

The REMOVAL trial: metformin reduces progression of mean carotid intima-media thickness (cIMT) in never smokers with type 1 diabetes

J.R. Petrie¹, N. Chaturvedi², I. Ford¹, M.C.G. Brouwers³, N. Greenlaw¹, I. Hramiak⁴, A.D. Hughes², A.J. Jenkins⁵, B.E.K. Klein⁶, R. Klein⁶, P. Rossing⁷, C.D.A. Stehouwer³, N. Sattar¹, H.M. Colhoun⁸, for the REMOVAL Study Group;

¹University of Glasgow, Glasgow, UK, ²University College London, London, UK, ³University of Maastricht, Maastricht, Netherlands, ⁴St Joseph's Health Care, London, Canada, ⁵University of Sydney, Sydney, Australia, ⁶University of Wisconsin, Madison, USA, ⁷Steno Diabetes Center, Gentofte, Denmark, ⁸University of Edinburgh, Edinburgh, UK.

Background and aims: In REMOVAL, metformin reduced the rate of progression of the tertiary carotid outcome (averaged maximal cIMT) over three years in middle-aged adults with longstanding type 1 diabetes but did not significantly reduce progression of the primary outcome (averaged mean cIMT). We now report subgroup analyses for the primary outcome (the only subgroup analyses that were pre-specified).

Materials and methods: 3-way interaction terms with treatment and time were calculated for the following baseline variables: age, duration of diabetes, baseline HbA1c, BMI, LDL cholesterol, systolic BP (all by above or below median), baseline cIMT (by tertiles), sex (male or female), smoking (ever or never), insulin pump user (yes or no) and history of cardiovascular disease (present or absent).

Results: The 3-way interaction term was significant for only one of the 11 pre-specified subgroup analyses: smoking status ($p=0.0373$). Of 428 randomised participants, [(mean±SD) age 55±8.5 years, HbA1c 8.0±0.82%, BMI 28.4±4.3 kg/m², 59% male, duration of diabetes 34±10.8 years, 12% with a history of cardiovascular disease, 82% on statin therapy], 227 (53%) were never smokers, 144 (34%) were ex-smokers and 57 (13%) were current smokers. Mean±SD duration of smoking was 22±13.2 years. The primary outcome mean cIMT was reduced by metformin in the 227 never smokers (-0.012 mm per year, 95% CI -0.021 to -0.002; $p=0.0137$) but not in the 201 ever smokers (0.003 mm per year, 95% CI -0.008 to 0.014; $p=0.5767$).

Conclusion: While subgroup analyses should be treated with caution, these data suggest that metformin may reduce progression of mean carotid IMT in type 1 diabetes in the absence of the powerful cardiovascular risk factor of smoking. This provides further support for a wider role of metformin in cardiovascular risk management.

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