One class of drug used to treat type 2 diabetes may not reduce the risk of death when compared with placebo

April 17 2018

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One class of drug used to treat type 2 diabetes may not reduce the risk of death when compared with placebo, suggests new findings.

The research, led by scientists from Imperial College London and published in the *Journal of the American Medical Association*, studied three types of diabetes treatment: sodium-glucose cotransporter 2 (SGLT-2) inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and dipeptidyl peptidase 4 (DPP-4) inhibitors. Previous studies suggest these treatments are currently prescribed to at least one in three people with type 2 diabetes.

The team investigated whether these drugs were associated with a lower mortality risk, and conducted a network meta-analysis of 236 trials comparing all the drugs against each other, a placebo, or no treatment at all, and involving 176,310 patients.

All the drugs lower blood sugar levels but the results revealed that while two of the drugs reduced the risk of death when compared with a placebo, one did not.

The results revealed that SGLT-2 inhibitor drugs were associated with a 20 per cent reduction in risk of death, compared to patients taking an inactive placebo pill, or people taking no medication at all.

The class of GLP-1 agonist drugs meanwhile reduced risk of death by 18 per cent.

However the DPP-4 inhibitor drugs were not associated with a reduced risk of mortality compared to people taking placebo or no treatment at all. Furthermore, SGLT-2 inhibitor drugs and GLP-1 agonist drugs reduced the risk of death compared with DPP-4 inhibitor drugs. There was no significant difference between the SGLT-2 inhibitor and GLP-1 agonist drugs.

Dr Sean Zheng, lead author of the study from National Heart and Lung Institute at Imperial, said: "Type 2 diabetes has become a global

epidemic, with more cases than ever before. The three drug classes assessed here are being increasingly prescribed, yet until now there have been no clinical trials studying how these drugs compare to each other, and which type of drug could be the best option for patients."

Type 2 diabetes is thought to affect 2.8 million people in the UK, and 422 million people worldwide. The condition causes levels of sugar in the blood to become too high, usually because of a lack of insulin - the hormone that mops up blood sugar.

Treatments include diet and exercise, but most people also need medication to control blood sugar. The most commonly prescribed drug is called metformin, but if this doesn't work, or triggers side effects, patients are usually offered other drugs. The three most recent drugs that have been developed are the SGLT-2 inhibitors, GLP-1 agonists and DPP-4 inhibitors. These work in slightly different ways: SGLT-2 inhibitors increase the amount of sugar excreted by the body, while GLP-1 agonists and DPP-4 inhibitors increase natural insulin levels.

But although these drugs all lower blood sugar, doctors were unclear if one was more effective than another, explained Dr Zheng: "Patients with type 2 diabetes are at higher risk of dying from heart attacks or strokes, so we wanted to investigate which of these three treatments are most efficient at preventing death and cardiovascular diseases. Our hope is that in the crowded market that is diabetes medications, patients and their doctors have the necessary information to allow them to make informed decisions about long-term treatment strategies."

The team assessed all randomised-controlled trials - the gold-standard trial that randomly assigns patients to a drug or a placebo pill, or no drug at all - and compared the treatments with each other. The results suggested DPP-4 inhibitor drugs were not associated with a reduced risk of death.

The findings also suggested SGLT-2 inhibitor drugs were linked to a 1 per cent decrease in absolute risk of death. The GLP-1 agonist medications were associated with a decrease in absolute risk of death by 0.6 per cent.

Further analysis revealed SGLT-2 inhibitor drugs were associated with a 21 per cent reduction in risk of dying specifically from a cardiovascular event such as a heart attack or stroke (absolute risk of 0.8 per cent), while GLP-1 agonist medication was associated with a 15 per cent drop in risk of death from a cardiovascular event (absolute risk reduction of 0.5 per cent). Further research also suggested that SGLT-2 inhibitor drugs were associated with significant reductions in risk of heart failure compared with both the other treatments.

There was no reduction in risk of death from a cardiovascular event for the drugs DPP-4 inhibitors.

Dr Zheng explained that the reasons behind the apparent reduced effectiveness of DPP-4 inhibitors is unclear, though it may be they are simply less powerful than the other two types of medication.

However, he cautioned that further work is now needed to confirm these findings, and stressed that anyone concerned about their drug regimen should consult their healthcare team. There was no evidence that any of the treatments caused harm.

The team also pointed out that because these drugs are relatively new, most trials only tracked patients for a few years - therefore more research is needed to look at the long-term risks and benefits of these drugs.

More information: *Journal of the American Medical Association* (2018). jamanetwork.com/journals/jama/ … .1001/jama.2018.3024

Provided by Imperial College London