Some diabetes drugs are better than others, according to new study

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New research suggests that several commonly prescribed drugs for type 2 diabetes may not be as effective at preventing death and cardiovascular diseases, such as heart attacks and stroke, as the oral anti-diabetic drug, metformin.

Insulin secretagogues (ISs), such as glimepiride, glibenclamide (known as glyburide in the USA and Canada), gliclazide and tolbutamide, have been used to treat type 2 diabetes since the 1950-1970s, Nevertheless, the long-term risk associated with these drugs has largely been unknown. Metformin is the first drug of choice in type 2 diabetes, but, until now, there have not been studies investigating the long-term risk of individual ISs compared with metformin.

A study published online today in the *European Heart Journal* [1] followed a large, unselected group of everyone living in Denmark, aged over 20, who had been treated with either an IS or metformin (monotherapy) between 1997 and 2006 – a total of 107,806 people. It found that, compared to metformin treatment, monotherapy with most ISs, including glimepiride, glibenclamide, glipizide and tolbutamide, was associated with a greater risk of death from any cause, and a greater risk of heart attacks, stroke or death from cardiovascular diseases. This was the case both for patients who had already suffered a heart attack and for patients who had not. Two other ISs, gliclazide and repaglinide, showed no significant difference to metformin in their effectiveness in patients with and without a history of heart attacks.

Compared to metformin, patients who had not suffered a heart attack had approximately a fifth to a third higher risk of death from any cause if they were taking glimepiride, glibenclamide, glipizide or tolbutamide. In patients with a history of heart attacks, the risk was approximately a third to a half higher.

The researchers, led by Dr Tina Ken Schramm, a senior resident doctor at the Heart Centre at the Rigshospitalet Copenhagen University Hospital (Copenhagen, Denmark), stress that the findings may not mean that these ISs actually cause harm, but only that they appear to be less effective than metformin.

"Previous studies have shown that ISs, in particular sulphonylureas, are associated with a reduction in long-term risk. Therefore, the increased risk from ISs shown in our study presumably has more to do with the beneficial effects of metformin, gliclazide and repaglinide, than the detrimental effect of the other ISs," explained Dr Schramm. "This is the first study to compare all ISs with metformin despite a wide debate on the possible cardiovascular risk associated with ISs for about three decades. Our findings emphasise how important it is to conduct long-term follow up studies of glucose-lowering medications."

In an accompanying editorial [2], Drs Odette Gore and Darren McGuire of the University of Texas Southwestern Medical Center (Dallas, Texas, USA), write that the study's findings are "among the most robust published", and continue: "It is of key importance to note that the observation of less benefit with most sulphonylureas [ISs] in the study compared with metformin should not be interpreted as causing harm."

Dr McGuire explained: "Patients taking metformin had the best outcomes, supporting prior evidence of metformin benefit and making it the first-line drug recommended for almost all patients with type 2 diabetes. Compared against this beneficial drug, most of the ISs were

associated with worse outcomes, but they would almost certainly be similar to, or better, had the comparison been made against placebo treatment, with the added benefit on kidney, eye, and nerve disease of the glucose control they yield. So patients should not stop their medications based on this study, but certainly should discuss any concerns with their doctor."

He added: "It's important to remember that these are observational analyses and not randomised comparisons, so it is impossible to tease out what if any of the difference in outcomes is due to the drugs compared versus differences in the patients – those taking ISs might have an increased risk to begin with."

Dr Schramm and her colleagues say that the mechanisms underlying the effects of different ISs and metformin are not fully understood and require further research.

She concluded: "Our study supports previous studies demonstrating that metformin may be less hazardous or more beneficial than most ISs. This suggests that metformin should be the first drug of choice in type 2 diabetes in most patients. The study shows there are important differences in the risk associated with different ISs, suggesting that gliclazide and maybe repaglinide are preferable, although in patients who have had a previous heart attack the most beneficial agents are metformin and gliclazide. As a result of our findings it is important now that there should be randomised studies focusing on patients at low and high cardiovascular risk."

More information: [1] "Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study". European Heart Journal. doi:10.1093/eurheartj/ehr077

[2] "Resolving drug effects from class effects among drugs for type 2 diabetes mellitus: more support for cardiovascular outcome assessments". European Heart Journal. doi:10.1093/eurheartj/ehr019

[3] ISs act by causing insulin to be released, thereby dealing with the problem of insufficient insulin production seen in type 2 diabetes. Metformin combats insulin resistance – one of the characteristics of diabetes – by increasing the action of insulin on insulin receptors, thereby reducing blood glucose in the liver, muscles and fat. During the period of the study, about 50-60% of those receiving glucose-lowering medications received monotherapy with metformin or ISs in Denmark. The initial treatment for diabetes patients is usually monotherapy with either metformin or ISs, and then later, when the diabetes becomes more advanced, insulin treatment or a combination of treatments becomes an option.

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