RESEARCH

Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data

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ABSTRACT

Background: Hyperglycemia is associated with increased mortality in critically ill patients. Randomized trials of intensive insulin therapy have reported inconsistent effects on mortality and increased rates of severe hypoglycemia. We conducted a meta-analysis to update the totality of evidence regarding the influence of intensive insulin therapy compared with conventional insulin therapy on mortality and severe hypoglycemia in the intensive care unit (ICU).

Methods: We conducted searches of electronic databases, abstracts from scientific conferences and bibliographies of relevant articles. We included published randomized controlled trials conducted in the ICU that directly compared intensive insulin therapy with conventional glucose management and that documented mortality. We included in our meta-analysis the data from the recent NICE-SUGAR (Normoglycemia in Intensive Care Evaluation — Survival Using Glucose Algorithm Regulation) study.

Results: We included 26 trials involving a total of 13 567 patients in our meta-analysis. Among the 26 trials that reported mortality, the pooled relative risk (RR) of death with intensive insulin therapy compared with conventional therapy was 0.93 (95% confidence interval [CI] 0.83–1.04). Among the 14 trials that reported hypoglycemia, the pooled RR with intensive insulin therapy was 6.0 (95% CI 4.5–8.0). The ICU setting was a contributing factor, with patients in surgical ICUs appearing to benefit from intensive insulin therapy (RR 0.63, 95% CI 0.44–0.91); patients in the other ICU settings did not (medical ICU: RR 1.0, 95% CI 0.78–1.28; mixed ICU: RR 0.99, 95% CI 0.86–1.12). The different targets of intensive insulin therapy (glucose level ≤ 6.1 mmol/L v. ≤ 8.3 mmol/L) did not influence either mortality or risk of hypoglycemia.

Interpretation: Intensive insulin therapy significantly increased the risk of hypoglycemia and conferred no overall mortality benefit among critically ill patients. However, this therapy may be beneficial to patients admitted to a surgical ICU.

Une version française de ce résumé est disponible à l'adresse www.cmaj.ca/cgi/content/full/180/8/821/DC1

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Hyperglycemia is associated with adverse outcomes, including increased mortality, in acutely ill patients.[1–7] In 2001, a randomized trial involving patients admitted to a surgical intensive care unit (ICU) showed that intensive insulin therapy, targeting a blood glucose concentration of 4.4–6.1 mmol/L, significantly reduced in-hospital mortality.[8] Subsequent trials have failed to confirm a mortality benefit with intensive insulin therapy among critically ill patients, in whom stress hyperglycemia is common.[9–13] A recent meta-analysis concluded that such therapy did not reduce mortality among critically ill patients.[14] Despite conflicting evidence, intensive insulin therapy has been recommended as the standard of care for critically ill patients by the American Diabetes Association,[15] the American Association of Clinical Endocrinologists[16] and other professional organizations.[17] A consistent finding in trials of such therapy has been an increased risk of severe hypoglycemia, which was the impetus for early termination of 2 large European trials.[11,13] The Normoglycemia in Intensive Care Evaluation — Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, an international multicentre trial involving 6104 patients, is the largest trial of intensive insulin therapy to date.[18] It has reported 1580 deaths. In light of the recently published NICE-SUGAR data, we conducted a systematic review and meta-analysis of randomized trials of intensive insulin therapy in critically ill patients to provide an updated estimate of the effect of such therapy on the risk of hypoglycemia and death.

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Methods

Search strategy

We systematically searched MEDLINE (1966–March 2008), EMBASE (1977–March 2008) and the Cochrane Central Register of Controlled Trials (CENTRAL) (1948–March 2008) for randomized trials examining the effect of intensive insulin therapy on mortality among critically ill patients. In addition, we conducted a manual search of abstracts from selected conferences held from 2000 to 2008, including conferences of the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, the American Thoracic Society and the American College of Chest Physicians. We also searched by hand the bibliographies of all relevant trials. We obtained a confidential prepublication copy of the NICE-SUGAR report from the study's management committee. We included the NICE-SUGAR data subject to publication of the primary report and with the agreement of the journal publishing the trial.

For the bibliographic review, we constructed search filters for each of the concepts of critical care, intensive insulin therapy and clinical trials using a combination of exploded Medical Subject Heading (MeSH) terms and text words, all combined with the Boolean OR operator. The critical care filter contained the following MeSH terms: "critical care," "intensive care," "intensive care units," "cardiac care facilities," "critical illness," "postoperative care" with text words "intensive care," "ICU," "critical care," "CCU," "coronary care," "recovery room," "PAR," "critical illness," "burn unit," "critically ill" or "cardiac care." The intensive insulin filter contained the MeSH terms "insulin," "blood glucose," "hypoglycemic agents" with text words "intensive insulin," "glycemic control," "blood glucose" or "insulin." The clinical trials filter included the MeSH terms "clinical trials [publication type]," "clinical trials as topic," "placebos" with text words "trial*," "random*" or "placebo." We then combined all 3 filters using the Boolean operator AND. We used a similar search strategy to identify relevant articles in the EMBASE and CENTRAL databases (Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.090206/DC1).

Selection criteria

In duplicate and independently, 2 of us (D.G. and R.D.) screened all of the articles and abstracts. Articles were selected if they met the following inclusion criteria: the study was a randomized controlled trial; the study participants were adults; a critical care setting was used; the intensive insulin therapy was defined by a target blood glucose concentration of 8.3 mmol/L or less; and the study documented mortality. We excluded trials that had not been published either in full or as abstracts in indexed journals.

Data abstraction and methodologic quality

Independently and in duplicate, the same 2 authors (D.G. and R.D.) abstracted data. They also assessed the methodologic quality of the trials using the Jadad score[19] (Appendix 2, available at www.cmaj.ca/cgi/content/full/cmaj.090206/DC1). Disagreement was resolved by group discussion and arbitration by a third author (D.T.) if necessary. We abstracted year of publication, sample size, population (medical, surgical or mixed ICU), patient age, reported illness severity score, initiation and maintenance criteria for insulin infusion in both the treatment and control arms, mean glucose concentration achieved in the treatment and control arms, length of ICU stay, and mortality. Hypoglycemic events were defined by a blood glucose level of ≤ 2.2 mmol/L. For trials published in a language other than English, the translator abstracted the data in duplicate. We contacted investigators for missing data as necessary.

Statistical analysis

We used the risk ratio (RR) as the summary measure of association. We obtained the RR by pooling trial-specific cumulative incidence ratios from each arm of the included trials. If event rates were zero, we added a 0.5 continuity correction to all 4 cells. We generated a pooled-effect estimate and 95% confidence intervals (CI) using the DerSimonian and Laird random-effects model,[20] which yields a more conservative pooled estimate than a fixed-effects model if true between-study heterogeneity exists. We estimated the degree of heterogeneity among trial results using Cochran's Q statistic (with a p value less than 0.10 considered significant) and the I^2 statistic.[21] The I^2 statistic indicates the percentage of variation in the study results that is because of between-study heterogeneity rather than sampling error. We identified potential sources of heterogeneity a priori as type of ICU (medical, surgical or mixed) and glycemic target in the intervention arm (≤ 6.1 mmol/L v. ≤ 8.3 mmol/L). We evaluated whether the trial results differed according to these criteria using random-effects meta-regression.

We selected 90-day mortality as our primary outcome measure. If this was not published in the primary report, we attempted to obtain these data from the trial authors. If this outcome was not recorded, we preferentially used the outcomes in the following order: hospital mortality, 28-day mortality and ICU mortality. The secondary outcome measure was hypoglycemic events (defined by a blood glucose level of ≤ 2.2 mmol/L).

We evaluated the presence of publication bias using Begg's and Egger's tests (p value < 0.05 considered significant) and by means of visual inspection of the funnel plot.

Results

Literature search

Through the electronic database search, we identified 2225 citations: 1079 from EMBASE, 785 from MEDLINE and 355 from the CENTRAL database (Figure 1). Of the 1474 unique citations, we excluded 1420 after screening the titles and abstracts. This left 54 articles for full-text review. The manual search of abstracts from conferences and of bibliographies yielded 8 additional trials that met our inclusion criteria. Overall, 28 articles were excluded (Figure 1). We included 26 trials[8–13,18,22–40] in the meta-analysis.

Study characteristics

Of the 26 included trials, 3 were published abstracts (Appendix 3, available at www.cmaj.ca/cgi/content/full/cmaj.090206/DC1). A total of 13 567 patients participated; 7 trials included more than 500 patients (range 10–6104). The intervention glycemic

target was ≤ 6.1 mmol/L in 16 trials,[8–13,18,25,30,32,33,35,36,38–40] and 9 trials used a more liberal target of ≤ 8.3 mmol/L.[22–24,26–28,31,34,37] One trial randomly assigned patients to 1 of 3 levels of glycemic control: 4.4–6.1 mmol/L, 6.7–8.3 mmol/L or 10.0–11.1 mmol/L.[29] Given our selection criteria of a target glucose level of 8.3 mmol/L or less, we combined data from the 2 intervention arms for our primary mortality analysis. Six trials were conducted in medical ICUs, 5 in surgical ICUs and 15 in mixed ICUs.

We used results from intention-to-treat analyses in our meta-analysis. However, 2 trials did not conduct this analysis because they excluded patients after randomization who did not survive at least 3 days.[27,32] For 1 of these trials,[32] we obtained the risk of both mortality and hypoglycemic events from the authors for the 18 patients excluded after randomization, which allowed us to include the intention-to-treat results for that trial.

Mortality

Data used in the primary analysis to determine the risk of death associated with intensive insulin therapy are listed in Appendix 4 (available at www.cmaj.ca/cgi/content/full/cmaj.090206/DC1). The pooled RR across all studies was 0.93
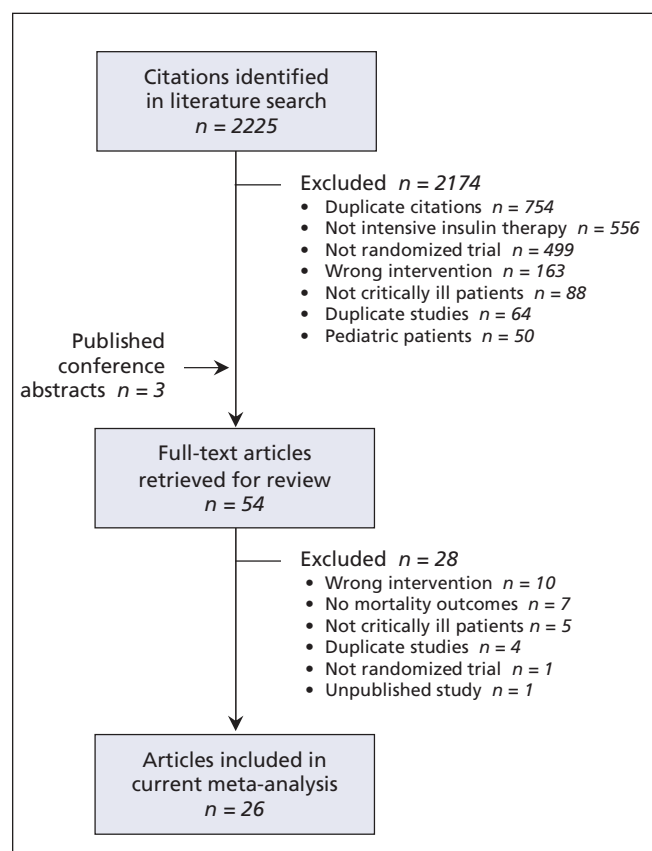

Figure 1: Section of studies for inclusion in the meta-analysis of the effect of intensive insulin therapy in critically ill patients. A total of 26 reports (23 published articles and 3 abstracts) were included in the final meta-analysis. Conferences included the Society of Critical Care Medicine, European Society of Intensive Care Medicine, American Thoracic Society and the American College of Chest Physicians.

(95% CI 0.83–1.04) (Figure 2). There was significant heterogeneity between studies in our primary analysis (Q statistic = 46.7, p = 0.005), with a corresponding I^2 statistic of 46% (95% CI 15%–66%). We examined the data for effect modification by type of ICU and target for intensive insulin therapy. In the meta-regression analysis, we found that patients in a surgical ICU benefitted from intensive insulin therapy compared with those in the control group (p = 0.02). The resultant pooled estimate RR by type of ICU were as follows: surgical ICU: RR 0.63 (95% CI 0.44–0.91); medical ICU: RR 1.00 (95% CI 0.78–1.28); and mixed ICU: RR 0.99 (95% CI 0.86–1.12). Although only 5 trials enrolled patients in exclusively surgical ICUs, there was no statistical heterogeneity (Q statistic = 2.8, p = 0.60), with a corresponding I^2 statistic of 0% (95% CI 0%–79%).

The intensity of insulin therapy (target glucose ≤ 6.1 mmol/L v. ≤ 8.3 mmol/L) did not explain the heterogeneity of the trial results in the meta-regression (p = 0.81). For the trial that had 3 levels of glycemic control,[29] we found no change in the overall pooled estimate when we considered a target glucose concentration of ≤ 6.1 mmol/L rather than ≤ 8.3 mmol/L (RR 0.94, 95% CI 0.85–1.05, p = 0.29); the same was true in the meta-regression analysis examining the intensity of insulin therapy (p = 0.94).

Hypoglycemic events

Fourteen trials provided sufficient data on hypoglycemic events (Figure 3).[8–13,18,22,25,31–33,35,36] The pooled RR was 6.0 (95% CI 4.5–8.0), with some evidence of heterogeneity between studies (Q statistic = 20.7, p = 0.08), with a corresponding I^2 statistic of 37% (95% CI 0%–67%). We were unable to examine the data for effect modification by intensity of insulin therapy because only 1 trial that reported severe hypoglycemia used a target blood glucose level of 8.3 mmol/L or less.[31] The risk of hypoglycemic events did not differ by type of ICU (data not shown).

Publication bias

We found no evidence of publication bias, either by funnel plot (data not shown) or by Begg's (p = 0.97) or Egger's (p = 0.06) test.

Interpretation

In our updated meta-analysis of randomized trials of intensive insulin therapy in critically ill patients, we found that such therapy had no effect on the overall risk of death. By including data from the largest trial of intensive insulin therapy, which was recently published,[18] we provide the most current and precise estimate of the effect of intensive insulin therapy on mortality and severe hypoglycemia in the ICU setting. We found significant heterogeneity between studies, which was driven primarily by the 2 trials involving surgical patient populations.[8,29] In keeping with this observation, our meta-regression analysis suggested that intensive insulin therapy may benefit patients in surgical ICUs. Finally, there was a 6-fold increased risk of severe hypoglycemia among patients given intensive insulin therapy compared with the control

treatment. The risk of hypoglycemic events did not differ by type of ICU, or by intensity of insulin therapy.

Our meta-analysis showed a similar overall pooled estimate of effect on mortality, and similar confidence intervals, as the meta-analysis by Wiener and colleagues.[14] One important difference between these 2 reviews is our finding that the effect of intensive insulin therapy differed by ICU setting, with a benefit demonstrated among surgical patients. Weiner and colleagues did not find this. These discordant results may be explained by the inclusion of different trials. We excluded 3 unpublished trials that had been included by Wiener and colleagues. Although we found no evidence of publication
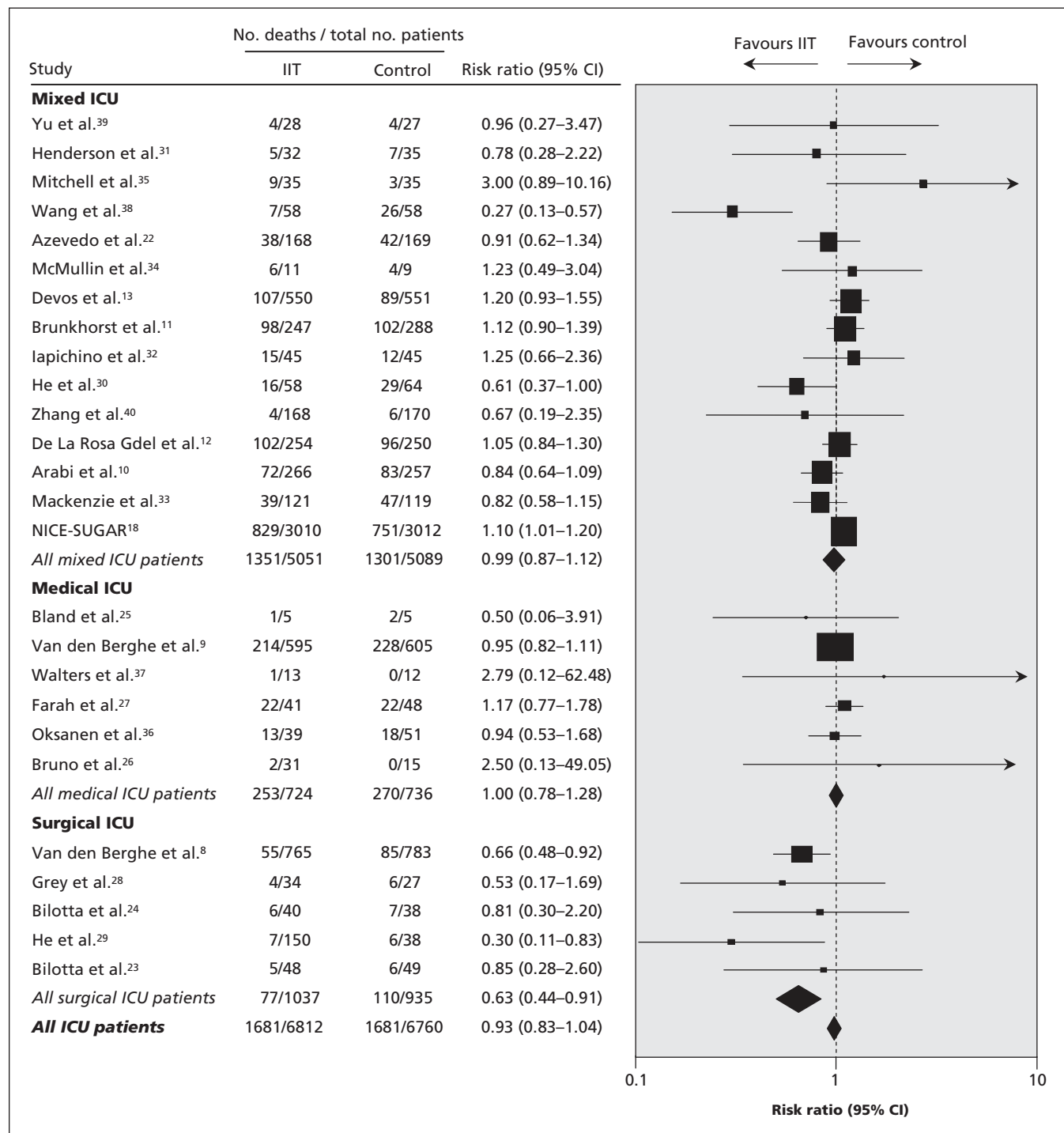
| Study | No. deaths / total no. patients | | Risk ratio (95% CI) | |
	IIT	Control		
Mixed ICU				
Yu et al.[39]	4/28	4/27	0.96 (0.27–3.47)	
Henderson et al.[31]	5/32	7/35	0.78 (0.28–2.22)	
Mitchell et al.[35]	9/35	3/35	3.00 (0.89–10.16)	
Wang et al.[38]	7/58	26/58	0.27 (0.13–0.57)	
Azevedo et al.[22]	38/168	42/169	0.91 (0.62–1.34)	
McMullin et al.[34]	6/11	4/9	1.23 (0.49–3.04)	
Devos et al.[13]	107/550	89/551	1.20 (0.93–1.55)	
Brunkhorst et al.[11]	98/247	102/288	1.12 (0.90–1.39)	
Iapichino et al.[32]	15/45	12/45	1.25 (0.66–2.36)	
He et al.[30]	16/58	29/64	0.61 (0.37–1.00)	
Zhang et al.[40]	4/168	6/170	0.67 (0.19–2.35)	
De La Rosa Gdel et al.[12]	102/254	96/250	1.05 (0.84–1.30)	
Arabi et al.[10]	72/266	83/257	0.84 (0.64–1.09)	
Mackenzie et al.[33]	39/121	47/119	0.82 (0.58–1.15)	
NICE-SUGAR[18]	829/3010	751/3012	1.10 (1.01–1.20)	
All mixed ICU patients	1351/5051	1301/5089	0.99 (0.87–1.12)	
Medical ICU				
Bland et al.[25]	1/5	2/5	0.50 (0.06–3.91)	
Van den Berghe et al.[9]	214/595	228/605	0.95 (0.82–1.11)	
Walters et al.[37]	1/13	0/12	2.79 (0.12–62.48)	
Farah et al.[27]	22/41	22/48	1.17 (0.77–1.78)	
Oksanen et al.[36]	13/39	18/51	0.94 (0.53–1.68)	
Bruno et al.[26]	2/31	0/15	2.50 (0.13–49.05)	
All medical ICU patients	253/724	270/736	1.00 (0.78–1.28)	
Surgical ICU				
Van den Berghe et al.[8]	55/765	85/783	0.66 (0.48–0.92)	
Grey et al.[28]	4/34	6/27	0.53 (0.17–1.69)	
Bilotta et al.[24]	6/40	7/38	0.81 (0.30–2.20)	
He et al.[29]	7/150	6/38	0.30 (0.11–0.83)	
Bilotta et al.[23]	5/48	6/49	0.85 (0.28–2.60)	
All surgical ICU patients	77/1037	110/935	0.63 (0.44–0.91)	
All ICU patients	1681/6812	1681/6760	0.93 (0.83–1.04)	

Figure 2: Risk ratios of mortality in clinical trials comparing intensive insulin therapy (IIT) to conventional glycemic control stratified by type of ICU. Tests for heterogeneity: mixed ICU: Q statistic = 29.54 ($p < 0.01$), I^2 = 52.6%; medical ICU: Q statistic = 2.05 (p = 0.84), I^2 = 0.0%; surgical ICU: Q statistic = 2.78 (p = 0.60), I^2 statistic 0.0%; all ICU patients: Q statistic = 46.67 ($p < 0.01$), I^2 = 46.4%. Note: CI = confidence interval.

bias in our analysis, the tests we used may be unreliable in the presence of significant heterogeneity.[41] However, since neither peer reviewers nor we have been able to assess the methodologic quality of the unpublished trials, we decided to include only trials published either in full or as abstracts in indexed journals.[42] In addition, following translation, data abstraction and quality assessment, we included 1 trial that had been excluded by Wiener and colleagues;[29] this trial was conducted in a surgical ICU and strongly favoured intensive insulin therapy. Although the NICE-SUGAR study included 2233 surgical patients and mortality was significantly increased in this subgroup, this study was conducted in mixed ICUs and was analyzed accordingly in our meta-analysis. The increased mortality in surgical patients enrolled in the NICE-SUGAR trial, the majority of whom were admitted to the ICU following emergency surgery, suggests that the benefit of intensive insulin therapy in patients treated in surgical ICUs requires confirmation.

Our findings of a significantly increased risk of hypoglycemia with intensive insulin therapy are in keeping with those reported by Wiener and colleagues.[14] However, the analysis of differences in the risk of hypoglycemia between subgroups is limited by the low number of included studies.

Finally, our findings do not support the guidelines of organizations such as the American Diabetes Association, the American Association of Clinical Endocrinologists and other organizations, including the Surviving Sepsis Campaign, who recommend intensive insulin therapy for all critically ill patients.[15–17,43] Our meta-analysis incorporates the results of the largest trial to date. We are not aware of any ongoing trial of sufficient size to affect these results; thus, we suggest that policy-makers reconsider recommendations promoting the use of intensive insulin therapy in all critically ill patients. However, ours was a pooled analysis of trials conducted in different populations with differing severity of illnesses and event rates; therefore, we cannot exclude the possibility that some patients may benefit from intensive insulin therapy. A meta-analysis of individual patient data and additional randomized trials may help to delineate which patients may benefit from intensive insulin therapy and be at lower risk of hypoglycemic events.

This review highlights a number of important questions that remain to be answered; most notable, why the beneficial treatment effect observed in Van den Berghe's first trial[8] has not been observed in subsequent multicentre trials involving adults. First, it may be that patients admitted to surgical ICUs after elective surgery benefit from intensive insulin therapy and that subsequent trials have not adequately examined this subgroup. Although this is suggested by our meta-regression showing a beneficial effect in patients admitted to surgical ICUs, subgroup analyses must be interpreted with caution, particularly in the setting of low event rates.[44,45] In the surgical ICU subgroup, there were only 77 deaths in the intensive insulin therapy group and 110 in the usual care group.
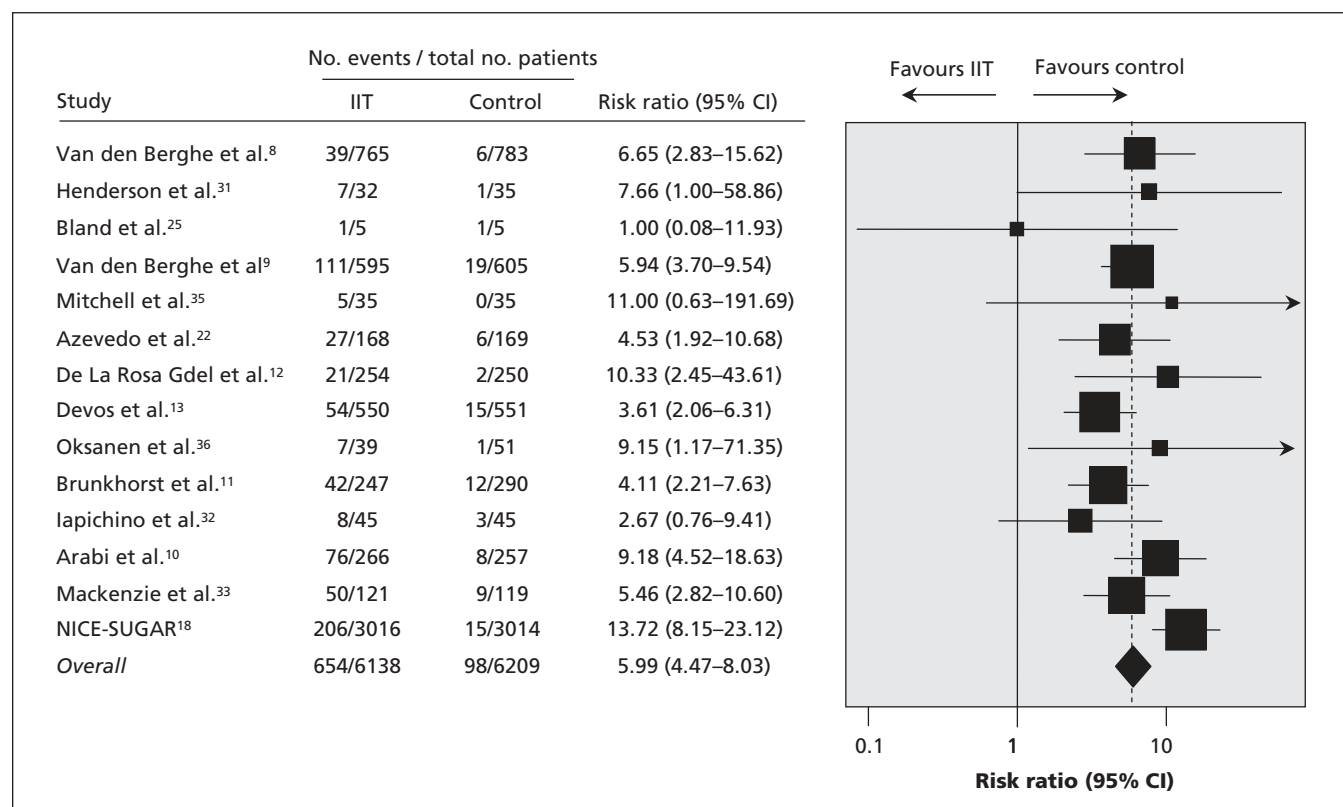

Figure 3: Risk ratios of hypoglycemic events in clinical trials comparing intensive insulin therapy (IIT) to conventional glycemic control. The dashed vertical line represents the pooled estimate. There was significant heterogeneity between trials (Q statistic = 20.71, p = 0.08, I^2 = 37.0%). Note: CI = confidence interval.

Study	IIT	Control	Risk ratio (95% CI)
Van den Berghe et al.[8]	39/765	6/783	6.65 (2.83–15.62)
Henderson et al.[31]	7/32	1/35	7.66 (1.00–58.86)
Bland et al.[25]	1/5	1/5	1.00 (0.08–11.93)
Van den Berghe et al[9]	111/595	19/605	5.94 (3.70–9.54)
Mitchell et al.[35]	5/35	0/35	11.00 (0.63–191.69)
Azevedo et al.[22]	27/168	6/169	4.53 (1.92–10.68)
De La Rosa Gdel et al.[12]	21/254	2/250	10.33 (2.45–43.61)
Devos et al.[13]	54/550	15/551	3.61 (2.06–6.31)
Oksanen et al.[36]	7/39	1/51	9.15 (1.17–71.35)
Brunkhorst et al.[11]	42/247	12/290	4.11 (2.21–7.63)
Iapichino et al.[32]	8/45	3/45	2.67 (0.76–9.41)
Arabi et al.[10]	76/266	8/257	9.18 (4.52–18.63)
Mackenzie et al.[33]	50/121	9/119	5.46 (2.82–10.60)
NICE-SUGAR[18]	206/3016	15/3014	13.72 (8.15–23.12)
Overall	654/6138	98/6209	5.99 (4.47–8.03)

A second possibility is that, because intensive insulin therapy is a complex treatment and the results may be dependent on the implementation of the intervention and the accuracy of blood glucose measurement,[46] these factors may have differed between Van den Berghe's first trial and subsequent trials. There is some evidence for this in the wide range of hypoglycemic events in the intervention arms between trials (from 5.1%–28.6%). A further explanation is the considerable variability in what constitutes "usual care." In the trial by Van den Berghe and colleagues, the control group targeted a blood glucose level of 10.0–11.1 mmol/L. In contrast, some of the trials included in our analysis used a lower glucose target in the control group. For example, in the control arms of the trials by the NICE-SUGAR group and by Oksanen and colleagues,[36] the targeted blood glucose level was less than 10.0 mmol/L and 6.0–8.0 mmol/L, respectively. In settings where usual care is to target a blood glucose level of less than 10.0 mmol/L, intensive insulin therapy may offer no benefit.

Another possible explanation for the discordant results between trials is that the degree with which blood glucose levels fluctuates in an individual patient may be as important as the average blood glucose concentration achieved.[47] It is possible for 2 trials to report having achieved similar mean blood glucose concentration while obscuring the fact that blood glucose variability was markedly different between the 2 trials. Finally, the impact of feeding regimens on the effect of intensive insulin therapy requires urgent clarification. The patients in the trial by Van den Berghe and colleagues[8] were fed largely by the parenteral route and received large doses of intravenous glucose.[9] In contrast, patients in other studies, such as the NICE-SUGAR study, received predominantly enteral nutrition.[18] We hypothesize that the treatment effect of intensive insulin therapy may be dependent on the means of controlling blood glucose, the accuracy of blood glucose monitoring, the degree of within-patient variation in blood glucose and the feeding regimen used. These hypotheses can be further explored through meta-analysis of individual patient data[48] and by rigorous, adequately powered and carefully conducted randomized controlled trials.

Conclusion

In summary, the results of our updated meta-analysis do not support widespread adoption of intensive insulin therapy in critically ill patients. We cannot exclude the possibility that some patients may benefit from intensive insulin therapy, although the characteristics of such patients remain to be clearly defined; as does the effect of different blood glucose algorithms, the method of measuring blood glucose and the influence of nutritional strategies. An individual patient data meta-analysis would help to address these questions.

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