Common diabetes drug fails to fulfill promise of improving cardiovascular risk in people without diabetes

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Despite high expectations for the commonly used diabetes drug metformin to improve risk factors for heart disease in people without diabetes, few beneficial effects have been found in a randomised trial of patients with established cardiovascular disease, published in *The Lancet Diabetes & Endocrinology*.

"There has been a lot of anticipation based on research in diabetic patients suggesting that metformin has cardiovascular benefits beyond its effects on blood glucose. We were hoping to find that it might also prevent hardening of the arteries, a warning sign for future heart attacks and strokes, in people without diabetes already on a statin", explains study leader Dr David Preiss from the University of Glasgow in the UK.

Metformin is a safe, inexpensive drug that is recommended as the first-line treatment for people with type 2 diabetes. It works by reducing the overactive glucose production associated with diabetes but it has also been shown to reduce other related risk factors for heart disease such as cholesterol levels, and inflammatory and blood clotting markers in earlier studies conducted before the common use of statins.

The landmark UKPDS trial found that metformin treatment led to a 39% reduction in risk of heart attack over 10 years in diabetic patients, but whether its potential cardiovascular benefits could be replicated in individuals without diabetes had not been tested until now.

The Carotid Atherosclerosis: MEtformin for insulin ResistAnce (CAMERA) trial, was designed to investigate the effect of metformin on changes in carotid intima-media thickness (cIMT; an established marker of atherosclerosis) in non-diabetic individuals with heart disease taking statins. A total of 173 patients were randomly assigned to metformin (850 mg twice daily; 86 individuals) or matching placebo (87) for 18 months. The trial was funded by the Chief Scientist Office, Scotland.

After 18 months, no improvement in cIMT or the extent of atherosclerotic plaque in the carotid arteries was noted in patients taking metformin. The average cIMT increased significantly in both groups (0.024mm per year for metformin, 0.017mm for placebo).

However, metformin significantly reduced all measures of adiposity (body weight [by over 3kg], body fat, body mass index, and waist circumference) compared with placebo, similar to what is often achieved on weight loss drugs, alongside improvements in other risk factors for the development of type 2 diabetes (eg, lower insulin and haemoglobin A1c [HbA1c, reflecting blood glucose levels]).

Overall, 251 adverse events were reported—136 in 63 patients taking metformin and 115 in 58 patients given placebo. Gastrointestinal events (diarrhoea, nausea, vomiting) were more common in patients taking metformin. According to Dr Preiss, "Major cardiovascular outcome trials are needed to conclusively assess metformin's cardiovascular effects in people without type 2 diabetes—such trials are underway at present. We cannot dismiss the potential cardiovascular benefit of metformin in patients without diabetes but CAMERA suggests that metformin has limited impact on important cardiovascular risk factors when patients are already on a statin."

Writing in a linked Comment, Chris Lexis and Iwan van der Horst from the University Medical Center Groningen in the Netherlands caution, "The

CAMERA study shows that the effect of metformin—in addition to current best treatment, including statins—on cIMT is probably small or negligible…[but] whether the primary endpoint of CAMERA or secondary endpoints such as HbA1c best represent cardiovascular outcome is unclear. The definitive evidence for the role of metformin in non-diabetic cardiovascular disease will have to be provided by large randomised clinical trials powered for cardiovascular outcomes such as the Glucose Lowering In Non-diabetic hyperglycaemia Trial (GLINT; ISRCTN34875079), in which 12 000 patients with high cardiovascular risk and dysglycaemia but without diabetes, will be assigned to metformin or placebo for 5 years. Until then, the role of metformin for improving cardiovacular outcomes has promise, but is still largely unproven."

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