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Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial

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Summary

Background

Metformin might reduce insulin requirement and improve glycaemia in patients with type 1 diabetes, but whether it has cardiovascular benefits is unknown. We aimed to investigate whether metformin treatment (added to titrated insulin therapy) reduced atherosclerosis, as measured by progression of common carotid artery intima-media thickness (cIMT), in adults with type 1 diabetes at increased risk for cardiovascular

disease.

Methods

REMOVAL was a double-blind, placebo-controlled trial undertaken at 23 hospital diabetes clinics in five countries (Australia, Canada, Denmark, the Netherlands, and the UK). Adults aged 40 years and older with type 1 diabetes of at least 5 years' duration and at least three of ten specific cardiovascular risk factors were randomly assigned (via an interactive voice response system) to oral metformin 1000 mg twice daily or placebo. Participants and site staff were masked to treatment allocation. The primary outcome was averaged mean far-wall cIMT, quantified annually for 3 years, analysed in a modified intention-to-treat population (all randomly assigned participants with post-randomisation data available for the outcome of interest at any given timepoint, irrespective of subsequent adherence or study participation), using repeated measures regression. Secondary outcomes were HbA_{1c}, LDL cholesterol, estimated glomerular filtration rate (eGFR), incident microalbuminuria (not reported), incident retinopathy, bodyweight, insulin dose, and endothelial function, also analysed in all participants with post-randomisation data available for the outcome of interest at any given timepoint. This trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01483560), number [NCT01483560](https://clinicaltrials.gov/ct2/show/study/NCT01483560).

Findings

Between Dec 14, 2011, and June 24, 2014, 493 participants entered a 3 month run-in to optimise risk factor and glycaemic control (single-blind placebo in the final month). Of 428 randomly assigned patients, 219 were allocated to metformin and 209 to placebo. Progression of mean cIMT was not significantly reduced with metformin ($\hat{\mu} = 0.005$ mm per year, 95% CI $\hat{\mu} = 0.012$ to 0.002 ; $p = 0.1664$), although maximal cIMT (a prespecified tertiary outcome) was significantly reduced ($\hat{\mu} = 0.013$ mm per year, $\hat{\mu} = 0.024$ to $\hat{\mu} = 0.003$; $p = 0.0093$). HbA_{1c} (mean 8.1% [SD 0.9] for metformin and 8.0% [0.8] for placebo at baseline) was reduced on average over 3 years by metformin ($\hat{\mu} = 0.13\%$, 95% CI $\hat{\mu} = 0.22$ to $\hat{\mu} = 0.037$; $p = 0.0060$), but this was accounted for by a reduction at the 3-month timepoint ($\hat{\mu} = 0.24\%$, $\hat{\mu} = 0.34$ to $\hat{\mu} = 0.13$; $p < 0.0001$) that was not sustained thereafter ($p = 0.0163$ for visit-by-treatment interaction). Bodyweight ($\hat{\mu} = 1.17$ kg, 95% CI $\hat{\mu} = 1.66$ to $\hat{\mu} = 0.69$; $p < 0.0001$) and LDL cholesterol ($\hat{\mu} = 0.13$ mmol/L, $\hat{\mu} = 0.24$ to $\hat{\mu} = 0.03$; $p = 0.0117$) were reduced with metformin over 3 years of treatment, and eGFR was increased (4.0 mL/min per 1.73m^2 , 2.19 to 5.82 ; $p < 0.0001$). Insulin requirement was not reduced on average over 3 years ($\hat{\mu} = 0.005$ units per kg, 95% CI $\hat{\mu} = 0.022$ to 0.012 ; $p = 0.545$), but there was a significant visit-by-treatment interaction ($p = 0.0018$).

There was no effect on endothelial function as measured by reactive hyperaemia index, or on retinopathy. Discontinuation of treatment in 59 (27%) participants on metformin versus 26 (12%) on placebo ($p=0.0002$) was mainly due to an excess of gastrointestinal adverse effects, and there was no increase in hypoglycaemia with metformin. Five deaths occurred among patients allocated to metformin and two occurred among those allocated to placebo; none were judged by site principal investigators to be related to study medication.

Interpretation

These data do not support use of metformin to improve glycaemic control in adults with long-standing type 1 diabetes as suggested by current guidelines, but suggest that it might have a wider role in cardiovascular risk management.

Funding

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