Series: Cardiovascular outcome trials for diabetes drugs
Sitagliptin and TECOS

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Abstract
TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) was an investigator-initiated cardiovascular outcome trial with sitagliptin. It compared sitagliptin and placebo in 14,671 subjects with type 2 diabetes and demonstrated non-inferiority for major cardiovascular events plus hospitalisation for unstable angina (cardiovascular death, myocardial infarction, stroke, unstable angina) but not superiority. Rates of hospitalisation for heart failure did not differ between the sitagliptin and placebo groups, and there were no significant between-group differences in rates of acute pancreatitis or pancreatic cancer. The clinical role for dipeptidyl peptidase-4 (DPP-4) inhibitors is diminishing as they have not been demonstrated to reduce cardiovascular events and are not associated with weight reduction, but if a DPP-4 inhibitor is indicated, the results of TECOS show that sitagliptin appears safer than saxagliptin or alogliptin.

Br J Diabetes 2020;20:55-57

Key words: diabetes, cardiovascular outcome trial, sitagliptin

Introduction
Licensing requirements for new anti-diabetes drugs changed in the USA and Europe in 2008 and 2012, and a dedicated randomised controlled cardiovascular outcome trial (CVOT) was usually required either before or after licensing. This is the third article in a series which describes and summarises the results of each of these CVOTs in the chronological order in which they were published, describing the primary endpoint and important secondary outcomes from the principal publication, but also directs attention to important subsequent publications of data from subgroups and post hoc analyses. The first published trial with saxagliptin, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53), showed an increase in hospitalisation for heart failure, and there was a similar effect in a subgroup in the Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care (EXAMINE) trial with alogliptin, so the heart failure results with sitagliptin in the TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) trial were awaited with interest.

Background
The dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin was the first DPP-4 inhibitor to receive a licence in the USA and Europe and was licensed in 2006 by the Food and Drug Administration (FDA) for use in the USA and in 2007 by the European Medicines Agency (EMA) for use in Europe (ie, prior to the 2008 FDA announcement). A post hoc assessment of cardiovascular safety in 14,611 patients was published in 2013 using patient-level data from 25 double-blind studies of duration 12 weeks to 2 years. No difference was observed in the incidence rate ratio of major adverse cardiovascular events (MACE), which was defined by a wide range of Medical Dictionary for Regulatory Activities (MedRA) cardiovascular events. Seventy-eight patients had at least one reported MACE event, 40 in the sitagliptin group and 38 in the non-exposed group.
were no significant between-group differences in rates of acute pancreatitis or pancreatic cancer.

**Other results from TECOS**

Further publications from TECOS are detailed in Box 2. The most important of these was a further detailed analysis of the heart failure results. There was no difference between sitagliptin and placebo for prespecified secondary analyses comparing the effects of sitagliptin and various composites including hospitalisation for heart failure, cardiovascular death and all-cause mortality or in defined subgroups. Total hospitalisation for heart failure events and death following hospitalisation for heart failure also were similar in the two groups. The analysis included a meta-analysis of TECOS, SAVOR-TIMI 53 and EXAMINE, which revealed moderate heterogeneity and suggested that statistical differences were unlikely to account for the discordance in the heart failure findings.

**Discussion**

TECOS was the third published CVOT with a new diabetes drug and, like the two previous DPP-4 inhibitor trials with saxagliptin and alogliptin, it showed that sitagliptin had no effect on atherosclerotic endpoints. No increase in hospitalisation for heart failure was seen in TECOS or the later Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA) and Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes (CAROLINA) trials with linagliptin. For patients with existing heart failure or those who are at a high risk of developing heart failure, including following an acute coronary syndrome, other alternatives are available, including sodium-glucose cotransporter 2 inhibitors which significantly reduce heart failure outcomes in people with diabetes.

In the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial with lixisenatide, which was presented at the same time as TECOS and published later in 2015, lixisenatide had no effect on atherosclerotic endpoints or hospitalisation for heart failure. As the four completed CVOTs (SAVOR-TIMI 53, EXAMINE, TECOS, ELIXA) had been non-inferior but not superior, some commentators raised questions as to whether the large cost of these trials was justified and whether population-based observational studies or registry-based trials would be more externally valid and cost effective. Later in 2015 the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was the first of many diabetes
CVOTs to show positive results, and there are now few doubts expressed about the value of these trials.

Conflict of interest The author has received payment for advisory boards and/or lectures from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, MSD, NAPP, Novartis, Novo Nordisk, Sanofi, Takeda.

Funding None.

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Current topics

Key messages

• TECOS was the third published cardiovascular outcome trial of a diabetes drug, comparing sitagliptin and placebo
• In TECOS sitagliptin had no effect on cardiovascular death, myocardial infarction, stroke or unstable angina
• No increase was seen in the rate of hospitalisation for heart failure with sitagliptin, but for patients with existing heart failure or those at high risk of developing heart failure, sodium-glucose transport protein 2 (SGLT2) inhibitors are a better alternative