CV outcome trials of incretin therapy (SAVOR-TIMI 53 , EXAMINE, TECOS, ELIXA)

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Dipeptidyl peptidase 4 (DPP4) inhibitors have been touted as promising antihyperglycemic agents due to their beneficial effects on glycemia without inducing hypoglycemia or body weight gain and their good tolerability. Beyond their glucose-lowering effects, numerous clinical trials and experimental studies have suggested that DPP4 inhibitors may exert cardioprotective effects through their pleiotropic actions via glucagon-like peptide 1-dependent mechanisms or involving other substrates.

Since 2008, regulatory agencies have required an assessment of cardiovascular disease (CVD) safety for the approval of all new anti-hyperglycemic agents, including incretin-based therapies. Three large prospective DPP4 inhibitor trials with cardiovascular (CV) outcomes have recently been published. According to the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53) and EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE) trials, DPP4 inhibitors, including saxagliptin and alogliptin, did not appear to increase the risk of CV events in patients with type 2 diabetes and established CVD or high risk factors. Unexpectedly, saxagliptin significantly increased the risk of hospitalization for heart failure by 27%, a finding that has not been explained and that requires further exploration. More recently, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trial demonstrated the CV safety of sitagliptin, including assessments of the primary composite CV endpoint and hospitalization for heart failure in patients with type 2 diabetes and established CVD. The CV outcomes of an ongoing linagliptin trial are expected to provide new evidence about the CV effects of a DPP4-inhibitor in patients with type 2 diabetes.

In ELIXA study, patients with type 2 diabetes and a recent acute coronary syndrome, treatment with the GLP-1–receptor agonist lixisenatide, added to conventional therapy, was not associated with a significant difference in rates of cardiovascular events as compared with conventional therapy plus placebo. This conclusion is supported by additional sensitivity analyses that excluded events

occurring more than 30 days after the discontinuation of lixisenatide or placebo, as well as by a

post hoc analysis in which the model was adjusted for minor between group imbalances observed at baseline. among patients with type 2 diabetes and a recent acute coronary syndrome, treatment with lixisenatide resulted in rates of

major cardiovascular events, including heart failure and death from any cause, that were similar to those observed with placebo. 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 hemoglobin level safely, with no observed augmentation of the risks of hypoglycemia or pancreatitis.