QUESTION: In patients with type 2 diabetes mellitus, does metformin increase the risk for fatal and non-fatal lactic acidosis or increase blood lactate concentrations compared with placebo or other hypoglycaemic treatments?

Data sources

Study selection
Clinical trials and cohort studies were selected if they included patients with type 2 diabetes, lasted ≥1 month, compared metformin alone or combined with other treatments with placebo or any other hypoglycaemic treatment, and reported the number of patients and duration of treatment.

Data extraction
Data were extracted on study methods and quality, participants, interventions, and outcomes. Attempts were made to contact authors for missing data.

Main results
176 studies (118 prospective comparative trials, 46 prospective cohort studies, and 12 retrospective cohort studies; mean study duration 2.1 y, mean drop out rate 9.2%) met the selection criteria. 26 099 participants (mean age 57 y, 61% men) were followed for 65 021 patient-years (17 156 participants [35 619 patient-y] in the metformin group and 8 943 participants [30 002 patient-y] in the nonmetformin group). 92 studies were randomised trials, 25 were non-randomised trials, and 58 were cohort studies. Metformin was given in doses of 1 to 3 g/day. Comparisons included placebo, diet, insulin, glyburide, glitazide, glipizide, glibenclamide, glimepiride, chlorpropamide, tolbutamide, acarbose, nateglinide, repaglinide, miglitol, troglitazone, rosiglitazone, and guar gum. Pooled results from the 176 studies showed no occurrences of fatal or non-fatal lactic acidosis in the metformin or non-metformin groups. Metformin and placebo or other non-biguanide treatments did not differ for mean change from baseline in blood lactate concentrations (weighted mean difference [WMD] 0.12 mmol/l, CI -0.86 to -0.65 mmol/l; fixed-effects model).

Conclusion
In patients with type 2 diabetes mellitus, metformin does not increase the risk for fatal or non-fatal lactic acidosis or increase blood lactate concentrations compared with placebo or other hypoglycaemic treatments.

COMMENTARY
Metformin improves glycaemic control in type 2 diabetes without causing weight gain or hypoglycaemia and is the only oral hypoglycaemic drug that has reduced cardiovascular morbidity and mortality in a randomised trial.1 However, metformin might increase the risk for lactic acidosis. For this reason, many prescribing guidelines suggest that metformin should be contraindicated in patients at higher than average risk for lactic acidosis.

Salpeter et al hoped to compare the incidence of lactic acidosis in metformin users with those taking other medications or placebo, but this proved impossible because not a single case of lactic acidosis was found in any of these studies. Although many of the included studies did not specifically exclude people with renal, hepatic, cardiac, or pulmonary disease, it is possible that not enough people with these comorbid conditions were enrolled in the studies to allow accurate risk estimates. In Saskatchewan, where comprehensive, linkable databases of prescriptions and healthcare encounters are maintained, only 2 cases of lactic acidosis were found among 11 797 people who filled metformin prescriptions over a 15 year period (9 cases/100 000 patient-y).2 This risk is strikingly similar to the lactic acidosis rate of 9.7/100 000 patient-years in a large US Health Maintenance Organisation in 1995 to 1994, when metformin was not yet available in the United States.3 Because >25% of people receiving metformin have ≥1 “absolute” contraindication to it, the low observed risk for lactic acidosis in metformin users cannot be attributed solely to “prudent” prescribing. In contrast to phenformin, no credible evidence exists that metformin increases the risk for lactic acidosis beyond what would be expected from underlying diseases. It is possible that overly restrictive contraindications to metformin might result in many people being denied an excellent drug while preventing few if any cases of lactic acidosis.

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