Management & prevention of type 2 diabetes

Do newer type 2 diabetes therapies affect CV outcomes? Results from the first two studies

Roger Gadsby, GP and Senior Lecturer, Centre for Primary Healthcare Studies, Warwick University

Following concerns about rosiglitazone, the US Food and Drug Administration (FDA) now expects all new glucose-lowering therapies to provide data from a long-term study specifically looking at adverse cardiovascular disease (CVD) outcomes and that is sufficiently powered to confirm that these new therapies do not significantly increase CVD risk. Most dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors are, therefore, the subject of such trials. The first two drugs to report are the DPP-4 inhibitors alogliptin and saxagliptin, and these are the subject of this commentary.

The EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) group studied 5380 people with type 2 diabetes who had had a recent acute cardiovascular episode (infarction or angina; summarised alongside). Participants were randomly assigned to either alogliptin or placebo and followed for a median of 18 months. In addition, all participants received full standard secondary CVD prevention measures. The main outcome was a composite of death from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke. A total of 305 of these end points occurred in the alogliptin group and 316 in the placebo group, demonstrating no signal for increased CVD ischaemic risk in those treated with alogliptin. The HbA_{1c}, which was 63 mmol/mol (8%) in both groups at baseline, dropped 3.6 mmol/mol (0.33%) in the alogliptin arm and rose by 0.3 mmol/mol (0.03%) in the placebo group. Serious hypoglycaemia was very rare and only occurred in people who were also taking sulphonylurea and/or insulin. There were no differences in the rates of pancreatitis or cancer in the alogliptin and placebo groups.

The SAVOR–TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53) study involved 16 492 people with type 2 diabetes and established CVD, or who had risk factors for CVD (summarised on the next page). The study randomised participants to receive saxagliptin or placebo and followed them for a median of 2.1 years. The primary end point was the same as in the EXAMINE study, and this occurred in 613 people in the saxagliptin group and 609 in the placebo group, demonstrating no signal for increased ischaemic CVD risk in those treated with saxagliptin. The HbA_{1c} dropped by 3.2 mmol/mol (0.3%) in the saxagliptin group. There were no differences in the rates of pancreatitis or cancer between the saxagliptin and placebo groups. There was a slightly increased number of people hospitalised for congestive cardiac failure (CCF) in the saxagliptin group compared to the placebo group (3.5% versus 2.8%, respectively). In total, 78% of the trial participants were on statin therapy at the start and 90% after 1 year.

These trials have delivered exactly what they were designed to do: that is, to demonstrate non-inferiority to placebo for CVD ischaemic events. They have been criticised for not demonstrating superiority, but reducing HbA_{1c} by 3.2 mmol/mol (0.3%) and 3.6 mmol/mol (0.33%) over around 2 years is hardly likely to reduce CVD ischaemic events significantly. In my opinion, reducing glucose does improve CVD outcomes. This takes around 10 years, as demonstrated in the UKPDS (UK Prospective Diabetes Study) follow-up study (Holman et al, 2008). The increase in hospital admissions for CCF seen in the saxagliptin group may be of concern and will require more investigation.

At a symposium at the recent European Association for the Study of Diabetes (EASD) conference, the EXAMINE group said they had looked at their CCF admission data, which were not statistically different between the case and control groups. Both studies reassuringly show no increased risk of pancreatitis or cancer, which have been concerns of incretin-based therapies, although both trials were of relatively short duration. It remains to be seen what effect these results will have on DPP-4 inhibitor prescribing patterns following the imminent launch of alogliptin (at the time of writing) into the UK market.

Holman RR, Paul SK, Bethel MA et al (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* **359**: 1577–89

THE NEW ENGLAND JOURNAL OF MEDICINE

Alogliptin does not increase mortality in high CVD risk individuals with T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 Alogliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor and has recently been licensed in the UK for T2D.

2 This randomised, double-blind, non-inferiority, multicentre trial aimed to test the safety of alogliptin for individuals with T2D and high cardiovascular (CV) risk.

3 In total, 5380 individuals with T2D who were hospitalised with a recent acute coronary syndrome 15–90 days prior to the start were assigned to either alogliptin or placebo, alongside any current medication, with a median 18-month follow-up. Exclusion criteria included a T1D diagnosis or unstable cardiac disorders.

4 The primary end point was a composite of non-fatal myocardial infarction, non-fatal stroke and death from a CV event.

5 There was no significant difference between the alogliptin and placebo arms for the primary end points: there were 305 deaths in the alogliptin arm (11.3%) and 316 from the placebo arm (11.8%).

6 The alogliptin cohort had significantly reduced HbA_{1c} levels compared to placebo ($P<0.001$) and, therefore, better glycaemic control.

7 In conclusion, alogliptin did not significantly increase the rates of CV events, so it should be considered as a potential therapy for individuals in this high-risk category.

White WB, Cannon CP, Heller SR et al (2013) Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* **369**: 1327–35

THE NEW ENGLAND JOURNAL OF MEDICINE

Saxagliptin and cardiovascular outcomes

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 Saxagliptin is a selective dipeptidyl peptidase-4 (DPP-4) inhibitor used for the treatment of T2D.

2 This randomised, double-blind, phase IV, multicentre clinical trial allocated saxagliptin or placebo to 16 492 individuals with T2D at high risk of cardiovascular (CV) events to test its safety and efficacy.

3 Inclusion criteria included T2D and the following: a history of established CV disease and being at least 40 years of age; or multiple risk factors for CV disease and being at least 55 or 60 years of age for men and women, respectively, plus one other additional risk factor.

4 The dose of saxagliptin administered was 5 mg daily or 2.5 mg daily in participants with an estimated glomular filtration rate of ≤50 mL/min/1.73 m^2.

5 The primary end point (non-fatal myocardial infarction, non-fatal stroke or death from a CV event) occurred in 613 participants in the saxagliptin group (7.3%) and 609 patients in the placebo group (7.2%; $P<0.001$ for non-inferiority).

6 Saxagliptin significantly lowered HbA_{1c} at 1 and 2 years, and at the study's end, and significantly lowered fasting plasma glucose levels after 2 years and at the study's end.

7 Saxagliptin did not significantly increase or decrease the rate of CV events and gave no CV benefits. It was associated with an increased risk of hospitalisation from heart failure and of hypoglycaemia.

Scirica BM, Bhatt DL, Braunwald E et al (2013) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* **369**: 1317–26

DIABETES CARE

Bladder cancer risk

Readability	✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓

1 This study used data from British Columbia, Canada, to determine if the risk of bladder cancer in people with T2D has been overestimated due to increased physician visits at T2D diagnosis.

2 During the 10-year study period, 603 individuals with T2D (0.33%) and 568 controls (0.31%) were diagnosed with bladder cancer.

3 There was a 13% statistically significant relative increase in bladder cancer risk after T2D diagnosis at the 10-year follow-up, but not at the 2-year follow-up. Bladder cancer risk was recorded at it's highest at the 1-year follow-up among those with the fewest physician visits in the previous 2 years.

4 Increased physician visits at early T2D diagnosis are believed to be the cause of the overestimation.

Colmers IN, Majumdar SR, Yasui Y et al (2013) Detection bias and overestimation of bladder cancer risk in type 2 diabetes: A matched cohort study. *Diabetes Care* **36**: 3070–5

DIABETES CARE

Time to treatment intensification to control glycaemia

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 People with T2D commonly experience extended periods of poor glycaemic control when other oral antidiabetes drugs (OADs) could be administered (termed clinical inertia). This UK retrospective cohort analysis investigated the time to intensify OAD treatment and compared this with the recommended guidelines.

2 The prescription data from the Clinical Practice Research Datalink database were used for individuals taking one, two or three OADs from January 2004 to December 2006 with follow-up to April 2011.

3 The study found that individuals had poor glycaemic control for a median of >7 years before intensifying with another OAD or insulin if required.

4 When intensification of an OAD or insulin occurred, the mean HbA_{1c} levels for people taking one, two or three OADs were 72 mmol/mol, 76 mmol/mol and 83 mmol/mol (8.7%, 9.1% and 9.7%), respectively.

Khunti K, Wolden ML, Thorsted BL et al (2013) Clinical inertia in people with type 2 diabetes: A retrospective cohort study of more than 80,000 people. *Diabetes Care* 22 Jul [Epub ahead of print]

DIABETIC MEDICINE

Primary versus tertiary care model

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 This Australian prospective open-controlled trial compared clinical outcomes of primary community care given by specialised GPs and nurses (already in use in the UK) with usual tertiary care as outpatients.

2 An HbA_{1c} target of 53 mmol/mol (7%) at 12 months was the primary end point.

3 The mean HbA_{1c} changes in the intervention and control group were –9 mmol/mol (–0.8%) and –2 mmol/mol (–0.2%), respectively. The percentage of participants achieving the HbA_{1c} target of ≤53 mmol/mol (7%) in the intervention group increased from 21 to 42% ($P<0.001$), and, in the usual care group, there was a 1% increase to 39% ($P=0.99$).

Russell AW, Baxter KA, Askew DA et al (2013) Model of care for the management of complex type 2 diabetes managed in the community by primary care physicians with specialist support. *Diabet Med* **30**: 1112–21

"When intensification of an oral antidiabetes drug (OAD) or insulin occurred, the mean HbA_{1c} levels for people taking one, two or three OADs were 72 mmol/mol, 76 mmol/mol and 83 mmol/mol (8.7%, 9.1% and 9.7%), respectively."