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PHARMACOTHERAPY

Cardiovascular safety of antihyperglycaemic drugs in patients with type 2 diabetes mellitus

Two large trials published in the *New England Journal of Medicine* demonstrate that the dipeptidyl peptidase 4 (DPP4) inhibitors alogliptin and saxagliptin are safe in patients with type 2 diabetes mellitus (T2DM).

Concerns have been raised over the past few years regarding the cardiovascular safety of new therapies for T2DM, particularly sulphonylureas and rosiglitazone. As a result, the FDA and regulatory agencies in other countries now require that the cardiovascular safety of all new diabetes drugs be assessed.

Many glucose-lowering drugs cause hypoglycaemia, which has been linked to an increased risk of future cardiovascular events. As DPP4 inhibitors do not seem to induce hypoglycaemia, they have been suggested as a safe class of drugs in patients at high risk of cardiovascular events. Two trials have now assessed the safety of these drugs in line with the new FDA guidance.

The first trial (EXAMINE) included 5,380 patients with T2DM who had an acute myocardial infarction or unstable angina requiring hospitalization within the past 15–90 days. The patients were randomly assigned to receive alogliptin or placebo, in addition to their usual antihyperglycaemic and cardiovascular medication, and were followed up for a median of 18 months.

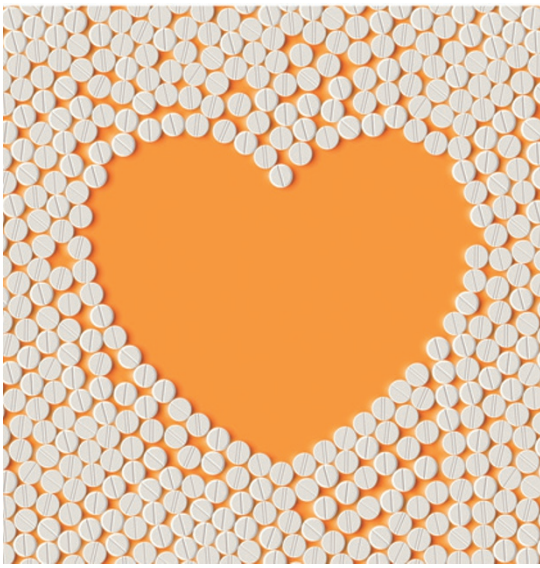
"The most important finding of the EXAMINE trial was that the primary end points of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke were not increased by alogliptin," explains lead investigator William B. White (University of Connecticut School of Medicine, USA). The primary end point occurred in 305 patients in the alogliptin group and in 316 study participants in the placebo group. In addition, alogliptin did not increase the risk of hypoglycaemia, poor renal function or disorders of the pancreas compared with placebo.

White and colleagues plan to continue exploring the data generated during the trial. They hope to investigate other cardiovascular events and perform a detailed assessment of subgroups of patients. "The results of these analyses might generate new hypotheses that could be studied in future prospective studies or in registry studies of the DPP4 inhibitors," explains White.

In the second trial (SAVOR-TIMI), 16,492 patients with T2DM who had a history of cardiovascular events or were at risk of such events were randomly assigned to receive saxagliptin or placebo. The patients were followed up for a median of 2.1 years. "In addition, we wanted to see if a strategy of DPP4 inhibition would actually reduce cardiovascular events, as some prior small studies suggested," says corresponding author Deepak Bhatt (Harvard Medical School, USA).

The researchers found that saxagliptin did not increase the risk of the primary end points of cardiovascular death, myocardial infarction or ischaemic stroke (613 patients in the saxagliptin group versus 609 patients in the placebo group). However, saxagliptin was not found to reduce the risk of cardiovascular events, as the researchers had hoped it would. In addition, a slight increase in the rate of hospitalization for heart failure was observed in the patients who received saxagliptin. "The significance of this finding is unclear and is not seen in any other ongoing trials of drugs of this class, so might be a spurious finding," says Hertzel Gerstein of McMaster University, Canada, who was not involved with either trial.

Bhatt and co-workers are now conducting further analyses of the data generated in the SAVOR-TIMI trial. In particular, they are trying to find predictors of the observed increase in hospitalization for heart failure, including analyses of biomarkers associated with heart failure.



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The researchers of both trials conclude that alogliptin and saxagliptin are safe to use in patients with T2DM in terms of cardiovascular events. However, the trials are limited by the length of the follow-up. These time frames might enable the recognition of short-term adverse events, but long-term cardiovascular benefits are unlikely to be identified. "Indeed, research suggests that antidiabetic drugs require several years to positively affect cardiovascular outcomes," explains Gerstein. "Notwithstanding the limitations, these findings are clearly important for patient care and will reassure patients that these drugs both seem to be safe."

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Original articles White, W. B. *et al.* Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N. Engl. J. Med.* doi:10.1056/NEJMoa1305889 | Scirica, B. M. *et al.* Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N. Engl. J. Med.* doi:10.1056/NEJMoa1307684