Nature Reviews Cardiology | Published online 24 Dec 2015; doi:10.1038/nrcardio.2015.199

DIABETES

Lixisenatide does not increase rates of CVD events

> lixisenatide, added to conventional therapy for patients with type 2 diabetes and acute coronary disease, did not increase rates of cardiovascular events

Preliminary studies have shown that glucagon-like peptide 1 (GLP-1) receptor agonists, used for the treatment of type 2 diabetes mellitus in adults, might have cardioprotective properties. Findings from the ELIXA trial published in *The New England Journal of Medicine* show that lixisenatide, a once-daily GLP-1 receptor agonist, has no effect on cardiovascular outcomes in patients with type 2 diabetes and acute coronary syndrome.

GLP-1 receptor agonists exert their antihyperglycaemic effects by inhibiting glucagon secretion and promoting insulin release in response to rising glucose levels. Although lixisenatide has been approved for use as an antihyperglycaemic agent in adults with type 2 diabetes, its effect on cardiovascular morbidity and mortality was unknown. The ELIXA trial was a multicentre, randomized, double-blind study to assess the effect of lixisenatide on cardiovascular outcomes in patients with diabetes and acute coronary disease. Patients with type 2 diabetes who experienced an acute coronary event (myocardial infarction or unstable angina) within 180 days of screening were enrolled into the study. Participants were randomly assigned to receive a subcutaneous injection of lixisenatide (starting dose of 10 μg, increasing to a maximum dose of 20 μg) or volume-matched placebo once daily, in addition to conventional therapy. The trial was powered to determine whether lixisenatide was noninferior or superior to placebo using the primary composite end point of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina. The incidence of hypoglycaemia and hyperglycaemia, pancreatitis, systemic allergic reactions, as well as other safety end points were also assessed.

In total, 6,068 patients from 49 countries were enrolled into the study and followed up for a median of 25 months. A primary end point event occurred in 13.4% ($n = 406$) of the lixisenatide group and in 13.2% ($n = 399$) of the placebo group (HR 1.02, 95% CI 0.89–1.17). Statistical analyses of the primary end point events indicated that lixisenatide was noninferior to placebo ($P < 0.001$), but not superior ($P = 0.81$). Treatment with lixisenatide was not associated with an increased occurrence of severe adverse events, such as hypoglycaemia or pancreatic neoplasms. However, adverse events that resulted in discontinuation of treatment occurred in more patients in the lixisenatide group ($n = 347$) than in the placebo group ($n = 217$; $P < 0.001$).

To summarize, these findings indicate that lixisenatide, added to conventional therapy for patients with type 2 diabetes and acute coronary disease, did not increase rates of cardiovascular events. The investigators in the ELIXA trial conclude that "the neutral cardiovascular profile associated with lixisenatide will inform physicians' and patients' decisions regarding the use of this agent as an adjunctive therapy to control the glycated haemoglobin level safely, with no observed augmentation of the risks of hypoglycaemia or pancreatitis".

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ORIGINAL ARTICLE Pfeffer, M. A. *et al.* Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N. Engl. J. Med.* **373**, 2247–2257 (2015)