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

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CRD summary
This review found that intensive insulin therapy significantly increased the risk of hypoglycaemia and conferred no overall mortality benefit among critically ill patients, but may be beneficial to patients admitted to a surgical intensive care unit. In light of the unexplained heterogeneity between trials the authors’ conclusions may not be reliable.

Authors’ objectives
To compare the effects of intensive insulin therapy with conventional insulin therapy on mortality and severe hypoglycaemia in the intensive care unit.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Search dates spanned 1948 to March 2008. Search terms were reported. Selected conference abstracts were searched (2000 to 2008). Bibliographies of relevant trials were handsearched. NICE-SUGAR data was obtained pre-publication. It appeared that all languages were searched. Trials not published either in full or as abstracts in indexed journals were excluded.

Study selection
Randomised controlled trials (RCTs) of adults in a critical care setting in which the intensive insulin therapy was defined by a target blood glucose concentration of 8.3mmol/L or less and the study outcome was mortality were eligible for inclusion. Ninety-day mortality was the primary outcome measure. Hypoglycaemic events were of interest (defined as a blood glucose level of ≤2.2mmol/L). The included studies were conducted in Saudi Arabia, South America, North America, Europe, Israel, Australia, New Zealand and China. Participant age ranged from 46 to 75 years old. Most patients were male. Patients were admitted with a range of admission diagnoses and received different feeding regimens. Most of the included trials had a glycaemic target of 6.1mmol/L or less as the intervention target; the rest had a target of 8.3mmol/L or less. The glucose targets in the control groups were greater than in the intervention groups. Most trials were conducted in mixed surgical and medical intensive care units; some were conducted in either surgical or medical alone.

Two reviewers independently selected studies.

Assessment of study quality
Methodological quality was assessed independently by two reviewers using the Jadad score to give a quality rating (maximum 5). Disagreements were resolved by group discussion and arbitration by a third reviewer if necessary.

Data extraction
Risk ratios (RRs) were calculated by pooling trial-specific cumulative incidence ratios from each arm of the included trials. Where event rates were zero, 0.5 was added to each cell. Authors were contacted for missing data if necessary. If 90-day mortality data were unobtainable, the following outcomes were used in order of preference: hospital mortality; 28-day mortality; and intensive care unit mortality. Intention to treat (ITT) data were used where available.

Data were extracted independently by two reviewers. Disagreements were resolved by group discussion and arbitration by a third reviewer if necessary.

Methods of synthesis
Risk ratios were pooled in a DerSimonian and Laird random-effects meta-analysis and 95% confidence intervals (CIs) were calculated. Statistical heterogeneity was assessed with Cochran’s Q (p<0.10) and I² statistics. A random-effects meta-regression was performed for potential sources of heterogeneity identified a priori (type of intensive care unit and...
glycaemic target in the intervention arm). Publication bias was assessed using Begg's and Egger's tests and through visual inspection of a funnel plot.

**Results of the review**
Twenty-six RCTs were included (n=13,657, range 10 to 6,104). Sixteen RCTs had a Jadad score of 3 and the rest had a score of 2.

There was no significant difference between intensive insulin therapy and conventional insulin therapy in mortality (RR 0.93, 95% CI 0.83 to 1.04; 26 RCTs). This was associated with significant heterogeneity (Q statistic 46.7, p=0.005, $I^2=46\%$). In analysis of effect modification by type of intensive care unit, patients in a surgical intensive care unit showed significant benefit from intensive insulin therapy compared to the control group (RR 0.63, 95% CI 0.44 to 0.91; five RCTs), but not for patients in mixed or medical intensive care units. No significant statistical heterogeneity was detected. Meta-regression found that the intensity of insulin therapy did not explain the heterogeneity of the trial results.

There was a significant increase in the risk of hypoglycaemic events among patients given intensive insulin therapy compared with control (RR 6.0, 95% CI 4.5 to 8.0; 14 RCTs). There was evidence of heterogeneity (Q statistic 20.7, p=0.08, $I^2=37\%$). Risk of hypoglycaemic events did not differ by type of intensive care unit or intensity of insulin therapy (data not shown).

There was no evidence of publication bias.

**Authors’ conclusions**
Intensive insulin therapy significantly increased the risk of hypoglycaemia and conferred no overall mortality benefit among critically ill patients. However, this therapy may be beneficial to patients admitted to a surgical intensive care unit.

**CRD commentary**
The review question was supported by inclusion criteria for participants, study design, intervention and outcome. Only selected sources of unpublished data were searched and potentially relevant papers may have been missed, but there was no evidence of publication bias. It appeared that all languages were searched, which reduced the risk of language bias. Study selection, data extraction and validity assessment were performed in duplicate, which reduced the possibility of reviewer error and bias. Study quality was assessed using an appropriate tool. However, the included studies were not high quality and confidence intervals were wide. There was potential for clinical and methodological heterogeneity. The results of meta-analyses were associated with statistical heterogeneity, which was not explained by meta-regression. In light of the unexplained heterogeneity between trials the authors’ conclusions may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that an individual patient data meta-analysis may help to clarify the characteristics of patients who may benefit from intensive insulin therapy, the effect of different blood glucose algorithms and the influence of nutritional strategies.

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No external funding was received.

**Bibliographic details**

**PubMedID**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.