Incretin-based therapies: Emerging evidence

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Safety and efficiency are crucial to effective prescribing for people with diabetes. Criticism about the manner in which the US Food and Drug Administration (FDA) managed the safety of rosiglitazone cast a long shadow over the organization. In 2008, the FDA updated its guidance for industry, requiring the conducting of studies to rule out excess cardiovascular (CV) risk for all new antidiabetes drugs (FDA, 2008). This guidance recognises that although improved long-term glycaemic control measured by HbA_{1c} leads to reduced risk of microvascular complications, consideration of CV risk in treatment decisions is important owing to the elevated risk of CV disease in people with diabetes. The FDA's stipulation has proved to be challenging and expensive for all pharmaceutical companies intending to launch products onto the US market.

There is a requirement for postmarketing trials to be conducted unless the FDA is satisfied that a lack of CV toxicity is clearly demonstrated in the preclinical or regulatory studies. Pragmatically, such a demonstration of non-inferiority is unlikely based on the typical total number of major CV events that are going to be seen in the preclinical and regulatory studies. Furthermore, ensuring that the postmarketing trials are adequately powered is a crucial aspect of their design. This is at a time when CV events are falling in people with diabetes.

The first two of these studies, both of which involve the dipeptidyl peptidase-4 (DPP-4) inhibitor class, have completed and been reported recently. The EXAMINE study assessed alogliptin (White et al, 2013) and the SAVOR–TIMI 53 study examined saxagliptin (Scirica et al, 2013). In this editorial, I appraise these studies and, in the light of recent concerns about the DPP-4 class of drugs, ask what these studies may have to tell us about the overall safety of this drug class.

EXAMINE

Alogliptin is a DPP-4 inhibitor that has been available in the US since the start of the year, and the European Medicines Agency has recently also granted it marketing authorisation (UK Medicines Information, 2013). It is the fifth DPP-4 inhibitor to be made available in the UK, but the first to come to market with a CV outcomes study (this was requested by the FDA following an initial filing).

The EXAMINE study was carried out to determine whether alogliptin was non-inferior to placebo (both added on to existing antidiabetes and CV therapies) with respect to major CV events in people with type 2 diabetes. To give it sufficient power the study recruited only participants at very high CV risk (they were required to have had recent acute coronary syndromes). In total, 5380 people with type 2 diabetes were randomised and followed up for a median period of 18 months. A primary endpoint CV event occurred in 305 people assigned to alogliptin and in 316 individuals assigned to placebo, and there was deemed to be no excess CV risk in the alogliptin arm ($P<0.001$ for non-inferiority).

HbA_{1c} levels were significantly lower with alogliptin than with placebo, although the overall effect was quite small, with the placebo group being actively treated as well with a range of antidiabetes therapies. A *post hoc* analysis covered in an oral presentation at the recent *49th Annual Meeting of the European Association for the Study of Diabetes* showed that hospitalisations for heart failure were numerically higher in the alogliptin group than in the placebo-treated group, but the difference was not statistically significant (White and Heller, 2013). Importantly, there was no excess pancreatitis or pancreatic cancer in the active treatment group (White et al, 2013).

SAVOR–TIMI 53

Saxagliptin is a DPP-4 inhibitor that has been available in the UK since 2009. In phase II and III studies, saxagliptin appeared to reduce the risk of major CV events (Cobble and Frederich, 2012). The SAVOR–TIMI 53 trial was designed to evaluate the safety and efficacy of saxagliptin in people with type 2 diabetes who had a history or a risk of CV events. Like the EXAMINE study, it was a multi-centre, randomised, double-blind, placebo-controlled trial. The primary endpoint, a composite of CV death, non-fatal myocardial

Study acronyms

EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care

SAVOR–TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53

Cobble ME, Frederich R (2012) Saxagliptin for the treatment of type 2 diabetes mellitus: assessing cardiovascular data. *Cardiovascular Diabetology* **11**: 6

McMurray J (2013). The Vildagliptin in Ventricular Dysfunction Diabetes trial (VIVIDD). Presented at: *Heart Failure 2013*, 25–28 May, Lisbon, Portugal

Scirica BM, Bhatt DL, Braunwald E et al (2013) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2 Sep 2 [Epub ahead of print]

UK Medicines Information (2013) *New Drugs Online Report for alogliptin*. Available at: http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=4476 (accessed 02.10.13)

US Food and Drug Administration (2008). *Guidance for Industry: diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes*. FDA, Silver Spring, MD, USA

White W, Heller S (2013). Results from EXAMINE study presentation. Presented at: *49th Annual Meeting of the European Association for the Study of Diabetes*, 23–27 September, Barcelona, Spain

White WB, Cannon CP, Heller SR et al (2013) Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2 Sep [Epub ahead of print]

Study acronyms

CAROLINA = the Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes

ELIXA = Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes after Acute Coronary Syndrome during Treatment with AVE0010 (Lixisenatide)

EXSCEL = the Exenatide Study of Cardiovascular Event Lowering

LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results

TECOS = the Trial Evaluating Cardiovascular Outcomes with Sitagliptin

VIVIDD = Vildagliptin in Ventricular Dysfunction Diabetes

infarction and non-fatal ischaemic stroke, was tested for both non-inferiority and superiority in the trial. So that the study was adequately powered to test this ambitious primary endpoint, 16 492 patients were randomised. The median follow-up period was 2.1 years.

As with the EXAMINE study, saxagliptin neither reduced nor increased the risk of the composite primary endpoint. As would be expected, the study showed a significant improvement in glycaemic control with saxagliptin. In addition, saxagliptin was linked to a reduction in the development and progression of microalbuminuria. There was no increased risk of either pancreatitis or pancreatic cancer in the saxagliptin group. The DPP-4 inhibitor did increase the risk of hospitalisation for heart failure, as well as the risk of hypoglycaemic events when it was combined with other agents known to cause hypoglycaemia (Scirica et al, 2013).

Lessons learned

What are the lessons to be learned from the two recently published studies? Starting with safety concerns, it is reassuring that CV non-inferiority was demonstrated in both trials. We should also be pleased that the rates of adjudicated cases of acute and chronic pancreatitis in the DPP-4 inhibitor arms were similar to those in the placebo arms in both studies. Pancreatic cancer incidence was not increased in the DPP-4 inhibitor arm of either of these recent studies.

Neither of the two studies set out to examine heart failure in isolation as a major outcome. Nevertheless, there seems to be an increased likelihood of developing, or being hospitalised for, heart failure among people with diabetes using these DPP-4 inhibitors. It is worth observing that the VIVIDD trial, while demonstrating non-inferiority of vildagliptin compared against placebo with regard to left-ventricular ejection fraction as its primary objective, did show a statistically significant increase in left-ventricular end-diastolic and end-systolic volume in the vildagliptin-treated group. This emerging narrative about heart failure will continue, and some prescribers will choose to exercise caution in using these DPP-4 inhibitors in people with established heart failure, especially at New York Heart Association Functional Classification 3 or 4.

Ultimately these large expensive cardiovascular risk studies, both recently published and ongoing (see *Box 1*), will serve people with diabetes by adding new safety data to inform clinical decision-making. These large randomised trials provide a much clearer view of relationships between drugs and outcomes than do observational studies. It might be optimistic to hope that the ongoing trials investigating other incretin-based therapies will show a conclusive CV benefit, but it is worth remembering that they have been designed first and foremost to address the question of non-inferiority. In any case, primary care teams need to actively address increased CV risk in people with diabetes by early tight glycaemic control, by blood pressure optimisation and lipid lowering, as well as by smoking cessation. ■

Box 1. Ongoing trials to assess cardiovascular (CV) risk in incretin-based therapies.*

DPP-4 inhibitors

- **Sitagliptin** is being evaluated in TECOS, which is designed to assess CV outcomes with sitagliptin versus placebo (Clinicaltrials.gov identifier: NCT00790205).
- **Linagliptin** is being evaluated for CV outcomes against glimepiride in CAROLINA (Clinicaltrials.gov identifier: NCT01243424).
- No relevant trials with **vildagliptin** are ongoing, although a study of left ventricular function – the VIVIDD trial – has completed (McMurray, 2013).

GLP-1 receptor agonists

- **Exenatide once weekly** is being tested against placebo in the CV outcomes trial EXSCEL. This is expected to enrol more than 9000 participants, with an estimated completion in 2017 (Clinicaltrials.gov identifier: NCT01144338).
- **Liraglutide** is being compared with placebo in the LEADER trial, which is also aiming to enrol more than 9000 participants and is expected to complete in 2016 (Clinicaltrials.gov identifier: NCT01179048).
- **Lixisenatide** is being examined versus placebo in the ELIXA trial, which has an estimated enrolment of 6000 and expected completion date of 2014 (Clinicaltrials.gov identifier: NCT01147250).

*There are additional ongoing studies in other diabetes treatments, besides incretin-based therapies.