The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus: a systematic review

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CRD summary
This review examined the effects of metformin on blood-pressure and lipid profile in type 2 diabetes. The authors concluded that metformin reduces total and low-density lipoprotein cholesterol slightly more than control treatments but has no effect on other outcomes. The review included a large number of trials and was reasonably well-conducted, and the authors' conclusions are likely to be reliable.

Authors' objectives
To assess the efficacy of metformin in lowering the blood-pressure (BP) and lipid profile in patients with type 2 diabetes mellitus.

Searching
MEDLINE and EMBASE were searched up to 2002; some search terms were listed. In addition, the manufacturer of metformin was contacted and the references of publications retrieved by the search were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included in the review. Trials with crossover or parallel designs and blinded or open-label trials were all eligible for inclusion.

Specific interventions included in the review
Studies that employed metformin for a treatment period of at least 6 weeks were eligible for inclusion. The comparison groups in the included trials used sulphonylurea derivatives, diet, placebo, insulin, thiazolidinediones, arcabose and guar.

Participants included in the review
Studies of patients with type 2 diabetes mellitus were eligible for inclusion. The authors' definitions of type 2 diabetes mellitus were accepted.

Outcomes assessed in the review
The primary outcomes included in the review were systolic and diastolic BP and lipid profile. The lipid profile comprised levels of plasma triglycerides, plasma total, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol. Levels of glycated haemoglobin (HbA1c) were also assessed in the review.

How were decisions on the relevance of primary studies made?
The authors stated how studies were selected for the review, but not how many reviewers performed the selection.

Assessment of study quality
The validity of the studies was assessed using the Delphi list. This produces scores ranging from A for the highest quality study to C for the lowest quality study with the highest risk of bias. Two reviewers blinded to the study identity independently assessed all studies for validity. Any disagreements were resolved by consensus.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
extraction. Data on trial characteristics, patient characteristics and primary outcomes were extracted. The authors of the identified studies were contacted for missing data. Where a study contained more than two treatment groups, data on monotherapy were used for the intervention and control groups. The control groups were prioritised as follows: placebo, insulin therapy, other treatments. Mean differences between the baseline and treatment data were calculated for each outcome measure where this was not reported in the primary study.

**Methods of synthesis**

**How were the studies combined?**
The weighted mean differences (WMDs) between the baseline and treatment data were pooled in fixed-effect meta-analyses for each outcome measure. Publication bias was assessed using a funnel plot.

**How were differences between studies investigated?**
Statistical heterogeneity was assessed using chi-squared tests. A priori subgroup analyses were conducted on the basis of the dose of metformin employed. Where there was a significant difference between the groups, additional subgroup analyses were conducted: studies were divided into tertiles on the basis of difference in glycaemic control between metformin and the control group, body mass index, the duration of treatment follow-up and metformin dose; metformin administered as monotherapy or in conjunction with another antidiabetic treatment; and on the basis of the control treatment used. Analyses of the effect of methodological quality, year of publication and study design (parallel versus crossover) were also carried out.

**Results of the review**
Forty-one RCTs (n=3,074) were included in the review: 33 parallel trials and 8 crossover trials.

The authors reported that there was no evidence of publication bias, although this analysis was not shown. They also reported that there was no statistically significant heterogeneity between the studies; this was also not shown.

Systolic BP (21 trials, n=1,667): the pooled WMD showed no significant difference between the groups (WMD -1.09 mmHg, 95% confidence interval, CI: -3.01, 0.82). This was also the case in the trials using the highest doses of metformin (at least 2,550 mg/day): WMD 0.54 mmHg (95% CI: -1.94, 3.02).

Diastolic BP (19 trials, n=1,609): the pooled WMD showed no significant difference between the groups (WMD -0.97 mmHg, 95% CI: -2.15, 0.21). This was also the case in the trials using the highest doses of metformin (at least 2,550 mg/day): WMD -0.17 mmHg (95% CI: -1.62, 1.27).

HbA1c: there was a small but statistically significant increase in glycaemic control with metformin compared with the comparator (-0.74, 95% CI: -0.84, -0.65).

Plasma triglycerides (37 trials, n=2,891): the pooled WMD showed a significantly greater reduction in concentration of plasma triglycerides in the metformin groups than in the control groups (WMD -0.13 mmol/L, 95% CI: -0.21, -0.04). Sensitivity analyses showed that metformin significantly reduced triglycerides compared with control treatment only in the following: studies with the greatest difference in glycaemic control in favour of metformin; studies using the two highest range of doses of metformin; studies with intermediate length of follow-up; studies that compared metformin with insulin therapy; and studies in which metformin was administered as monotherapy.

Plasma total cholesterol (38 trials, n=2,973): the pooled WMD showed a significantly greater reduction in concentration of plasma total cholesterol in the metformin groups than in the control groups (WMD -0.26 mmol/L, 95% CI: -0.34, -0.18). Sensitivity analyses found no relationship between this effect and any of the variables investigated.

Plasma LDL cholesterol (24 trials, n=1,867): the pooled WMD showed a significantly greater reduction in concentration of plasma LDL cholesterol in the metformin groups than in the control groups (WMD -0.22 mmol/L, 95% CI: -0.31, -0.13). Sensitivity analyses generally found no relationship between this effect and any of the variables investigated, with the exception of a stronger effect of metformin in those studies using a higher dose.

Plasma HDL cholesterol (29 trials, n=2,037): the pooled WMD showed no significant difference between the groups.
(WMD 0.01 mmol/L, 95% CI: -0.02, 0.03).

**Authors' conclusions**
Metformin does not affect BP or levels of HDL cholesterol and triglycerides in patients with type 2 diabetes, but it does produce small but significant reductions in total and LDL cholesterol levels which are independent of its effect on glycaemia.

**CRD commentary**
The review question and inclusion criteria were specific and clear. Although the authors searched only two relevant electronic databases, they also took steps to identify unpublished studies, which reduces the likelihood of publication bias. They also stated that they assessed publication bias, but this assessment was not presented in the review. The use of language restrictions was not reported, so it was unclear whether the likelihood of language bias was addressed. The authors carried out an appropriate validity assessment and undertook pre-planned analyses on the basis of this. Appropriate methods were used to minimise bias and error in the validity assessment process, but the methods used to select studies and extract data for the review were not reported. The use of meta-analyses to pool the data statistically was appropriate and although a large number of subgroup analyses were used, these were planned a priori. This was a large and reasonably well-conducted meta-analysis, and the authors' conclusions are likely to be reliable.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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