Intensive insulin therapy in hospitalized patients: a systematic review
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CRD summary
This review concluded that intensive insulin therapy did not reduce mortality or improve health outcomes in hospitalised patients, but that it was associated with increased risk of severe hypoglycaemia. The authors' conclusions reflected the evidence presented, but in view of the potential for language bias and the clinical variation between trials, the conclusions should be viewed with caution.

Authors' objectives
To assess the benefits and harms of intensive insulin therapy in hospitalised patients.

Searching
MEDLINE and the Cochrane Database of Systematic Reviews were searched from inception to January 2010 for studies published in English. Search terms were reported. Reference lists of relevant papers were reviewed. ClinicalTrials.gov was searched for unpublished studies. Experts were contacted for additional studies.

Study selection
Randomised controlled trials (RCTs) that assessed the efficacy of intensive insulin therapy in hospitalised patients and the risk of developing hypoglycaemia were eligible for inclusion. Eligible trials had to report at least one pre-specified outcome of mortality, cardiovascular events, congestive heart failure, disability, wound infection, sepsis, or renal failure requiring haemodialysis. Controlled and uncontrolled studies were also eligible for the evaluation of the safety of intensive insulin therapy. The eligible controls were hospitalised patients that received less strict insulin therapy. Studies were excluded if they: evaluated fixed-dose insulin and glucose-insulin-potassium infusions; did not report rates of hypoglycaemia; or evaluated the intervention over a period of six months or less. Prospective cohort studies that did not consecutively enrol patients or had excessive loss to follow-up were excluded.

The primary outcome was short-term mortality, defined as death occurring within 28 days in intensive care unit or during the period in the intensive care unit, or 28 days of hospital stay or during the period of hospitalisation. Secondary outcomes included 90-day or 180-day mortality, infection, length of hospital stay, and hypoglycaemia.

In included trials, the types of patients were perioperative or critically-ill patients or patients with acute myocardial infarction or stroke. Settings varied between the included trials. Hypoglycaemia was classified in the included trials as glucose level ranging from less than 2.2 to less than 4.0mmol/L (<40mg/dL to <72mg/dL); the proportion of patients with diabetes varied from 12 to 100% (where reported). Most of the intervention groups were treated using insulin infusion.

Three reviewers independently selected studies for inclusion.

Assessment of study quality
The quality of the included studies was assessed using the US Preventive Services Task Force criteria on: selection (including adequacy of randomisation and concealment of allocation) and maintenance of comparable groups; loss to follow-up; relevant, valuable and reliable outcome measures; clear definitions of interventions; and use of appropriate analysis. A study was rated as good, fair, or poor (details of the quality components assessed and their ratings were defined in a supplementary online appendix - see URL for Additional Information).

It appeared that more than one reviewer performed quality assessment. Disagreements were resolved by discussion with all the reviewers.

Data extraction
Two reviewers independently extracted the number of events in the intervention and control group to calculate the...
relative risk (RR) and 95% confidence intervals (CIs). The authors also extracted data to calculate effect sizes for inpatient length of stay.

Methods of synthesis
Relative risk and 95% confidence intervals were combined in a meta-analysis using random-effects model. Where studies reported more than one of the primary outcomes, authors selected 28-day mortality for analysis, followed by hospital and intensive care unit mortality. Combined effect sizes with 95% confidence intervals were also calculated. Heterogeneity between studies was assessed by the Q-test and the $I^2$ statistic.

Subgroup analyses were performed on intensive insulin therapy in intensive care unit versus non-intensive care unit. Sensitivity analyses were performed to determine the robustness of the results on short-term mortality, proportion of patients with diabetes, mean blood glucose level achieved in the intervention group, and study quality.

Results of the review
Thirty-one RCT met the inclusion criteria (number of participants not stated). Twenty-nine additional insulin protocol studies (not necessarily reporting health outcomes) were considered for the assessment of glycaemic control. None of the included studies were blinded. None of the studies were rated as good quality; all achieved fair or poor quality.

Intensive insulin therapy did not show statistically significant effect in reducing 28-day mortality (21 RCTs, n=14,768 patients) compared with control therapy; there was no heterogeneity between trials ($I^2=0.0\%$). These findings did not change in any of the subgroup or sensitivity analyses performed. No statistically significant effect of intensive insulin therapy was observed on long-term mortality (13 RCTs). There were mixed effects for hospital stay (17 RCTs).

Patients receiving intensive insulin therapy were at an increased risk of developing hypoglycaemia compared with control therapy (RR 6.0, 95% CI 4.06 to 8.87; 10 RCTs, n=11,899 patients); between-study heterogeneity was significant ($I^2=57.9\%$). Although a statistically significant effect on rate of infection was found (RR 0.78, 95% CI 0.62 to 0.97; 15 RCTs, n=11,674), heterogeneity between trials was significant ($I^2=50.7\%$).

There were mixed results for other outcomes.

Authors' conclusions
No consistent evidence demonstrated that intensive insulin therapy targeted to strict glycaemic control compared with less strict glycaemic control improved health outcomes in hospitalized patients, but intensive insulin therapy was associated with an increased risk of severe hypoglycaemia.

CRD commentary
This review addressed a well-defined question in terms of interventions, outcomes, and study design, but inclusion criteria for participants were not clearly defined. The search included relevant databases and sources, but the restriction to studies published in English meant that the potential for language bias could not be ruled out. To minimise bias and errors during the review process, more than one reviewer selected trials, extracted data, and assessed the quality of the included trials.

Relevant quality assessment criteria were applied; the results indicated that trial quality was less than optimal. Potential sources of heterogeneity were explored; the chosen method of synthesis appeared to be appropriate. Sensitivity analysis demonstrated that the results were robust to changes in the factors considered. There were some weaknesses, and clinical variation in the included trials that may limit generalisability of the findings. Few details of interventions of regimens were reported.

The authors’ conclusions reflected the evidence presented, but in view of the potential for language bias and the clinical variation between trials, the conclusions should be viewed with caution.

Implications of the review for practice and research
Practice: The authors stated that, given the lack of compelling evidence for benefit, the potential for serious harm...
should preclude efforts to routinely implement very strict targets for blood glucose control in hospitalised patients.

**Research:** The authors stated that future studies should evaluate the health benefits of achieving moderate blood glucose level targets, as well as the cost, patient, nurse, and physician acceptance of implementing insulin infusion protocols in hospitalised patients. The feasibility and safety of transitioning patients from insulin infusion to subcutaneous insulin and ultimately to a safe outpatient regimen should also be examined.

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