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Intensive glucose control for critically ill patients: an updated meta-analysis

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Abstract

This meta-analysis aims to update the evidence for the effects of intensive glucose control (IGC) on the outcomes among critically ill patients. We performed a systematic literature review from inception through December, 2017 by two independent authors by searching PubMed, EMBASE and Cochrane Library. Randomized clinical trials of the effects of IGC compared with conventional glucose control were selected. Random-effect models were applied to calculate summary relative risks (RRs) for the related outcomes. Of 4247 records identified, we abstracted data from 27 relevant trials for meta-analysis. Compared with patients receiving conventional glucose control (controls), patients with IGC did not have significantly decreased risk of short-term mortality (in-hospital mortality or intensive care unit (ICU) mortality) (RR 0.99, 95% CI 0.92–1.06) or 3- to 6-month mortality (RR 1.02, 95% CI 0.97–1.08). These results remained constant among different study settings including surgical ICUs, medical ICUs or mixed ICUs. Similarly, we also found that patients with IGC did not have significantly lower risk of sepsis (RR 1.00, 95% CI 0.89–1.11) or new need for dialysis (RR 0.97, 95% CI 0.84–1.11). However, patients with IGC had almost 4-fold increase in risk of hypoglycemia (RR 4.86, 95% CI 3.16–7.46). In conclusion, in this updated meta-analysis of published trials, critically ill patients receiving IGC were found to be at neutral risk for short-term or 3- 6-month mortality, risk of sepsis or new need for dialysis, but at higher risk of hypoglycemia.

Key Words

- intensive glucose control (IGC)
- intensive care unit (ICU)
- critically ill
- meta-analysis

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Introduction

The past two decades have witnessed great progress on the research regarding optimal glycemic control strategy for critically ill patients based on several randomized controlled trials (RCTs). However, there are still debates on this topic. Numerous studies have reported that dysglycemia including hyperglycemia, hypoglycemia or serum blood fluctuation is an independent risk factor of mortality for critically ill patients, especially for those with diabetes mellitus (1, 2, 3, 4).

In 2001, Berghe and his colleagues found that intensive glucose control (IGC) could significantly reduce the mortality for surgical patients with mechanical ventilation (5). Since then, IGC has become a general practice for those critically ill patients. However, several other clinical trials reported the neutral effects of IGC for these patients (6, 7, 8, 9, 10, 11). Moreover, one of the most famous trials, the Normogylcemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial (12), found that IGC increased mortality among adults in the intensive care unit (ICU), which could potentially result from the increased incidence of hypoglycemia based on a *post hoc* analysis

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of the same trial (13). Evidence also demonstrated that severe hypoglycemia was strongly associated with hospital mortality, which was considered as an interactive factor for mortality (3, 14, 15). With all those dubious results, we aimed to reassess the existing uncertain evidence regarding this issue using the systematic review and meta-analysis of all published literature.

Methods

Literature search

We performed the meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (16). Primary sources of the reviewed studies, including PubMed, EMBASE and the Cochrane Library were systematically searched for citations from initials through December 2017. The following words were searched through the combinations of the keywords and text words: (ICU OR intensive care unit OR intensive care OR critical care OR critical illness OR postoperative care OR cardiac care facility* OR coronary care OR recovery room OR burn unit OR critically ill OR cardiac care OR cardiac care unit OR CCU) AND (insulin OR blood glucose OR intensive insulin OR glycemic control) AND (randomized OR randomised OR placebo OR randomly OR trial). Three reviewers (F S M, M M and S P) independently conducted online database searches and manual searches of reference lists from potentially eligible articles. The search strategies for the three databases were provided in Supplementary Methods (see section on supplementary data given at the end of this article).

Eligibility criteria

RCTs evaluating the effects of IGC with conventional glucose control for the management of adult critically ill patients were eligible for inclusion. We involved trials reporting the outcomes like short-term mortality (in-hospital mortality or ICU mortality) or 3- to 6-month mortality, risk of hypoglycemia, sepsis and new need for dialysis.

Trials that did not include the above mentioned outcomes or have sufficient data to calculate effect estimates were excluded from meta-analysis. Three investigators (Y F, Y S and J Z) independently conducted trial selection. When overlapping trials were included, only the largest one with the most comprehensive data or analyses was involved.

Data extraction

Three authors (Y F, Y S and J Z) independently extracted data on relevant variables from all trials using a predesigned standardized abstraction form, which were cross-checked and finally determined by a third author (Y C). Study-level data included first author, publication year, ICU type, sample size patient disease, patient age, percent of the diabetes cases, follow-up duration, intervention, daily insulin dose, target blood glucose level, achieved blood glucose level and outcome reported. The corresponding authors of original articles were contacted for missing data if necessary.

Trial bias assessment

Two authors (Y F and Y C) independently assessed trial bias of each included trial using the Cochrane collaboration's tool (17). This validated scale covered three aspects to assess the methodological bias in terms of random allocation, double-blinding and withdrawals and dropouts for intervention or control groups, with higher scores representing lower risk of bias.

Outcome definitions

The primary outcomes were 3- to 6-month mortality and short-term mortality. The former was defined as in hospital mortality or ICU mortality, mainly within 28-day mortality. When both in-hospital mortality and ICU mortality were reported in the same trial, we selected in hospital mortality as 3- 6-month mortality. The latter was defined as mortality at the time of 3 and 6 months. The secondary outcomes included risk of hypoglycemia, sepsis and new need for dialysis. Hypoglycemia was defined as patients with serum glucose level less than 2.2 mmol/L or 40 mg/dL. Sepsis was defined as patients who were diagnosed as sepsis, septicemia, bacteremia or having positive blood cultures. We defined new need for dialysis as patients who required dialysis because of renal failure for the first time.

Data synthesis

The result of each trial outcome was allocated as dichotomous variable. All analyses were based on data reported as intention to treat. A P value less than 0.05 was considered as significant difference. Considering the clinical (patient demographics and treatment strategy), methodological (randomization or outcome reported) and statistical (sample size) heterogeneity among included trials, we have applied random-effect model to combine

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effect estimates. Summary RRs and the corresponding 95% CIs were calculated and compared with a DerSimonian and Laird random-effects model, a method accounting for both within-study variance and between-study heterogeneity. Between-study heterogeneity was assessed by Q test and quantified by I^2 statistic and with an I^2 value being less than 0.10 considering statistically significant (18). Furthermore, we conducted pre-planned subgroup analyses for all the five outcomes based on the clinical variables available to investigate the potential sources of heterogeneity. Sensitivity analyses were also performed by omitting a single trial each time and recalculating the effect estimates to investigate the robustness of our summary statistics. The presence of publication bias was evaluated by using the Begg's test and Egger's test besides funnel plot symmetry (19, 20). The Duvall and Tweedle trim-and-fill model was used to adjust effect estimates (21). All meta-analyses were performed and figures were generated in Stata, version 14.0 (StataCorp).

Results

Twenty-seven trials (Fig. 1), including 17,582 patients, assessed the effect of IGC therapy (IGC therapy vs conventional glucose control therapy) in patients with critical surgical or medical illness (6, 7, 8, 9, 10, 11, 12, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41). Detailed clinical characteristics of the trials are reported in Table 1. IGC therapy was conducted in surgical ICUs in eight trials, five medical ICUs and fourteen surgical mixed with medical ICUs. The median sample size of the included trials was 240 (range, 20–6104). The mean percent of diabetic patients was 22%. The two intervention procedures for most of trials were insulin infusion and subcutaneous insulin injection. Target blood glucose level ranged from less than 6.9–12.5 mmol/L in trial group and within 4.4–6.1 mmol/L ($n=25$) or 6.1–8.3 mmol/L ($n=2$) in the control group. Moderate to higher risk of bias was found due to inappropriate double-blinding method of trial design for most of the trials (data provided upon request).

Results of meta-analyses, sensitivity analyses and publication bias assessment

3–6 month mortality

The data for the risk of 3- to 6-month mortality were available in 14 trials. The summary RR was 1.02 (95% CI, 0.97–1.08; $P=0.374$). There was no evidence of heterogeneity ($I^2=0$; $P=0.619$) (Fig. 2 and Table 2).

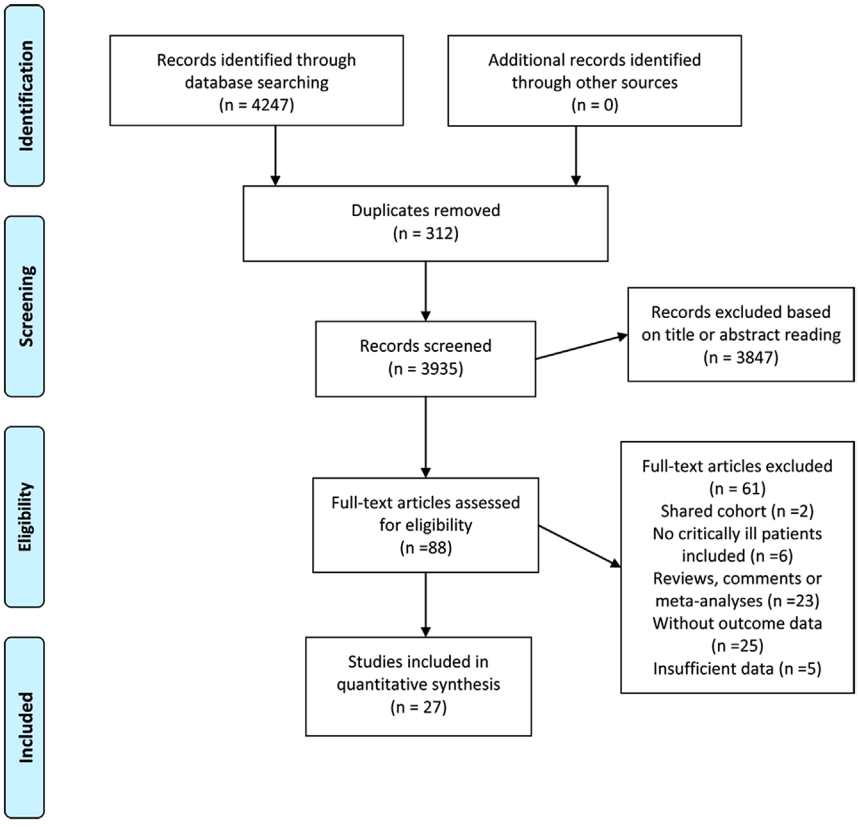

Figure 1
Flow chart of included articles selected for inclusion in the meta-analysis.

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Table 1 Characteristics of the included trials.

Study	Year	ICU type	Sample size	Patient disease	Mean age, year	Diabetes, %	Follow-up duration	Intervention	Mean daily insulin dose, IU/day	Target blood glucose level, mmol/L	Achieved blood glucose level, mmol/L	Outcomes included in meta-analysis
Wang *et al.*	2017	Surgical	88	Traumatic brain injury	TG 46.7; CG 45.1	19.3	6 months	Both groups: insulin infusion	NA	CG: <11.11 TG: 4.4–6.1	NA	Mortality
Finfer *et al.*	2015	Mixed	391	Operative: TG 80, CG 75; Non-operative: TG 123, CG 113	TG 41.9; CG 41.2	5.4	2 years	Both groups: insulin infusion	CG: 7.6 TG: 52.8	CG: <10.0 TG: 4.5–6.0	Mean BG CG: 7.7 TG: 7.7	Mortality, hypoglycemia, new need for dialysis, sepsis
Kalfon *et al.*	2014	Mixed	2648	Surgical (emergency): TG 417, CG 380; Surgical (scheduled): TG 121, CG 141; Nonsurgical: TG 798, CG 791; Polytrauma: TG 91, CG 85	TG 61; CG 62	TG 19.6; CG 20.9	90 days	Both groups: insulin infusion	Median dose TG: 43.1 CG:34.1	CG: ≤10.0 TG: 4.4–6.1	Mean BG CG: 9.1 TG: 9.4	Mortality, hypoglycemia, sepsis
Okabayashi *et al.*	2014	Surgical	447	Hepato-biliary pancreatic diseases	TG 66.7; CG 66.4	27.1	Hospital stay	Both groups: insulin infusion	CG: 77 TG: 101	CG: 7.7–10.0 TG: 4.4–6.1	NA	Mortality
Zuo *et al.*	2012	Mixed	30	Medical: severe acute pancreatitis	48	0	Hospital stay	CG: subcutaneous insulin injection TG: insulin infusion	CG: 32.4 TG: 71.4	CG: 10–11.1 TG: 6.1–8.3	Mean BG CG: NA TG: 7.46	Mortality
Cao *et al.*	2011	Surgical	179	Gastric cancer, 100	58.8	100	28 days	Both groups: insulin infusion	NA	CG: 10–11.0 TG: 4.4–6.1	Mean BG CG: 9.9 TG: 5.5	Mortality, hypoglycemia, sepsis
Arabi *et al.*	2011	Mixed	240	Medical: m83 Surgical: m17	51.1	40	180 days	Both groups: insulin infusion	CG: 23 TG: 62.8	CG: 10–11.1 TG: 4.4–6.1	Mean BG CG: 8.6 TG: 6.2	Mortality, hypoglycemia, new need for dialysis, sepsis
Coester *et al.*	2010	Surgical	88	Severe traumatic brain injury, 100	38.5	1.2	6 months	CG: subcutaneous insulin injection TG: insulin infusion	NA	CG: <10 TG: 4.4–6.1	Mean BG CG: 8.06 TG: 6.85	Mortality, hypoglycemia, sepsis
Green *et al.*	2010	Medical	81	Ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, 35; traumatic brain injury, 49	51	NA	90 days	CG: subcutaneous insulin injection TG: insulin infusion	CG: 1.4 IU/h TG: 2.39 IU/h	CG: ≤8.3 TG: 4.4–6.1	Mean BG CG: 7.9 TG: 6.2	Mortality, hypoglycemia, sepsis
Annan *et al.*	2010	Mixed	509	Medical: 75 Surgical: 11	64	NA	180 days	CG: subcutaneous insulin injection TG: insulin infusion	CG: 46 TG: 71 (median)	CG: not defined TG: 4.4–6.1	NA	Mortality, hypoglycemia
Bilotta *et al.*	2009	Surgical	483	Neurosurgery, 100	57.1	10	6 months	Both groups: insulin infusion	CG: 21 TG: 54	CG: <11.94 TG: 4.44–6.11	Mean BG CG: 7.96 TG: 5.13	Mortality, sepsis
Yang *et al.*	2009	Surgical	240	Severe traumatic brain injury, 100	45.5	10	6 months	Both groups: insulin infusion	NA	CG: 10–11.1 TG: 4.4–6.1	NA	Mortality, hypoglycemia
Cavalcanti *et al.*	2009	Medical	112	Respiratory, 32; sepsis, cardiovascular, neurologic, 44	59.9	30	90 days	CG: subcutaneous insulin injection TG: insulin infusion	NA	CG: <8.3 TG: 4.4–6.1	Median BG CG: 8.8 TG: 7.1	Hypoglycemia
Kreisel *et al.*	2009	Medical	40	Acute ischemic stroke, 100	71.6	33	120 days	CG: subcutaneous insulin injection TG: insulin infusion	CG: 5.4 TG: 13.3	CG: <11.1 TG: 4.44–6.11	Mean BG CG: 8.01 TG: 6.49	Mortality
Finfer *et al.*	2009	Mixed	6104	Medical: 62 Surgical: 38	62.2	20	90 days	Both groups: insulin infusion	CG: 16.9 TG: 50.2	CG: <10 TG: 4.5–6.0	Mean BG CG: 8.0w TG: 6.4	Mortality, hypoglycemia, new need for dialysis, sepsis

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Preiser *et al.*	2009	Mixed	1101	Medical: 40 Surgical: 47 Trauma: 13	64.6	18	Hospital stay	Both groups: insulin infusion	Median rate CG: 0.32 IU/h TG: 1.30 IU/h	CG: 7.8–10.0 TG: 4.4–6.1	Median BG CG: 8.0 TG: 6.5	Mortality, hypoglycemia
Taslimi *et al.*	2009	Mixed	129	Medical: 75 Surgical: 25	55.5	53	Hospital stay	Both groups: insulin infusion	NR	CG: 6.9–12.5 TG: 4.4–6.1	NA	Mortality, new need for dialysis
Savioli *et al.*	2009	Mixed	90	Medical: 62 Surgical: 38	61	13	90 days	Both groups: insulin infusion	CG: 36 TG: 57	CG: 10–11.1 TG: 4.4–6.1	Mean BG CG: 8.8 TG: 6.2	Mortality
Arabi *et al.*	2008	Mixed	523	Medical: 83 Surgical: 17	52.4	40	Hospital stay	Both groups: insulin infusion	CG: 31.4 TG: 71.2	CG: 10–11.1 TG: 4.4–6.1	Mean BG CG: 9.5 TG: 6.4	Mortality, hypoglycemia, new need for dialysis, sepsis
Brunkhorst *et al.*	2008	Mixed	537	Sepsis Medical: 47 Surgical: 53	64.6	30	90 days	Both groups: insulin infusion	CG: 5 TG: 32 (median)	CG: 10–11.1 TG: 4.4–6.1	Mean morning BG CG: 8.4 TG: 6.2	Mortality, hypoglycemia, new need for dialysis
De La Rosa *et al.*	2008	Mixed	504	Medical: 49 Surgical: 16 Trauma: 35	46.6	12	Hospital stay	Both groups: insulin infusion	CG: 12.5 TG: 52.4	CG: 10–11.1 TG: 4.4–6.1	Median morning BG CG: 8.2 TG: 6.5	Mortality, hypoglycemia, new need for dialysis
Iapichino *et al.*	2008	Mixed	90	Sepsis Medical: 64 Surgical: 32	62.3	17	90 days	Both groups: insulin infusion	CG: 38.8 TG: 74.5	CG: 10–11.1 TG: 4.4–6.1	Mean BG CG: 9.0 TG: 6.1	Mortality, hypoglycemia
Oksanen *et al.*	2007	Medical	90	Out of hospital ventricular fibrillation, 100	63.7	12	30 days	Both groups: insulin infusion	CG: 12.5 TG: 22	CG: 6.0–8.0 TG: 4.0–6.0	Median BG CG: 6.4 TG: 5.0	Mortality, hypoglycemia
Mitchell *et al.*	2006	Mixed	70	Medical: 61 Surgical: 3 9	65.4	14	Hospital stay	Both groups: insulin infusion	CG: 0 TG: 35.7 (median)	CG: 10–11.1 TG: 4.4–6.1	Median BG CG: 7.9 TG: 5.4	Mortality, hypoglycemia
Hoedemaekers *et al.*	2005	Surgical	20	CABG, 100	64.2	0	Hospital stay	Both groups: insulin infusion	NA	CG: <11.1 TG: 4.4–6.1	NA	Hypoglycemia
Van den Berghe *et al.*	2001	Surgical	1548	Cardiac surgery, 63	62.8	13	Hospital stay	Both groups: insulin infusion	CG: 33 TG: 71	CG: 10–11.1 TG: 4.4–6.1	Mean morning BG CG: 8.5 TG: 5.7	Mortality, hypoglycemia, new need for dialysis, sepsis
Van den Berghe *et al.*	2001	Medical	1200	Respiratory, 42.7; gastrointestinal, liver, 25.5	63.5	17	90 days	Both groups: insulin infusion	CG: 10 TG: 59	CG: 10–11.1 TG: 4.4–6.1	Mean morning BG CG: 8.49 TG: 6.16	Mortality, hypoglycemia, new need for dialysis, sepsis

BG, blood glucose; CG, conventional glucose control; ICU, intensive care unit; NA, not available; TG, intensive glucose control.

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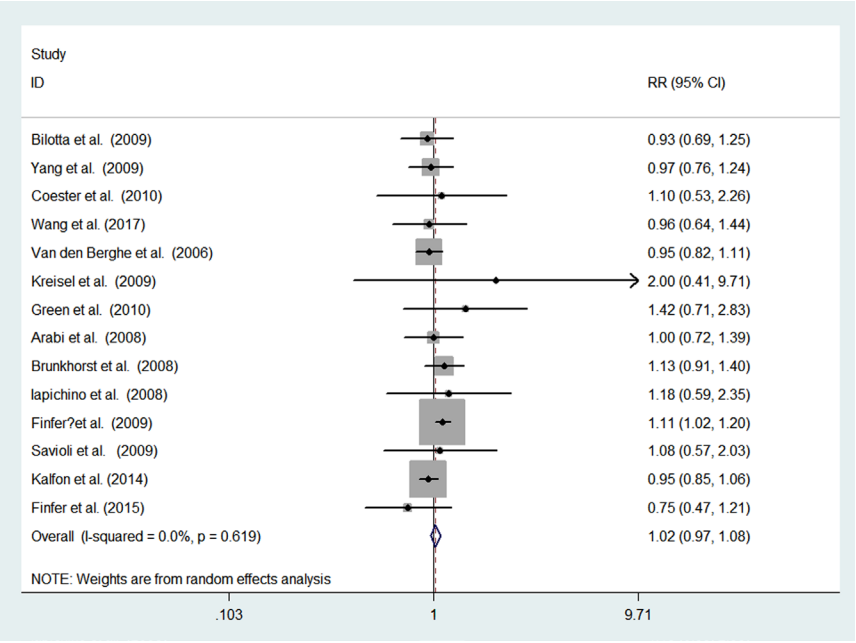

Figure 2
Forest plots comparing the effects of intensive glucose control on the risk of 3- to 6-month mortality with that of conventional glucose control.

Subgroup analyses indicated that for different ICU types of surgical, medical and mixed ICUs, the pooled RRs were 0.96 (95% CI, 0.81–1.13), 0.98 (95% CI, 0.84–1.16) and 1.04 (95% CI, 0.95–1.12), respectively, which was consistent with the result of the main analysis. Excluding one study at a time did not significantly alter the summary RR (Supplementary Fig. 1 and Supplementary Table 6). There was no evidence of publication bias using the Egger's test (P=0.847) or Begg's test (P=0.101) (Supplementary Table 1).

Short-term mortality

Twenty trials reported the data regarding IGC and the risk of short-term mortality. The pooled RR was 0.99 (95% CI, 0.92–1.06; P=0.741). There was low evidence of heterogeneity (I^2=15.8%; P=0.257) (Fig. 3 and Table 3). Subgroup analyses revealed that the summary RRs for surgical, medical and mixed ICUs were 0.82 (95% CI, 0.63–1.05), 0.99 (95% CI, 0.84–1.17) and 1.01 (95% CI, 0.94–1.10), respectively, which was in accord with the result of the main analysis. Sensitivity analysis did not significantly change the summary RR (Supplementary Fig. 2 and Supplementary Table 7). No evidence of publication bias was detected using the Egger's test (P=0.975) or Begg's test (P=0.871).

Risk of hypoglycemia

The data for the risk of hypoglycemia were available in 19 trials. The summary RR was 4.86 (95% CI, 3.16–7.46; P<0.001) with significant heterogeneity (I^2=76.1%; P<0.001) (Supplementary Fig. 6 and Supplementary Table 2), indicating patients with IGC had almost 4-fold increase in risk of hypoglycemia. Subgroup analyses indicated that for different ICU types of surgical, medical and mixed ICUs, the pooled RRs were 3.90 (95% CI, 1.60–9.49), 6.03 (95% CI, 3.89–9.34) and 5.07 (95% CI, 2.80–9.18), respectively, which was consistent with the result of the main analysis. Sensitivity analysis by excluding one study at a time indicated the robustness of the pooled result (Supplementary Fig. 3 and Supplementary Table 8). There was no evidence of publication bias using the Egger's test (P=0.149) or Begg's test (P=0.726).

Risk of sepsis

Thirteen trials provided the data regarding analysis of IGC and the risk of sepsis. The pooled RR was 1.00 (95% CI, 0.89–1.11; P=0.973). There was low evidence of heterogeneity (I^2=19.8%; P=0.243) (Supplementary Fig. 7 and Supplementary Table 3). Subgroup analyses found that the pooled RRs for surgical, medical and mixed ICUs were 0.79 (95% CI, 0.42–1.48), 0.62 (95% CI, 0.22–1.72) and 1.03 (95% CI, 0.94–1.13), respectively, which was in accord with the result of the main analysis. Sensitivity analysis did not significantly change the summary RR (Supplementary Fig. 4 and Supplementary Table 9). No evidence of publication bias was detected using the Egger's test (P=0.384) or Begg's test (P=0.360).

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Table 2 Subgroup analyses for effects of intensive glucose control on the risk of 3–6 month mortality for critically ill patients stratified by covariates.

Stratification covariates	RR	95% CI	Heterogeneity (I^2 statistics; %)	No. of included studies	*P* for interaction
Total	1.03	0.97–1.09	0	14	0.307
Trial setting					0.517
Surgical ICU	0.96	0.81–1.13	0	4	
Medical ICU	0.98	0.84–1.16	1.6	3	
Mixed ICU	1.04	0.95–1.12	18.5	7	
Trial year					0.074
Year 2001–2009	1.06	0.99–1.13	0	9	
Year 2010–2017	1.02	0.97–1.08	0	5	
Study region					0.615
America	1.26	0.76–2.07	0	2	
Europe	0.97	0.90–1.05	0	7	
Asia	0.97	0.82–1.16	0	3	
Sample size					0.477
≥500	1.02	0.94–1.11	40.4	5	
<500	0.98	0.84–1.13	0	9	
Patient mean age					0.325
≥60	1.03	0.98–1.09	0	10	
<60	0.94	0.78–1.13	0	4	
Diabetes, %					0.435
≥30	1.10	0.91–1.31	0	3	
<30	1.02	0.96–1.07	0	10	
Mean/median daily insulin dose					0.257
≥50 IU/day	1.05	0.98–1.13	0	8	
<50 IU/day	1.01	0.87–1.17	27.3	3	

CI, confidence interval; RR, relative risk.

Risk of new dialysis

Nine trials were included in the analysis of IGC and the risk of new dialysis. The summary RR was 0.97 (95% CI, 0.84–1.11; $P=0.631$) with low-to-moderate heterogeneity ($I^2=29.1\%$; $P=0.186$) (Supplementary Fig. 8 and Supplementary Table 4). Subgroup analysis revealed that for different ICU types of surgical, medical and mixed ICUs, the pooled RRs were 0.59 (95% CI, 0.40–0.88), 0.92 (95% CI, 0.74–1.14) and 1.06 (95% CI, 0.96–1.17), respectively, which was consistent with the result of the main analysis. Sensitivity analysis by excluding one study at a time did not alter the main result (Supplementary Fig. 5 and Supplementary Table 10). There was no evidence of publication bias using the Egger's test ($P=0.459$) or Begg's test ($P=0.917$).

Discussion

In this meta-analysis of randomized controlled studies, neutral effects in the risk of 3- to 6-month mortality, short-term mortality, sepsis and new dialysis for critically ill patients with IGC intervention. However, significant increase in the risk of hypoglycemia was noted for those patients. These effects appeared to have similar trend in different ICU settings including surgical, medical and mixed ICUs.

Our findings are consistent with three previous meta-analyses and network meta-analyses of IGC and outcome in critically ill patient (42, 43, 44), but included more outcome measures including risk of 3- to 6-month mortality, short-term mortality, hypoglycemia, sepsis and new dialysis with a relative larger sample size and more detailed sensitivity and trim-and-fill method analyses. To our knowledge, this is the most comprehensive meta-analysis summarizing results for the effects of IGC and adult critically ill patients treated in ICUs. The null effects for IGC intervention might result from the few studies included in this subset with limited sample size which should be further studied in the future.

The strengths of this updated meta-analysis were as follows. Firstly, we developed sensitive and comprehensive search strategies of all the electronic databases, enabling the process of literature screening and eligibility criteria more rigorously, and reporting the findings of meta-analyses more transparently. Second, we did not apply language or publication date limits during the search of

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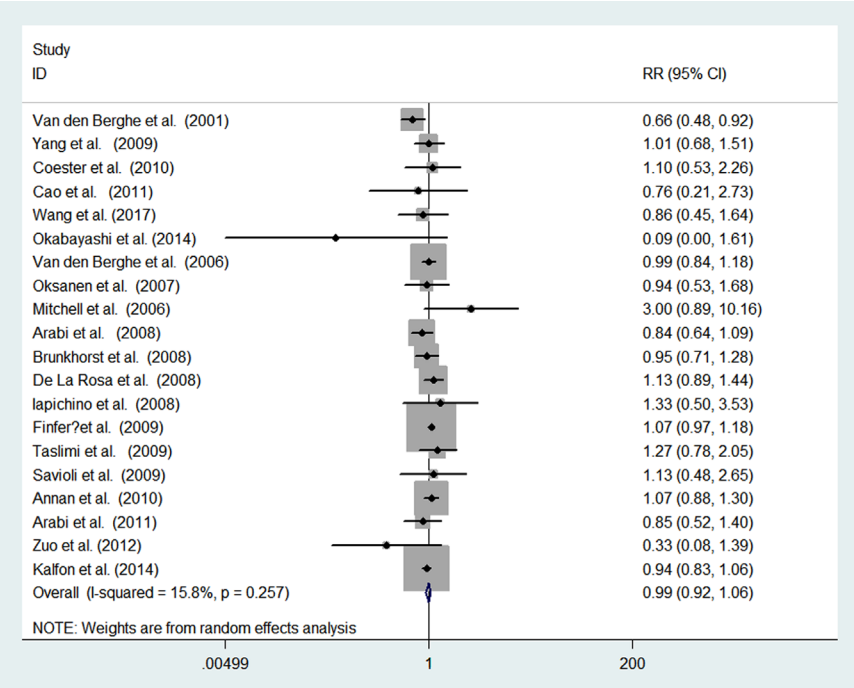

Figure 3
Forest plots comparing the effects of intensive glucose control on the risk of short-term mortality with that of conventional glucose control.

Table 3 Subgroup analyses for effects of intensive glucose control on the risk of short-term mortality for critically ill patients stratified by covariates.

Stratification covariates	RR	95% CI	Heterogeneity (I^2 statistics; %)	No. of included studies	*P* for interaction
Total	0.99	0.94–1.05	15.8	20	0.826
Trial setting					0.134
Surgical ICU	0.82	0.63–1.05	13.5	6	
Medical ICU	0.99	0.84–1.17	0	2	
Mixed ICU	1.01	0.94–1.10	14.5	12	
Trial year					0.313
Year 2001–2009	1.00	0.90–1.10	26.4	12	
Year 2010–2017	0.96	0.87–1.06	0	8	
Study region					0.301
America	1.13	0.90–1.03	0	2	
Europe	0.96	0.88–1.04	1.9	8	
Asia	0.90	0.75–1.08	1.1	8	
Sample size					0.896
≥500	0.98	0.90–1.07	42.8	8	
<500	1.01	0.83–1.23	0	12	
Patient mean age					0.644
≥60	0.98	0.90–1.06	15.8	15	
<60	1.05	0.87–1.27	0	5	
Diabetes, %					0.360
≥30	0.92	0.78–1.09	0	5	
<30	0.99	0.89–1.09	30.8	14	
Mean/median daily insulin dose					0.281
≥50 IU/day	1.01	0.90–1.13	37.7	11	
<50 IU/day	0.96	0.83–1.10	32.5	5	

CI, confidence interval; RR, relative risk.

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the three major databases, making it less possible to miss some important publications which could be one major source of publication bias. Thirdly, at least two or three investigators independently selected trials, cross-checked them and identified the final included trials. Finally, one important strength was that we included five most commonly investigated and major outcomes to make the study one of the most comprehensive ones regarding this topic. Moreover, we conducted thorough subgroup analyses, sensitivity analyses and applied trim-and-filled method to test between-study heterogeneity and confirm the robustness of the results for each outcome, which made the results more reliable with the largest sample size ever involved.

This meta-analysis has some limitations. First, though low statistical heterogeneity for most of the meta-analyses was detected (with I^2 statistic less than 20% in four of five outcomes except risk of hypoglycemia), still we noted that the included patients were rather different among trials, including surgical ICUs, medical ICUs or mixed ones. Another potential limitation of this meta-analysis is the lack of patient-level data. There was variation in the type of insulin, the dose and mode of administration (subcutaneous vs infusion), the duration of follow-up and the combination of concomitant therapy, which we did not explore most of these factors with subgroup analyses due to the unavailability of the data. Thirdly, not all trials reported on all outcomes of interest, and some of the trials were not designed to measure these outcomes. However, this updated meta-analysis has been strengthened by the inclusion of all RCTs regarding this topic.

On the basis of this updated meta-analysis, we conclude that IGC offers no significant benefits for critically ill patients in terms of 3- to 6-month mortality, short-term mortality, sepsis and new dialysis, but adds the risk of hypoglycemia. We advocated that future well-designed RCTs in specific subgroups (eg. in diabetic or non-diabetic patients, in patients with different daily insulin dose, etc.) or with other study outcomes (such as cardiovascular related mortality) should be conducted.

Supplementary data

This is linked to the online version of the paper at https://doi.org/10.1530/EC-18-0393.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

1 Krinsley J, Schultz M, Spronk P, Harmsen R, van Braam Houckgeest F, van der Sluijs J, Mélot C & Preiser J. Mild hypoglycemia is independently associated with increased mortality in the critically ill. *Critical Care* 2011 **15** R173. (https://doi.org/10.1186/cc10322)

2 Krinsley J. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Critical Care Medicine* 2008 **36** 3008–3013. (https://doi.org/10.1097/CCM.0b013e31818b38d2)

3 Krinsley J & Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Critical Care Medicine* 2007 **35** 2262–2267. (https://doi.org/10.1097/01.CCM.0000282073.98414.4B)

4 Krinsley J. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clinic Proceedings* 2003 **78** 1471–1478. (https://doi.org/10.4065/78.12.1471)

5 van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P & Bouillon R. Intensive insulin therapy in critically ill patients. *New England Journal of Medicine* 2001 **345** 1359–1367. (https://doi.org/10.1056/NEJMoa011300)

6 Yang M, Guo Q, Zhang X, Sun S, Wang Y, Zhao L, Hu E & Li C. Intensive insulin therapy on infection rate, days in NICU, in-hospital mortality and neurological outcome in severe traumatic brain injury patients: a randomized controlled trial. *International Journal of Nursing Studies* 2009 **46** 753–758. (https://doi.org/10.1016/j.ijnurstu.2009.01.004)

7 Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H & Bouillon R. Intensive insulin therapy in the medical ICU. *New England Journal of Medicine* 2006 **354** 449–461. (https://doi.org/10.1056/NEJMoa052521)

8 Kalfon P, Giraudeau B, Ichai C, Guerrini A, Brechot N, Cinotti R, Dequin PF, Riu-Poulenc B, Montravers P, Annane D, *et al*. Tight computerized versus conventional glucose control in the ICU: a randomized controlled trial. *Intensive Care Medicine* 2014 **40** 171–181. (https://doi.org/10.1007/s00134-013-3189-0)

9 Finfer S, Chittock D, Li Y, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Hebert P, Henderson W, *et al*. Intensive versus conventional glucose control in critically ill patients with traumatic brain injury: long-term follow-up of a subgroup of patients from the NICE-SUGAR study. *Intensive Care Medicine* 2015 **41** 1037–1047. (https://doi.org/10.1007/s00134-015-3757-6)

10 Coester A, Neumann CR & Schmidt MI. Intensive insulin therapy in severe traumatic brain injury: a randomized trial. *Journal of Trauma* 2010 **68** 904–911. (https://doi.org/10.1097/TA.0b013e3181c9afc2)

11 Bilotta F, Caramia R, Paoloni FP, Delfini R & Rosa G. Safety and efficacy of intensive insulin therapy in critical neurosurgical patients. *Anesthesiology* 2009 **110** 611–619. (https://doi.org/10.1097/ALN.0b013e318198004b)

12 Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, *et al*. Intensive versus conventional glucose control in critically ill patients. *New England Journal of Medicine* 2009 **360** 1283–1297. (https://doi.org/10.1056/NEJMoa0810625)

13 Finfer S, Liu B, Chittock D, Norton R, Myburgh J, McArthur C, Mitchell I, Foster D, Dhingra V, Henderson W, *et al*. Hypoglycemia and risk of death in critically ill patients. *New England Journal of Medicine* 2012 **367** 1108–1118. (https://doi.org/10.1056/NEJMoa1204942)

14 Egi M, Bellomo R, Stachowski E, French C, Hart G, Taori G, Hegarty C & Bailey M. Hypoglycemia and outcome in critically ill patients. *Mayo Clinic Proceedings* 2010 **85** 217–224. (https://doi.org/10.4065/mcp.2009.0394)

15 Hermanides J, Bosman R, Vriesendorp T, Dotsch R, Rosendaal F, Zandstra D, Hoekstra J & DeVries J. Hypoglycemia is associated with intensive care unit mortality. *Critical Care Medicine* 2010 **38** 1430–1434. (https://doi.org/10.1097/CCM.0b013e3181de562c)

16 Moher D, Liberati A, Tetzlaff J & Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009 **62** 1006–1012. (https://doi.org/10.1016/j.jclinepi.2009.06.005)

17 Higgins JP, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011 **343** d5928. (https://doi.org/10.1136/bmj.d5928)

18 Higgins J, Thompson S, Deeks J & Altman D. Measuring inconsistency in meta-analyses. *BMJ* 2003 **327** 557–560. (https://doi.org/10.1136/bmj.327.7414.557)

19 Egger M, Davey Smith G, Schneider M & Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997 **315** 629–634. (https://doi.org/10.1136/bmj.315.7109.629)

20 Begg C & Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994 **50** 1088–1101. (https://doi.org/10.2307/2533446)

21 Duval S & Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000 **56** 455–463. (https://doi.org/10.1111/j.0006-341X.2000.00455.x)

22 Shojima N, Hara K, Noma H, Yamauchi T, Kadowaki T, Wang Y, Li JP, Song YL & Zhao QH. Intensive insulin therapy for preventing postoperative infection in patients with traumatic brain injury: a randomized controlled trial. *Intensive Care Medicine* 2017 **96** e6458. (https://doi.org/10.1097/MD.0000000000006458)

23 Okabayashi T, Shima Y, Sumiyoshi T, Kozuki A, Tokumaru T, Iiyama T, Sugimoto T, Kobayashi M, Yokoyama M & Hanazaki K. Intensive versus intermediate glucose control in surgical intensive care unit patients. *Diabetes Care* 2014 **37** 1516–1524. (https://doi.org/10.2337/dc13-1771)

24 Zuo YY, Kang Y, Wang B & Yin WH. [Short-term intensive glucose control in patients with severe acute pancreatitis]. *Zhongguo wei zhong bing ji jiu yi xue = Chinese critical care medicine = Zhongguo weizhongbing jijiuyixue* 2012 **24** 24–28.

25 Cao SG, Ren JA, Shen B, Chen D, Zhou YB & Li JS. Intensive versus conventional insulin therapy in type 2 diabetes patients undergoing D2 gastrectomy for gastric cancer: a randomized controlled trial. *World Journal of Surgery* 2011 **35** 85–92. (https://doi.org/10.1007/s00268-010-0797-5)

26 Arabi YM, Tamim HM, Dhar GS, Al-Dawood A, Al-Sultan M, Sakkijha MH, Kahoul SH & Brits R. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. *American Journal of Clinical Nutrition* 2011 **93** 569–577. (https://doi.org/10.3945/ajcn.110.005074)

27 Green DM, O'Phelan KH, Bassin SL, Chang CW, Stern TS & Asai SM. Intensive versus conventional insulin therapy in critically ill neurologic patients. *Neurocritical Care* 2010 **13** 299–306. (https://doi.org/10.1007/s12028-010-9417-3)

28 Annane D, Cariou A, Maxime V, Azoulay E, D'Honneur G, Timsit JF, Cohen Y, Wolf M, Fartoukh M, Adrie C, *et al*. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA* 2010 **303** 341–348. (https://doi.org/10.1001/jama.2010.2)

29 Taslimi R, Azizkhani R, Talebian MH, Abtahi HR, Jalili M, Nejati A & Labbaf A. The efficacy of intensive glucose management on hospitalized critically ill patients associated mortality rate in intensive care unit. *DARU* 2009 **2** 1438–1441.

30 Savioli M, Cugno M, Polli F, Taccone P, Bellani G, Spanu P, Pesenti A, Iapichino G & Gattinoni L. Tight glycemic control may favor fibrinolysis in patients with sepsis. *Critical Care Medicine* 2009 **37** 424–431. (https://doi.org/10.1097/CCM.0b013e31819542da)

31 Preiser JC, Devos P, Ruiz-Santana S, Melot C, Annane D, Groeneveld J, Iapichino G, Leverve X, Nitenberg G, Singer P, *et al*. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Medicine* 2009 **35** 1738–1748. (https://doi.org/10.1007/s00134-009-1585-2)

32 Kreisel SH, Berschin UM, Hammes HP, Leweling H, Bertsch T, Hennerici MG & Schwarz S. Pragmatic management of hyperglycaemia in acute ischaemic stroke: safety and feasibility of intensive intravenous insulin treatment. *Cerebrovascular Diseases* 2009 **27** 167–175. (https://doi.org/10.1159/000185608)

33 Cavalcanti AB, Silva E, Pereira AJ, Caldeira-Filho M, Almeida FP, Westphal GA, Beims R, Fernandes CC, Correa TD, Gouvea MR, *et al*. A randomized controlled trial comparing a computer-assisted insulin infusion protocol with a strict and a conventional protocol for glucose control in critically ill patients. *Journal of Critical Care* 2009 **24** 371–378. (https://doi.org/10.1016/j.jcrc.2009.05.005)

34 Iapichino G, Albicini M, Umbrello M, Sacconi F, Fermo I, Pavlovich R, Paroni R, Bellani G, Mistraletti G, Cugno M, *et al*. Tight glycemic control does not affect asymmetric-dimethylarginine in septic patients. *Intensive Care Medicine* 2008 **34** 1843–1850. (https://doi.org/10.1007/s00134-008-1158-9)

35 De La Rosa Gdel C, Donado JH, Restrepo AH, Quintero AM, Gonzalez LG, Saldarriaga NE, Bedoya M, Toro JM, Velasquez JB, Valencia JC, *et al*. Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. *Critical Care* 2008 **12** R120. (https://doi.org/10.1186/cc7017)

36 Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, *et al*. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *New England Journal of Medicine* 2008 **358** 125–139. (https://doi.org/10.1056/NEJMoa070716)

37 Arabi YM, Dabbagh OC, Tamim HM, Al-Shimemeri AA, Memish ZA, Haddad SH, Syed SJ, Giridhar HR, Rishu AH, Al-Daker MO, *et al*. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. *Critical Care Medicine* 2008 **36** 3190–3197. (https://doi.org/10.1097/CCM.0b013e31818f21aa)

38 Oksanen T, Skrifvars MB, Varpula T, Kuitunen A, Pettila V, Nurmi J & Castren M. Strict versus moderate glucose control after resuscitation from ventricular fibrillation. *Intensive Care Medicine* 2007 **33** 2093–2100. (https://doi.org/10.1007/s00134-007-0876-8)

39 Mitchell I, Knight E, Gissane J, Tamhane R, Kolli R, Leditschke IA, Bellomo R & Finfer S. A phase II randomised controlled trial of intensive insulin therapy in general intensive care patients. *Critical Care and Resuscitation* 2006 **8** 289–293.

40 Hoedemaekers CW, Pickkers P, Netea MG, van Deuren M & Van der Hoeven JG. Intensive insulin therapy does not alter the inflammatory response in patients undergoing coronary artery bypass grafting: a randomized controlled trial [ISRCTN95608630]. *Critical Care* 2005 **9** R790–R797. (https://doi.org/10.1186/cc3911)

41 van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P & Bouillon R. Intensive insulin therapy in critically ill patients. *New England*

Journal of Medicine 2001 **345** 1359–1367. (https://doi.org/10.1056/NEJMoa011300)

42 Ling Y, Li X & Gao X. Intensive versus conventional glucose control in critically ill patients: a meta-analysis of randomized controlled trials. *European Journal of Internal Medicine* 2012 **23** 564–574. (https://doi.org/10.1016/j.ejim.2012.02.013)

43 Yatabe T, Inoue S, Sakaguchi M & Egi M. The optimal target for acute glycemic control in critically ill patients: a network meta-analysis. *Intensive Care Medicine* 2017 **43** 16–28. (https://doi.org/10.1007/s00134-016-4558-2)

44 Yamada T, Shojima N, Noma H, Yamauchi T & Kadowaki T. Glycemic control, mortality, and hypoglycemia in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials. *Intensive Care Medicine* 2017 **43** 1–15. (https://doi.org/10.1007/s00134-016-4523-0)

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