial with close supervision. In fact, among the 72 comparison groups in the 36 RCTs we reviewed, 36 groups (50 %) did not

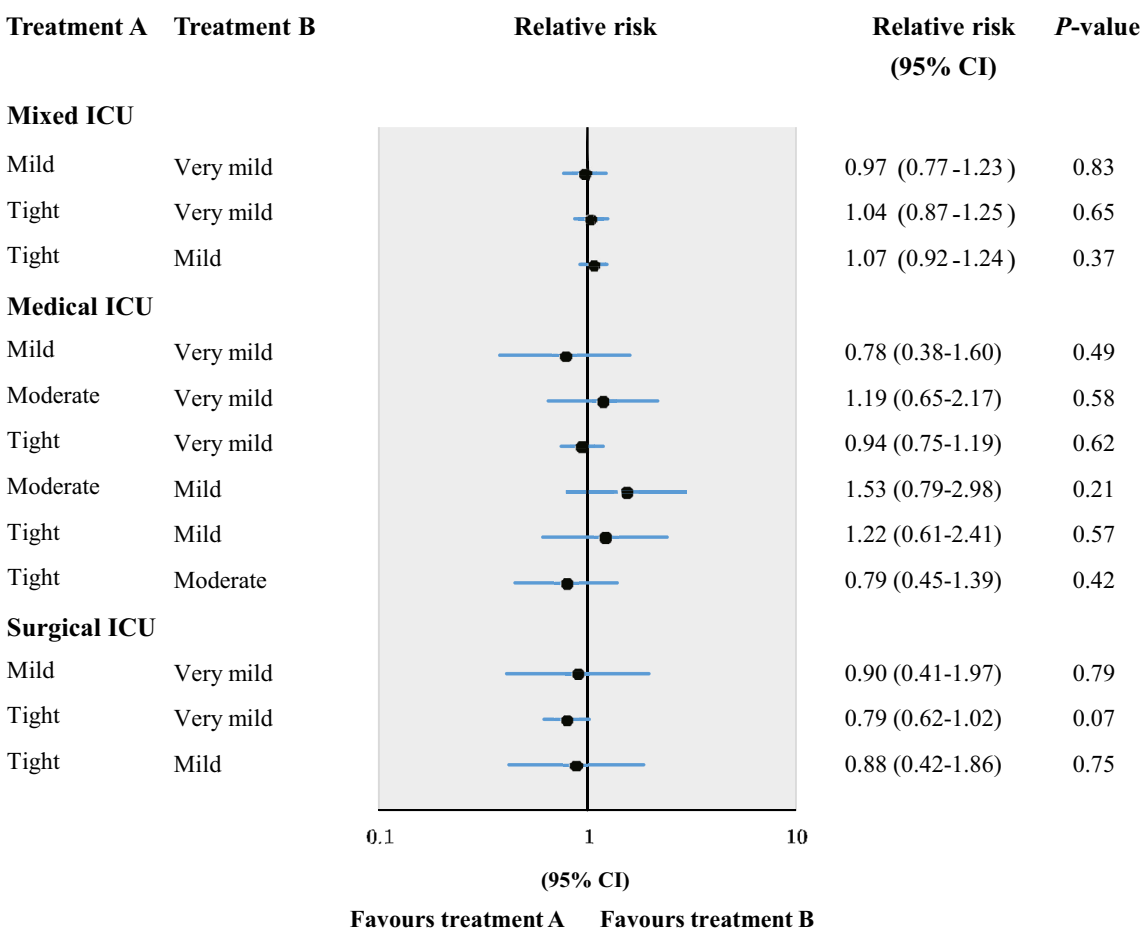


Fig. 5 Comparison of various glycemic targets using the mixed treatment comparison model stratified by the type of ICU (mixed ICU, medical ICU, or surgical ICU)

achieve a mean glucose level within the target range. Failure to achieve the target glucose level could also bias our findings in either direction. To overcome such problems, advanced glycemic control techniques using new devices (such as continuous glucose monitoring or an artificial pancreas) should be employed. As Friedrich [11] and Griesdale [9] have stated, performing individual meta-analyses could also help to obtain further insights into optimal glycemic control for critically ill patients [62].

In conclusion, tight glycemic control did not improve (or worsen) mortality in critically ill patients, but there was an approximately fivefold increase of hypoglycemia and severe hypoglycemia compared with mild or very mild glycemic control. Accordingly, we do not recommend tight control in critically ill patients, and our analyses support the selection of intermediate target glucose levels.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4523-0) contains supplementary material, which is available to authorized users.

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Compliance with ethical statement

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Duality of interest
The authors declare that there is no duality of interest associated with this manuscript.

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