Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomised controlled trials


CRD summary
This meta-analysis found no evidence of benefit from metformin versus control therapy for type 2 diabetes, for all-cause or cardiovascular mortality and cardiovascular events; it could increase or decrease the death rate. The authors' conclusions should be treated with caution, as they recommended, due to the limited evidence.

Authors' objectives
To evaluate the cardiovascular mortality and morbidity and all-cause mortality with metformin for type 2 diabetes.

Searching
MEDLINE, EMBASE and Cochrane Database of Systematic Reviews, were searched for articles from January 1950 to July 2010, with no language restrictions; search terms were reported. The reference lists of published meta-analyses were searched.

Study selection
Randomised controlled trials (RCTs) comparing metformin with diet alone, placebo, or no treatment, trials of metformin as an additional therapy, or trials of metformin withdrawal, in patients with type 2 diabetes, were eligible for inclusion. Trials that compared metformin monotherapy with an active control were excluded. Trials had to report cardiovascular morbidity and mortality and all-cause mortality as the primary outcomes. Secondary outcomes could be myocardial infarctions (fatal or nonfatal); stroke (fatal or nonfatal); congestive heart failure; peripheral vascular disease; leg amputations; and microvascular complications.

In the included trials, the comparisons varied. A third of comparisons were of metformin as an addition to sulphonylurea versus sulphonylurea alone or with placebo. Other comparisons included: metformin as an addition to insulin versus insulin plus placebo; metformin versus placebo or diet; and metformin plus usual care versus usual care. The mean patient age was 57.7 years (range 53 to 64); 50% were men (range 40 to 85); the baseline mean body mass index was 30kg per cm² (range 28.5 to 31.8), where reported (not all trials specified that participants had to be overweight). The mean glycated haemoglobin level ranged from 6.6% to 9.6% and the mean duration of diabetes was 4.8 years (range less than one to 14.5).

Two independent reviewers selected trials.

Assessment of study quality
Two independent reviewers assessed trial quality using the Jadad scale to produce a score out of five, for randomisation, blinding and withdrawals. Low-quality trials had a score of three or less and high-quality trials had a score of four or five.

Data extraction
Two reviewers extracted all data independently. The numbers of events were used to calculate relative risks, with 95% confidence intervals.

Methods of synthesis
Trial results were pooled to give relative risks, with 95% confidence intervals, using a fixed-effect model if between-study heterogeneity was low, and a (Mantel-Haenszel) random-effects model if heterogeneity was significant. Between-study heterogeneity was assessed using $X^2$, $I^2$ and $T^2$; significant heterogeneity was present if the probability was less than 0.1 or $I^2$ was over 50%.

Sensitivity analyses and an interaction test were performed, based on trial quality (low versus high) and sulphonylurea as an additional treatment (absent versus present). Intention-to-treat analyses were performed.
Results of the review

Thirteen RCTs were identified, with 13,110 participants (range 29 to 8,732). Nine RCTs had a Jadad score of four and were double-blind; and four RCTs had a score of three and were not double-blind. Follow-up ranged from four to 128 months.

Primary outcomes: There were no significant differences with metformin versus control therapy for all-cause mortality (RR 0.99, range 0.75 to 1.31; I²=41%; eight comparisons) and cardiovascular mortality (RR 1.05, range 0.67 to 1.64; I²=59%; seven comparisons). Random-effects models were used for both analyses, as both had significant heterogeneity.

Subgroup analyses: Subgroup analyses for trials of low or high quality did not change the results, but heterogeneity was no longer significant for the high-quality trials. There were significant increases in all-cause mortality (RR 1.53, 95% CI 1.02 to 2.31; I²=0; three comparisons) and cardiovascular mortality (RR 2.20, 95% CI 1.20 to 4.03; I²=0; two comparisons) for metformin plus sulphonylurea versus sulphonylurea alone. One large UK study had the most weight for the primary outcome analyses and, when it was excluded, the results were not significant and the high heterogeneity disappeared.

Secondary outcomes: There were no significant differences for metformin versus control for the secondary outcomes of all myocardial infarctions (10 comparisons), all strokes (four comparisons), heart failure (four comparisons), peripheral vascular events (three comparisons), leg amputation (three comparisons) and microvascular complications (three comparisons). Fixed-effect models were used for all analyses. These results did not change in the sensitivity analyses.

Authors’ conclusions

There was no proof that metformin could prevent cardiovascular deaths and events; it could increase or decrease the death rate.

CRD commentary

The review addressed a well-defined question for study design, participants, interventions, and outcomes. There was no specific search for unpublished trials and some relevant data might have been missed. The search of the Cochrane database did not include their controlled trials database. Publication bias was not assessed. Trial quality was assessed and suitable criteria were used; the quality was reasonable. Efforts were made to reduce error and bias throughout the review process. Relevant trial details were reported. The synthesis was appropriate, but there was variation between trials in the comparisons made, the length of follow-up, and the participant numbers.

The authors recommended that their conclusions should be treated with caution due to few RCTs being identified and the limited number of events.

Implications of the review for practice and research

Practice: The authors noted that diabetes experts recommended the use of metformin after one UK study found positive effects for mortality and cardiovascular disease, but this needed confirmation. Compared with other antidiabetic treatments, metformin might have fewest disadvantages.

Research: The authors recommended that further trials were urgently needed to confirm or clarify these results and metformin might not be the best comparator when evaluating new hypoglycaemic drugs.

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Record Status
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.