EDITORIAL

Does metformin lower CVD risk in type 2 diabetes?

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A RECENT META-ANALYSIS TO EVALUATE THE IMPACT OF METFORMIN ON CARDIOVASCULAR disease has been unable to demonstrate convincingly that it is associated with a reduction of risk.[1]

Metformin is the most widely prescribed hypoglycaemic medicine worldwide. It has been the first-line hypoglycaemic drug in UK guidance for two decades, a place that was justified by the reduction in glucose levels, low risk of hypoglycaemia and weight neutrality. The UKPDS study suggested that patients treated with metformin were at reduced risk of cardiovascular disease, which was taken as further justification for the early introduction of the drug.

Recently, accumulating research data on metformin has challenged whether the drug does improve cardiovascular outcomes as had previously been assumed. This meta-analysis, performed by researchers in Cambridge, investigated the evidence for a cardioprotective effect from metformin.

The investigators searched Medline, Embase and the Cochrane Library for relevant papers in all languages. Studies were eligible if they were randomised controlled trials of adults with type 2 diabetes comparing any dose, or formulation, of metformin with no intervention, placebo or a lifestyle intervention and reporting mortality or a cardiovascular outcome as a primary or secondary endpoint, or an adverse event. There was no restriction on duration of follow-up. Studies of metformin in combination with other hypoglycaemic drugs were admissible if the treatment and control group were using the same additional agents.

The original electronic search identified 20,268 studies, of which 98 were fully reviewed. The final yield was ten articles, reporting 13 trials of metformin, virtually all carried out in Northern Europe or North America. Only four were randomised controlled cardiovascular endpoint trials just comparing metformin with placebo in patients with type 2 diabetes.

In total, 2,079 patients with type 2 diabetes were allocated to metformin and a similar number to comparison groups. Duration of the studies ranged from six months to 17 years 8 months. The average age of the patients varied from 53 to 65 years. Participants were mainly white, overweight, with diabetes of 0-15 years' duration, and poor glycaemic control. None of the studies was assessed as having a low risk of bias.

The summary estimates were based on a relatively small number of events: 347 cardiovascular deaths in five studies, 416 myocardial infarctions/ischaemic heart disease events in seven studies and 111 strokes in four studies. Many of these events were documented from the UKPDS study.

All the outcomes, with the exception of stroke, favoured metformin but none achieved statistical significance. Effect sizes were:

- All cause mortality 0.96 (95% CI: 0.84-1.09)
- Cardiovascular death 0.97 (95% CI: 0.80-1.16)
- Myocardial infarction 0.89 (95% CI: 0.75-1.06)
- Stroke 1.04 (95% CI: 0.73-1.48)
- Peripheral vascular disease 0.81 (95% CI: 0.50-1.31)

The analysis suggests that there remains uncertainty about whether metformin really does have a beneficial effect on cardiovascular outcomes in type 2 diabetes.

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What surprises me about this study is the paucity of high quality evidence to underpin one of the most widely accepted tenets of diabetes guidance.

The authors state that metformin 'appears more likely to reduce risk of cardiovascular disease than increase it' but concede that this view 'is based on a few small trials, with notable limitations, among an unrepresentative subset of patients.'

'Newer agents that could potentially be used early in the course of the disease are now available, and are backed by data from recent rigorous cardiovascular endpoint trials. However, they remain very expensive and lack data on long-term use,' they add.

More extensive analysis of health records may help a definitive answer to be reached. I think that GPs should continue to use metformin first line in accordance with guidance, but should be aware that there may be future paradigm shifts in the attitude to our current pharmacological approach to type 2 diabetes as new evidence emerges.

REFERENCE
1 Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. *Diabetologia* 2017;60:1620-29

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