Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses

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CRD summary
This review found no evidence of a difference in risk of death between patients treated with metformin and insulin and those given insulin alone. Some significant differences were found for other outcomes. The authors’ conclusions reflect the limitations of the evidence and appear reliable.

Authors’ objectives
To compare the benefits and harms of metformin and insulin compared with insulin alone for patients with type 2 diabetes.

Searching
The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, Latin American Caribbean Health Sciences Literature, and CINAHL databases were searched up to March 2011. Search strategies were reported. There were no language restrictions. Meeting abstracts and reference lists of included trials and relevant systematic reviews were screened. The authors also searched the US Food and Drug Administration web site and contacted pharmaceutical companies and experts in the field to locate additional published or unpublished trials.

Study selection
Randomised controlled trials (RCTs) that compared metformin and insulin with insulin alone (with or without placebo) in adults with type 2 diabetes were eligible for the review. The intervention had to last at least 12 weeks. Trials that involved concomitant use of glucose-lowering drugs other than insulin or metformin were excluded. The primary outcomes of the review were all-cause mortality and cardiovascular mortality; secondary outcomes were predefined.

Duration of the included trials ranged from three to 24 months. About half of the trials included insulin-naive patients; most trials allowed patients to be on metformin at trial entry. Daily metformin dose in the intervention groups ranged from 1,000 to 2,550mg. Insulin regimens varied between trials; some trials included more than one type of insulin treatment. Mean age of included patients ranged from 53 to 66 years. The duration of diabetes ranged from five to 18 years.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Trial quality was assessed using the criteria of the Cochrane Collaboration, including generation of the allocation sequence, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias.

Two reviewers independently assessed study quality; any discrepancies were resolved with the involvement of a third reviewer.

Data extraction
Data were extracted to derive risk ratios (RRs) for dichotomous outcomes and mean differences for continuous outcomes, both with associated 95% confidence intervals (CIs). Medians reported in trials were assumed to be close to the arithmetic mean. If not reported, the standard deviation of change from baseline to the end of follow-up was calculated with a correlation coefficient from the largest and longest trial with complete data for each continuous outcome in each treatment group. Reported standard errors and confidence intervals were converted to standard deviations. Authors were contacted for additional data as necessary.

Two reviewers independently extracted data using standard forms.
Methods of synthesis
Meta-analysis was done using both a random-effects and a fixed-effect model; most reported results were from the random-effects analysis. Heterogeneity was assessed using $I^2$, with values of 50% or more taken to indicate substantial heterogeneity.

Subgroup analyses were conducted for primary and secondary outcomes if significant effect estimates were present using a test of interaction (details reported in the paper).

Trial sequential analysis was done to maintain an overall 5% risk of a type I error and 20% of a type II error. Based on criteria specified in advance, the required information size to detect or reject a 10% relative risk reduction was calculated. If the required information size was very large, post-hoc analyses were done for a 30% relative risk reduction. Required information sizes were also calculated for specific reductions in continuous outcomes.

Results of the review
Twenty-six RCTs met the inclusion criteria of which 23 trials (2,117 patients) provided data for the meta-analyses. None of the included trials were rated as low for risk of bias across all domains. Only two RCTs described all aspects of adequate sequence generation, allocation concealment, and blinding of participants and investigators.

Sixteen RCTs (1,627 patients) reported on all-cause mortality but only five reported any deaths. There was no significant difference between metformin plus insulin versus insulin alone (RR 1.30, 95% CI 0.57 to 2.99; $I^2=0\%$). Trial sequential analysis indicated that 2.93% of the required information size to detect or reject a 30% reduction in relative risk was accrued for all-cause mortality.

Fifteen RCTs (1,498 patients) reported on cardiovascular mortality but only three reported any deaths. Differences between treatment groups were not statistically significant (RR 1.70, 95% CI 0.35 to 8.30; $I^2=0\%$). Trial sequential analysis indicated that 0.65% of the required information size to detect or reject a 30% reduction in relative risk was accrued for cardiovascular mortality.

In a fixed-effect model, but not in a random-effects model, risk of severe hypoglycaemia was significantly higher with metformin plus insulin than with insulin alone (RR 2.83, 95% CI 1.17 to 6.86; $I^2=43\%$).

In a random-effects model, metformin plus insulin treatment was associated with reduced glycated haemoglobin ($\text{HbA}_{1c}$), reduced weight gain and reduced insulin dose compared with insulin alone. Trial sequential analysis indicated that there was sufficient evidence to support a $\text{HbA}_{1c}$ reduction of 0.5%, 1kg lower weight gain and 5U/day lower insulin dose.

Results of other analyses were reported.

Authors’ conclusions
There was no evidence of improved all-cause mortality or cardiovascular mortality with insulin plus metformin treatment compared with insulin alone in patients with type 2 diabetes.

CRD commentary
The review question and inclusion criteria were clear. The search was thorough and included attempts to locate unpublished trials. Appropriate measures were taken to minimise risk of errors or bias affecting the review process.

Included trial quality was assessed appropriately and the results were used in the synthesis. Standard methods were used for the meta-analyses. Statistical heterogeneity was assessed and differences between trials were investigated using subgroup analyses.

The authors’ conclusions reflect the limitations of the evidence for the primary outcomes (no evidence of a difference rather than evidence of no difference) and are likely to 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 more trials were needed to determine whether adding metformin to insulin had an effect on mortality and to investigate any possible harmful effects.

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Bibliographic details
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