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.

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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.[1,2] 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,[3] 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,[4] so the heart failure results with sitagliptin in the TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) trial were awaited with interest.

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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.[5] 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.

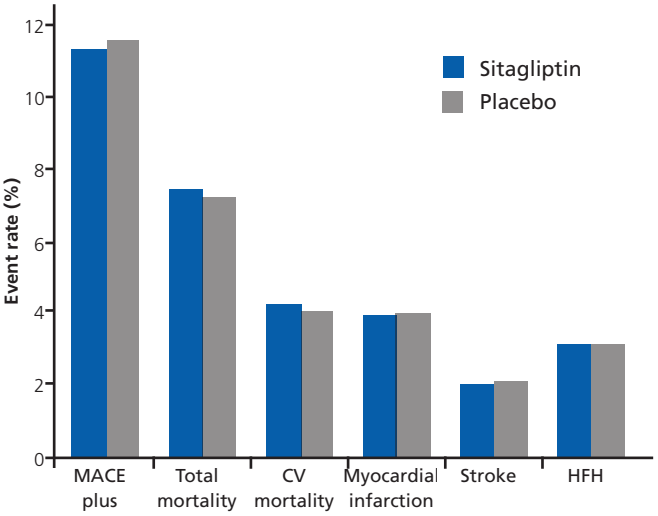
TECOS

A paper describing the design, rationale and organisation of TECOS was published in 2013,[6] with a paper in early 2015 describing the baseline characteristics.[7] The design of the study and key baseline characteristics are shown in Box 1. Although TECOS was planned prior to the new FDA/EMA guidance, its conduct and planned analyses were consistent with the agencies' recommendations.[6] The primary endpoint was major adverse cardiovascular events (MACE) plus hospitalisation for unstable angina (sometimes called 'MACE plus') comprising cardiovascular death, non-fatal myocardial infarction, non-fatal stoke, plus hospitalisation for unstable angina. Hospitalisation for heart failure was included as a secondary endpoint. The principal TECOS results were presented in 2015 at the meeting of the American Diabetes Association (ADA) and published simultaneously in the *New England Journal of Medicine*.[8] In TECOS there was no significant difference in 'MACE plus', so non-inferiority was established but not superiority (Figure 1, Box 2). Rates of unstable angina were very low at 1.5% in the sitagliptin group and 1.6% in the placebo group, and the frequency of hospitalisation for heart failure was similar at 3.1% in both study groups. There

Box 1 Key features of TECOS[6–8]

- TECOS compared sitagliptin versus placebo for a median of 3 years in 14,671 subjects
- TECOS was performed in a pragmatic fashion so study visits and procedures were integrated into the usual diabetes care schedule
- Mean age of subjects was 66 years with a mean duration of diabetes of 12 years
- Mean baseline HbA_{1c} was 7.3% (56 mmol/mol)
- All subjects had established atherosclerotic disease, 74% of subjects had prior cardiovascular disease, 43% had myocardial infarction, 24% had cerebrovascular disease and 18% had investigator-reported heart failure at baseline
- 82% of subjects were on metformin, 45% were on sulfonylureas, 3% were on thiazolidinediones and 23% were on insulin

Figure 1. Three-year estimated event rates (in %) comparing sitagliptin and placebo for 'MACE plus', total mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke and hospitalisation for heart failure (HFH)



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.[9] 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.

Box 2 Results of the TECOS trial

Principal result
- No reduction in MACE[8]

Other results from TECOS
- Heart failure events were similar in the sitagliptin and placebo groups, as was cardiovascular death, death following heart failure hospitalisation and total mortality[9]
- Numerically more subjects with sitagliptin developed pancreatitis (23 vs 12) and numerically fewer developed pancreatic cancer (9 vs 14)[17]
- Renal function declined at the same rate in both groups, with a marginally lower estimated glomerular filtration rate in the sitagliptin group compared with the placebo group, of uncertain significance[18]
- Severe hypoglycaemic events were not associated with sitagliptin therapy, but these events were in older subjects with a longer duration of diabetes, more renal disease, more women and non-white subjects, and were associated with an increase in cardiovascular events[19]
- Observational analysis showed no association between baseline use of beta-blockers and the risk of severe hypoglycaemia[20]
- Women in TECOS had a different cardiovascular disease burden, worse cardiovascular risk profiles and less use of indicated cardiovascular medications than men[21]
- Overall control of cardiovascular risk factors and use of aspirin and RAS blockade was low, indicating significant opportunities to improve the quality of cardiovascular secondary prevention care among people with diabetes[22]

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.[10,11] 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.[12]

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.[13] 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 trails was justified[14] and whether population-based observational studies or registry-based trials would be more externally valid and cost effective.[15] Later in 2015 the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was the first of many diabetes

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

CVOTs to show positive results,[16] 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.

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